A Mobility-Driven Spatially Explicit SEIQRD COVID-19 Model with VOCs, seasonality, and vaccines

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Abstract

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Key message: We add a number of features to a well-established epidemiological model: mobility, variants of concern, seasonality, and vaccination. All features are important for understanding the spread of SARS-CoV-2. All features except mobility strongly affect nation-wide COVID-19 transmission.

In this work we extend our previously developed compartmental SEIQRD model for sars-cov-2 in Belgium. The model is geographically stratified into eleven provinces and a telecommunication dataset provided by Belgium’s biggest operator is used to incorporate interprovincial mobility. We introduce variants, seasonality, and vaccines in our model, as their addition has proven critical for the description, forecasting and understanding of the COVID-19 pandemic in Belgium. We then calibrate the model using the daily number of hospitalisations in each province and...
serological data. We demonstrate how our model can be used to set up hypothetical scenarios to study the combined impacts of new variants, an ongoing nation-wide vaccination campaign and social relaxations. In this way, our model can be used to provide policymakers with relevant insights on the optimal timing of the release of social restrictions. We finally discuss the impact of locally altering social contact and mobility on shielding or containing epidemics and find that lowering social contact is more efficient than lowering mobility to tame a SARS-CoV-2 epidemic.

**Keywords:** COVID-19, compartmental model, spatially explicit, mobility, policy-making

## 1 Introduction

Coronavirus Disease 2019 (COVID-19) is a respiratory disease caused and spread by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The virus most likely originated in Wuhan, China in December 2019 [1] and has since spread globally. The pandemic continues up to the moment of writing and is characterised by sequential waves of COVID-19 cases and hospitalisations, warranting a series of preventive governmental policies. Fig. 1 provides a detailed overview of key events and policy changes for Belgium.

To better understand the spread of SARS-CoV-2 and inform policymakers, a nation-level compartmental metapopulation model for Belgium was developed [2]. Furthermore, likely future scenarios were bundled and discussed within an interuniversity mathematical modelling consortium named RESTORE. The findings were reported in several policy reports with accompanying press releases [3]. Reflecting the quickly expanding knowledge on COVID-19, the existing model (see ref. [2]) has proven to neatly fit past trends, as well as creating meaningful projections of future trends [4, 5]. The existing model has been under continuous development as a response to the ever-expanding knowledge on SARS-CoV-2. New knowledge includes firstly the influence of geography on viral spread, and secondly the effect of variants of concern (VOCs), seasonality, and vaccines on viral transmissibility and hospitalisation propensity. Consequently, the existing model was extended to incorporate these aspects.

Regarding the influence of geography, we have first shown in a parallel work that the viral spread was not spatially homogeneous but rather clustered, especially in the initial phase of the pandemic [6, 7]. Second, we have demonstrated a correlation between the mobility on the one hand, and the morphology and timing of local COVID-19-related time series on the other hand [6]. The same was clearly shown for France, Italy, and Spain as well [8]. Third, a national model cannot take into account local differences in
immunity, possibly leading to local herd immunity [9, 10]. Correcting for this may affect the national infection rate in a way that a nationally homogeneous model may not be able to capture. These three reasons suggest that a Belgian epidemiological model may benefit from a spatially explicit setup, as was successfully done for e.g. Spain [11], Brazil [12] and France [13]. Fourth, the inclusion of mobility and spatial heterogeneity into the metapopulation models allows scientists to advise policy-makers on the effect of localised measures, by predicting on a local level which areas face imminent danger, as well as which areas play a pivotal role in controlling the spread of the virus [4, 5]. This entails crucial and objective information in terms of e.g. preparation of local hospitals and the introduction of national mobility-related measures.

When it comes to VOCs and vaccines, the evidence for their influence on SARS-CoV-2 dynamics is decisive as well, which motivates their inclusion in the model. Subsequent VOCs are associated with different transmissibilities and hospitalisation propensities [14–16], and speculation on increase in severity is an important factor in policy advice [17]. Vaccination has the explicit goal of reducing viral transmission and/or disease severity and has been shown to do

![Fig. 1 Seven-day moving average of daily new COVID-19 hospitalisations in Belgium during 2020 and 2021 (maroon line). Vertical dashed lines are used to indicate events or policy changes with a possible impact on social contact behaviour relevant to this work. A green background colour is used to indicates school vacations. The horizontal arrows over the 2020 graph indicate the period of the first and second hard lockdown.](image-url)
this in both clinical trials [18] and society-scale follow-up studies [19]. In addition, vaccine efficacies differ between VOCs [20]. The direct or indirect effect of seasonal changes on the SARS-CoV-2 transmission rate is not supported by the same overwhelming amount of data due to the limited time since the start of the pandemic. However, seasonality plays a crucial role in many viral diseases [21], and has been required in recent COVID-19 modelling efforts [22]. Considering VOCs, vaccines, and seasonality in the model requires the time-, age- and location-dependent rescaling of the model parameters governing transmissibility and hospitalisation propensity.

In this work, we first demonstrate that after model development, the resulting simulations provide an adequate description of past COVID-19-related time series on the level of the Belgian provinces. We then demonstrate how the model can be used to explore hypothetical future scenarios to inform policymakers on the effects of social and pharmaceutical policies. Finally, in a purely hypothetical setup, we study the effect of locally altering the mobility and social contacts on the spread of SARS-CoV-2, which is only possible in a spatially explicit model. We find that (1) decreasing mobility as a means of slowing or stopping viral spread is not efficient, and (2) local decreased social contact does not help to effectively contain a global viral outbreak.

It is important to stress that while the model is calibrated on Belgian COVID-19 data, the underlying framework is in no way unique to Belgium nor to COVID-19. The mathematical setup of the model may therefore be applied to other countries and/or infectious diseases amongst humans as well.

2 Methods

The spatially explicit SEIQRD model presented here constitutes an extension of our national SEIQRD model for Belgium [2]. Here we first present the latter model. We then discuss the addition of a spatial dimension, and the dynamic rescaling of model parameters to include the effects of VOCs, seasonality, and vaccines. Finally, we discuss how the model is calibrated and how the hypothetical scenarios shown in the results section were set up.

2.1 SEIQRD model formulation

A metapopulation model assumes that a population is well mixed and is distributed over a number of compartments that correspond to a stage in the disease development. The flowchart depicting the various metapopulation compartments and their interaction in our COVID-19 model is shown in Fig. 2. In our previous model [2] the infectious compartment (I) in the original SEIRD formulation [23] is extended into six compartments to incorporate more expert knowledge on SARS-CoV-2. In this way, the model accounts for pre-symptomatic and asymptomatic transmission of SARS-CoV-2 [24–26], and for different COVID-19 severities, ranging from mild disease to hospitalisation. Our
model distinguishes between regular hospital wards (cohort) and intensive care units (ICUs) and further accounts for a recovery stay in cohort after an ICU stay. Using data from 22 136 COVID-19 patients in Belgian hospitals, we previously computed the probabilities of needing intensive care, the mortalities in both hospital wards, and we computed residence time distributions in both hospital wards [2]. Waning of antibodies (seroreversion) is included, enabling re-susceptibility after a prior infection. The model is age-stratified in 10 age classes, 0-12, 12-18, 18-25, 25-35, 35-45, 45-55, 55-65, 65-75, and 85-120 years of age, to account for the fact that social contact and disease severity differs substantially between individuals of different ages.

![Flowchart of the SEIQRD model](image)

Fig. 2 Flowchart of the SEIQRD model. Here, $S$ stands for susceptible, and $E$ for exposed but not yet infectious. Infected subjects in the $I$ compartments are those that are considered to actively drive the pandemic, because they are either presymptomatic ($I_{\text{presy}}$), or asymptomatic ($I_{\text{asy}}$). Subjects in the $Q$ compartments are supposedly quarantined due to heightened symptom awareness, whether they have mild symptoms ($Q_{\text{mild}}$), are hospitalised ($Q_{\text{hosp}}$), are accepted in the ICU ($Q_{\text{ICU}}$), or remain in a recovery stay in cohort coming from the ICU ($Q_{\text{ICU,rec}}$). After infection, subjects are either deceased ($D$) or recovered ($R$). Recovered subjects may again become susceptible. The model presented in this paper will stratify each of these compartments according to 10 age classes and 11 provinces.

2.2 Spatially explicit model extension

The first extension is to split Belgium in a collection of 11 geographical units: 10 provinces and the arrondissement Brussels-capital (NUTS3 level, Fig. A2, Table A1). We will refer to the latter as the “11th province” for convenience. Each of these 11 provinces exhibits its own SEIQRD dynamics, and the provinces are interconnected based on the mobility of subjects between them. We will also distinguish between social contact behaviour in the home province versus the visited province, and differentiate between transmission coefficients in a rural, urban and metropolitan province. All age-related and spatial stratifications are denoted with subscripts ($i$ or $j$) and superscripts ($g$, $h$ or $k$), respectively.
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Interprovincial mobility

Central to the quantification of the interprovincial connectivity is the telecommunication dataset provided by Belgium’s largest telecom operator Proximus (Appendix A.2). The use of this type of data as a proxy for mobility has been shown to be legitimate [27], and has been done in the particular context of COVID-19 in other analyses and modelling efforts [28–30]. The geographical spread of subjects between $G$ regions is quantified in a $G \times G$ time-dependent mobility matrix $P(t)$ with elements $P_{gh}(t)$. Element $P_{gh}(t)$ represents the estimated fraction of all the time available to all subjects in patch $g$, spent in patch $h$, in the day corresponding to time $t$. Fig. 3 depicts an abstract spatially explicit model with three spatial patches; for the actual model $G = 11$. As an example, two time series of $P_{gh}(t)$ for two different $(g,h)$ pairs are shown in Fig. 4.

The mobility matrix is used to determine the effective population sizes per model compartment in each province at time $t$ [11]. Mathematically, the
effective population size is computed as follows:

$$X_{i, \text{eff}}^g(t) = \sum_{h=1}^{G} P^{hg}(t) X_i^h(t), \quad (1)$$

where $X$ represents an arbitrary model compartment, or the total population $T$. This matrix multiplication effectively supports the geographical spread of sars-cov-2 in our model.

**Local social contact**

The contact between generations in our model drives the rate and spread of the infection, and is time-dependent [2]. Furthermore, the contact data has a double geographical stratification: we determine social contact per province, and we determine social contact depending on whether a subject is in their home province, or visiting another province.

The size and time dependence of the social contact matrix results from multiplying four factors and summing over six locations, i.e.

$$\tilde{N}^g_c(t) = \sum_{k \in \text{loc}} M(t) \Omega^k G^{k,g}(t) N^k_c, \quad (2)$$

with elements $\tilde{N}^g_{c,ij}(t)$ representing the average daily number of contacts at time $t$ between subjects in age class $i$ with those in age class $j$, in province $g$. The sum is over locations that are associated with distinct average contact behaviour: home, school, work, transport, leisure, and other. The factor $N^k_c$ is a social contact matrix taken from the socrates web tool [31] and based on a 2010-2011 social contact survey conducted in Flanders that was revisited recently in the context of covid-19 [32]. The observational time series $G^{k,g}(t)$ are taken from the Google Community Mobility Reports (GCMRs) [33] and constitute the primary tool for rescaling the pre-pandemic social contact survey results to more accurate values. This approach was preferred over using more recent Belgian social contact studies [34] because the GCMRs are available daily and at the provincial level. Both the $\Omega^k$ and $M(t)$ parameters range between 0 and 1, and their particular values (at time $t$) are calibrated. The $\Omega^k$ parameters have two physical interpretations. 1) They can be thought of as quantifying the degree to which a contact in place $k$ can contribute to sars-cov-2 spread. 2) Alternatively, they can be seen as the degree correlation between the Google mobility indicator in location $k$ and reductions in the spread of sars-cov-2. A low value of $\Omega_k$ suggests a change in the Google mobility indicator has limited effect on viral transmission, i.e. the Google indicator is inadequate. The mentality factors $M(t)$ were added to the social contact model because preliminary research indicated that public awareness triggers an apparent mentality change that reduces the number of social contacts even further than the GCMR data suggest. Two examples of resulting
Fig. 5 Example of time series $\tilde{N}_{c,ij}(t)$ for Brussels, which represent the local effective social contact between two age classes $i$ and $j$. These series result from the multiplication of four factors shown in Eq. (2). The solid maroon curve shows effective contact between 18-25 year-olds and 25-35 year-olds. The dashed olive curve shows the same information, but 45-45 year-olds contacting 65-75 year-olds, clearly following a similar overall trend but involving fewer contacts.

details are found in Appendix B.

We will additionally assume that, on average, one only has work-related contacts in visited provinces, whereas all types of contact are possible within the home province. That is to say that we express the social contact of an average subject from province $g$ visiting province $h$ as

$$
\bar{N}_{gh}^{e}(t) = \delta_{gh} \tilde{N}_{c}^{g}(t) + (1 - \delta_{gh})M_{work,h}^{work}(t)\Omega_{work}G_{work}^{h}(t)N_{c}^{work},
$$

where $\delta_{gh}$ is the Kronecker delta.

**Local population density dependence**

We assume that average population density affects the effective transmission coefficient (similar to [11]) because we observed transmissibility differences not explicable by differences in the degree of social contact between provinces. However, in order to avoid over-parametrisation of the model, we don’t define a unique transmissibility coefficient for each of the eleven provinces. Instead, we used three different transmission coefficients based on the population density. Essentially, this turns $\beta$ into a vector with three degrees of freedom,

$$
\beta \rightarrow \beta^{g} \in \{\beta^{R}, \beta^{U}, \beta^{M}\},
$$

depending on whether we consider the province $g$ to be predominantly rural, urban, or metropolitan (see Table A1).

### 2.3 Dynamical rescaling of model parameters to include VOCs, seasonality, and vaccines

Including the effects of VOCs and seasonality simply implies dynamically altering the effective value of a number of model parameters during the simulation, regardless of age or home province. We implemented the effect of imperfect (“leaky”) vaccines in a more sophisticated fashion, by further stratifying the metapopulation model. See below and Appendix C for details.
Variants of concern

Beyond the wild-type sars-cov-2 variant, we consider four VOCs identified by the World Health Organization [35]: Alpha, Beta, Gamma, and Delta. Due to their similar properties in our model [36], we aggregate the first three VOCs, denoted as $\alpha$-$\beta$-$\gamma$. To model the emergence of these variants, national prevalence data were used [37] (see Fig. C6, top). At every time $t$, a weighted average infectiousness of SARS-cov-2 variants was computed using the variant fractions, which effectively turns the (geographically stratified) transmission coefficient into a time-dependent function, i.e.

$$\beta(t) = \beta \sum_n \alpha_n(t) K_{inf,n}.$$  \hspace{1cm} (5)

Here $\alpha_n(t)$ represents the fraction of variant $n$ present in Belgium at time $t$, and $K_{inf,n}$ is the increase in infectivity compared to the wild type, which is determined during the calibration procedure (explained below). The variants were assumed to alter the serial interval and disease severity as well, which translates to dynamically changing the length of the average latent time ($\sigma$) and the hospitalisation propensity ($h$) in a similar fashion (see Fig. C6, bottom). The latter rescaling parameters are derived from literature [14–16, 38] and listed in Table C2.

Seasonality

Changes in climate have been recognised to play a role in the spread of many viral diseases amongst humans, notably influenza [21]. Seasonal effects influence the effective viral transmissibility, either directly by measurable physical changes in e.g. temperature, or indirectly by changes in social behaviour we remain agnostic about. Seasonality is included in our model by scaling the transmission coefficient of sars-cov-2 with a cosine function [22]. Its period is one year, and its amplitude is denoted by $A_s$, i.e.

$$\tilde{\beta}(t) = \beta(t) \left[ 1 + A_s \cos \left( \frac{2\pi t}{365 \text{ days}} \right) \right].$$ \hspace{1cm} (6)

Here $t$ is expressed in days since January 1st, at which time we assume the $\tilde{\beta}(t)$ values are maximal. Its simplicity reflects the current lack of understanding of seasonality’s actual effect on SARS-cov-2, mainly due to lack of long-term data. The amplitude $A_s$ is determined during the calibration procedure.

Vaccination

Vaccination against COVID-19 of susceptible subjects was shown to significantly decrease viral transmissibility and hospitalisation propensity, both in clinical trials [18] and in society-scale follow-up studies [19]. However, the protection offered by vaccination is imperfect (“leaky”) and was shown to decrease over time, from hereon referred to as waning [20]. Furthermore, the protection
against severe COVID-19 is more long-lasting than protection against SARS-
CoV-2 transmission [19]. We consider three vaccination stages: the first dose
(partial vaccination), the second dose (full vaccination), and the third dose
(booster shot). Our model approaches vaccination in the same fashion as the
age- and spatial stratification: every SEIQRD compartment $X$ is split in four
additional subcompartments depending on the vaccination stage, as follows

$$X_i^g \rightarrow \mathbf{X}_i^g$$

with elements $X_{i,v}^g$ for $v \in \{\text{none, first, full, booster}\}$. (7)

Subjects belonging to compartment $Y \in \{S, E, I_{\text{presy}}, I_{\text{asy}}, R\}$ are assumed to
be eligible for vaccination. They are transferred to another vaccination status
within the same compartment by dynamically updating the $Y_{i,v}(t)$ value at time
$t$,

$$Y_{i,v}^g(t) = Y_{i,v}^g(t) \phi_{i,v}^g(t),$$

where $\phi_{i,v}^g(t)$ represents the fraction of the population in age class $i$
and province $g$ in vaccination stage $v$ at time $t$ (see Figs. C8 and C9). Here we
have $\sum_v \phi_{i,v}^g(t) = 1$ such that $\sum_v Y_{i,v}^g(t) = Y_i^g(t)$. These data are publicly
available for all Belgian provinces and per age class [39]. Individuals not
eligible for vaccination cannot change vaccination status $v$.

In every metapopulation the vaccine offers protection through three mech-
nisms: 1) vaccines lower the susceptibility to SARS-CoV-2, 2) vaccines lower
the infectiousness of an individual infected with SARS-CoV-2, and 3) vac-
cines lower the hospital admission propensity of COVID-19. Vaccine efficacies
$E_{v,n,susc}, E_{v,n,inf}$ and $E_{v,n,hosp}$ are available for every vaccine stage $v$ and VOC
$n$ [20] (see Table C3), and in general also depend on age and province (see
Appendix C). This means that we further stratify the transmission coefficients

$$\bar{\beta}^g \rightarrow \bar{\beta}^g$$

with elements $\bar{\beta}_{ij,vw}^g = \bar{\beta}^g \sum_n \alpha_n(t)(1 - E_{v,n,susc,i}^g)(1 - E_{v,n,inf,j}^h),$ (9)

where $n$ runs over the VOCs, and the hospitalisation propensities

$$\bar{h}_i \rightarrow \bar{h}_i$$

with elements $\bar{h}_{i,v}^g = \bar{h}_i \sum_n \alpha_n(t)(1 - E_{v,n,hosp,i}^g).$ (10)

We do not explicitly distinguish between the different vaccines: all effica-
cies used were those of the mRNA-1273 (Pfizer) vaccine, as over 72% of
all administered doses in Belgium were Pfizer’s [39]. The vaccine does not
work immediately nor permanently. Vaccine onset is included by working with
vaccination stage fraction time series $\phi(t)$ that have been smoothed by an
exponential moving average (Figs. C8 and C9); this procedure imposes a de
facto two-week delay, which we assume to correspond to the vaccine onset
duration. Vaccine waning, on the other hand, is included after full vaccination
only, by including a time dependence on efficacies $E_{\text{full},n,susc}, E_{\text{full},n,inf}$ and
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$E_{\text{hosp},n,susc}$, based on vaccination incidence data and the assumption that the vaccine efficacy exponentially approaches zero (see Appendix C for details).

### 2.4 Governing equations

Incorporating the model extensions described in Sections 2.1-2.3, we present the $10 \times 10 \times 11 \times 4 = 4400$ coupled ordinary differential equations (ODEs) that govern the model in Appendix D. The central formula, which determines the number of newly infected subjects resulting from contact with pre- and asymptomatic subjects, is

$$
\dot{S}_{g,i,v} = - \sum_{h=1}^{G} p_{gh} S_{g,i,v} \sum_{w=1}^{N} \sum_{j=1}^{N} \bar{\beta}_{ij,vw} \bar{N}_{ij,c,tj} \left( I_{\text{presy}} \right)_{h,j,w,\text{eff}} + \left( I_{\text{asy}} \right)_{h,j,w,\text{eff}} T_{h,j,w,\text{eff}} + \zeta R_{g,i,v}.
$$

(11)

Here all variables except $\zeta$, which quantifies the average seroreversion rate, are time-dependent. The explicit time dependence is however omitted for readability. The system of ODEs is solved numerically using an explicit Runge-Kutta method of order 3(2) and results in what we will refer to as a “simulation”. In Appendix D, an overview of all model assumptions and parameters, as well as their chosen values, are given.

### 2.5 Model calibration

#### Calibrated parameters

The 11 model parameters $\beta^R, \beta^U, \beta^M, \Omega^{\text{home}}, \Omega^{\text{school}}, \Omega^{\text{work}}, \Omega^{\text{rest}}, M_{\text{cal}}, K_{\text{inf}}, \alpha, \gamma, K_{\text{inf}}, \delta, \gamma$ are considered to be a priori unknown and must be calibrated using the available data. The simulated daily number of hospitalisations is matched to the eleven time series of daily new hospitalisations in each province, starting on March 15th, 2020 and ending on October 1st, 2021. Further, assuming that on average half of the recovered subjects are again susceptible after one year (associated with seroreversion rate parameter $\zeta$), the simulated numbers of recovered individuals are matched to five serological measurements from Herzog et al., 2020 [40] and eight serological measurements from Sciensano [7], spanning the period from March 30th, 2020 until July 7th, 2020.

#### Statistical model

A quadratic relationship between the observed mean and variance of the daily hospitalisations timeseries data was observed, indicating that a negative binomial model is best fit to describe the relationship between the model outcome and observed data [41]. We therefore iteratively optimise the following loglikelihood function,

$$
\log L(\bar{x}|x) = - \sum_{g=1}^{G} \sum_{t=1}^{n} \left( \log \left[ \frac{\Gamma(a^g_t + 1/\alpha^g)}{\Gamma(1/\alpha^g)} \right] \right) +
$$
\[
\frac{1}{\alpha^g} \log \left( \frac{1}{1/\alpha^g + \tilde{x}_t^g} \right) + x_t^g \log \left( \frac{\tilde{x}_t^g}{1/\alpha^g + \tilde{x}_t^g} \right).
\] (12)

Here the outer sum is over all \( G = 11 \) provinces. The inner sum is over all \( n \) observed data points at times \( t \). \( \tilde{x} \) represents the simulated time series, and \( x \) the equivalent observed time series. The overdispersion parameter \( \alpha^g \) quantifies the presumed error on the data per province \( g \) (see Table E8), and \( \Gamma \) is the gamma function. Maximizing the result of Eq. (12) is computationally demanding and has local minima. We thus need an efficient way to scan through the eleven-dimensional parameter space. A good technique to initially broadly identify the region where the global maximum is situated is Particle Swarm Optimisation (PSO) [42]. Subsequently, once a region of interest has been identified, we use the maximum-likelihood estimates as initial values for the ensemble sampler for Markov Chain Monte Carlo (MCMC) [43]. For all parameters, uniform prior distributions were used. More details are found in Appendix E, and section 3.1 contains calibration results.

2.6 Scenario analyses

2.6.1 Scenarios for policymakers

Next, we illustrate how our model can be used to simulate the combined impacts of the emergence of new variants, an ongoing nation-wide vaccination campaign and social relaxations. Such simulations can be used to provide policymakers with insights on the optimal timing of the release of social restrictions and demonstrate the predictive capabilities of the model. We therefore calibrate our model up to March 1st, 2021, a point in time interesting because the \(\alpha-\beta-\gamma\) VOCs had just become dominant, the Belgian vaccination campaign was picking up speed, and there was a high pressure to relax social restrictions. Under the emergence of the \(\alpha-\beta-\gamma\) VOCs and vaccination campaign, we thus define four future scenarios in which social restrictions are released. The baseline scenario (S0) assumes average social contact behaviour of February 2021 to continue indefinitely. Scenarios S1 through S3 involve a gradual increase of social contact toward the behaviour of September 2020, starting at the first day of May (S1), April (S2) or March (S3) (see Fig. 6). In these scenarios, we assume that the Delta variant does not emerge and the observed number of administered vaccines are used. The number of vaccine doses that would be administered were of course not known on March 1st, 2021, but in policy advices given at that time projections for the future administered doses were used. Results are included in Section 3.2.1.

2.6.2 Spatially explicit scenarios

A particular strength of our model is its explicitly spatial nature. To illustrate this, we first analyse the effect on the timing and severity of COVID-19-related hospitalisations of limiting mobility to/from one particular province. Next we
assess the impact of limiting social contacts in one particular province. All simulations are started on January 1st 2020, upon which we inspect the resulting hospitalisations in the next four months. Due to their large demographic differences and their relatively weak connectivity, we inspect results for Brussels and Luxembourg.

**Regulating local mobility**

We define a parameter $p$ whose elements $p^g \in [0, 1]$ linearly controls the mobility to and from province $g$, compared to some static baseline mobility,

$$\bar{P} = \text{avg}\{P(t)\} \quad \text{for } t < \text{March 18th 2020}. \tag{13}$$

the values $p^g$ are defined implicitly as

$$\tilde{P}^{gh} = \bar{P}^{gh} p^h + \delta^{gh} \sum_{f=1}^{G} \bar{P}^{gf}(1 - p^f p^h), \tag{14}$$

where $\delta^{gh}$ is the Kronecker delta. We assume social contact behaviour remains the same and is independent of whether a province is a subject’s home province or a visited province. We run 25 simulations, one for every $p^g$ value logarithmically spaced between 1 and $10^{-3}$. In our analysis we change mobility to/from Brussels, and consider either the scenario where Brussels is shielded from an outbreak in Luxembourg (Mob. S.), or where the outbreak in Brussels is contained (Mob. C.).

**Regulating local social contact**

We implicitly define a parameter $n_c$ whose elements $n_c^g \in [0, 1]$ determine the local average social contact compared to the prepandemic baseline social contact $N_c$:

$$\bar{N}^{gh}_{c,ij}(t) = n^h_c(N_{c,ij} - N_{c,ij}^{\text{home}}) + N_{c,ij}^{\text{home}}. \tag{15}$$

Note that this quantity is independent of the province of origin $g$: we assume subjects follow the social rules of the province they visit. We also again assume that (for $n_c = 1$) no distinction is made between social contact in the home province compared to the visited province, which is different from what is expressed in Eq. (3) and used in non-fictitious analyses. We again run 25 simulations, one for every $n_c^g$ value, now equidistantly spaced between 1 and 0,
and all other parameters fixed (including mobility). Again altering values for Brussels, we perform a similar analysis for shielding and containing an initial outbreak. We call these scenarios Soc. S. and Soc. C., respectively.

3 Results and discussion

3.1 Model calibration

The nationally and regionally aggregated simulations between March 17th and October 1st 2021 are shown in Fig. 7. In Figs. E11 and E12, the fit of the calibrated model to each of the eleven provincial time series is given. In Fig. E14, the nationally aggregated fit to the seroprevalence data is given. Further, a corner plot showing the posterior distributions of all 11 calibrated parameters is shown in Fig. E10, and all calibrated parameter values are listed in Table E9. The time series of the normalised root-mean-square errors (RMSE) between the observed and simulated daily new hospitalisations of the spatially explicit model are given in Fig. E13, alongside the ones of the previously established national model [2].

Goodness-of-fit

In general, over the calibrated period (before the dashed line in Fig. 7), both the regional and national aggregates fit the observed number of daily hospitalisations well (Fig. 7). On the national level, the simulated number of daily hospitalisations at the peak of the second 2020 COVID-19 wave is slightly lower than the observed one. A possible explanation lies in the fact that on the 24th of September 2020, the federal government released all remaining social restrictions (Fig. 1). This may have caused a sudden increase in the number of social contacts during the one month period prior to the lockdown at the beginning of November 2021. This change in the degree of social contact is not observed in the GCMRs and is thus not captured by our social contact model. Survey-based contact studies under lockdown measures at the regional level could be used to explain the regional difference in the second 2020 COVID-19 peak height.

Beyond the calibrated range (after the dashed line in Fig. 7), during the Delta wave of October-December 2021, the forecasted number of new hospitalisations is higher than its observed counterpart on the national level. When looking at the regional breakdown of the forecast, the numbers of daily hospitalisations are slightly too low in Flanders, while they are much too high in Wallonia and Brussels. The large difference in model prediction between the regions is most likely due to the large differences in the regional vaccination degree. Flanders (91.4% of 18+ by October 1st 2021) has a much higher vaccination coverage than Wallonia (79.8%) and Brussels (66.5%) (Fig. C8). Given that the regional differences in vaccine incidence and the subsequent waning of the vaccines are incorporated in our model, the number of observed hospitalisations in Wallonia and Brussels are far below those expected. Still,
the model was qualitatively able to predict a Delta wave that would warrant social policy interventions.

Just like the second 2020 COVID-19 wave discussed earlier, regional differences in social contact behaviour provide the most likely explanation for the regional mismatches between the simulated and observed numbers. In this case, there still were some social restrictions in Wallonia and Brussels, while on October 1st, 2021, the Flemish government had released all measures. Another possible explanation for the overestimation of the Delta wave in general lies in the fact that seasonal change from summer to autumn, typically at the end of September in Western Europe, happens quite abruptly and with quite some variation in year-to-year timing. Meanwhile, the modelled seasonal wave is smooth and a small mismatch in timing between the seasons change may result in large differences in model outcome due to the exponential rise of hospitalisations. Therefore, accounting for seasonality using temperature observations could yield even better results.

In addition to the spatially explicit model, we calibrated our national model with the same implementation of VOCs, seasonality, and vaccines to the nationally aggregated daily number of COVID-19 hospitalisations. The model fit to the data, as well as the normalised RMSE time series of the fit are visualised in Fig. E13. Over the calibration period, we found a mean RMSE of 0.40 for the spatially explicit model and a mean RMSE of 0.38 for the national model. The difference in RMSE was found not to be statistically significant, indicating both models describe the national hospitalisation data equally well (Mann-Whitney U test [44], p-value: 0.32). The spatially explicit model is therefore also capable of producing the same results as its predecessor [2], which serves as a sanity check.

**Calibrated parameter values**

The values and 95% quantiles of the calibrated parameters are listed in Table E9 and shown in more detail in Fig. E10, some noteworthy values are discussed here. Even though the calibrated values for the transmission coefficients for rural or urban provinces are rather similar, the metropolitan $\beta^M$ value (0.053) is significantly larger than its rural $\beta^R$ and urban $\beta^U$ counterparts (0.040 and 0.041). This reflects that Brussels, with its much larger average population density, accommodates an increased effective viral transmission. The calibrated effectivity parameters $\Omega^k$ have well-resolved and distinct values. The effectivity for school-related social contact (0.02), and leisure contacts (0.13) are low, while the effectivity for work-related contacts is high (0.69). This indicates that the workplace mobility from the GCMRs informs the simulated number of daily COVID-19 hospitalisations best. The low inferred effectivity of school contacts does not necessarily imply that schools did not play a role in the epidemic, as changes in work mobility are intertwined with the opening and closing of schools. We found a calibrated
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Fig. 7 100 model realisations of the daily new hospitalisations between March 17th 2020 and January 1st 2022 (solid lines) with a negative binomial 95% confidence region (transparent band). Black crosses signify raw data from Sciensano [7] were used in the calibration procedure while red crosses signify data were not used during the calibration procedure. From top to bottom: Nationally aggregated daily number of hospitalisations, daily hospitalisations aggregated over all Flemish provinces, daily hospitalisations aggregated over Walloon provinces, daily hospitalisations in Brussels (see Table A1 and Fig. A2).

The mentality value of $M_{cal} \simeq 0.36$ during the time periods indicated in Fig. B5, corresponding to periods of high healthcare pressure. This implies that people’s overall awareness of the danger of sars-cov-2 during those periods roughly translates to a 64 percent additional reduction in social contact as compared to periods when sars-cov-2 poses no imminent threat.

Important is the significantly non-zero value for the seasonality amplitude. Since $A_s \simeq 0.30$ this implies that sars-cov-2 is 86% more transmissible during winter compared to summer time. The increases in sars-cov-2 infectivity $K_{inf,\alpha \beta \gamma}$ and $K_{inf,\delta}$ due to VOCs are significant. We find respectively a 57% and a 79% increase as compared to the wild-type variant. The estimate for the Delta variant is on the low side of the values cited in the literature [45]. However, the reduced serial interval (see Tab. C2) and lower vaccine efficacies (see Tab. C3) also contribute to an even greater infectivity.

3.2 Scenario analyses

3.2.1 Scenarios for policymakers

For these scenarios, we go back in time to March 1st, 2021 to study the combined impact of the emergence of the $\alpha-\beta-\gamma$ VOCs, an ongoing nationwide vaccination campaign and anticipated social relaxations. The nationally aggregated simulations are shown in the top panel of Fig. 8; the bottom panel illustrates the imposed social contact associated with each of the four scenarios. For the sake of brevity, we omit the regional results.
In line with expectations, more and earlier social contact translates into higher hospitalisation peaks. The projections in Fig. 8 strongly recommend against the relaxation of social relaxations on March 1st (S3), and on April 1st (S2), even if the measures are gradually relaxed over a two-month period. Doing so would result in hospitalisation peaks that far surpass those of the second 2020 COVID-19 wave, which would put the Belgian health care system on the brink of collapse. Relaxations starting on May 1st, 2021 (S1) contain the epidemic, likely due to the combined effect of vaccination and favourable seasonal changes during summer. Relaxations starting on June 1st, 2021 (S0) result in a near extinction of the epidemic in Belgium. In reality, measures were relaxed starting mid May 2021, corresponding to a situation roughly between S0 and S1.

It should be noted that translating the “number of social contacts” in a mathematical model into a concrete set of rules and regulations is not straightforward. However, scenario analyses like the one presented in this work have the potential to provide policymakers with high-level insights regarding the potential impact of their proposed policies. We stress that the output of one epidemiological model should be interpreted with care and if possible, results from different models should be combined in an ensemble to increase the robustness of the predictions [3, 17]. Relying on such an ensemble gives more weight to the overall trends in the policy advice than to the quantitative model outcomes, which are often disproportionately focused on by policymakers and press media. Ideally, epidemiological models like the one in this paper are further coupled to health economic and macro-economic models to provide even more comprehensive policy advice.

Fig. 8 Top: Combined impact of the $\alpha$-$\beta$-$\gamma$ VOCs, the ongoing nation-wide vaccination campaign and social relaxations on the number of daily hospitalisations, starting on March 1st 2021. Bottom: weighted average of the observed social contact matrix elements $N_{c,ij}(t)$ (grey). The coloured curves illustrate the social contact in the four different social relaxation scenarios.
3.2.2 Spatially explicit scenarios

Regulating local mobility

Fig. 9(a) shows the result of introducing 100 exposed subjects in every age class in the province of Luxembourg, and demonstrates the effect of progressively enforcing stricter mobility measures to and from Brussels from the start of the simulation (Mob. S). A similar result is shown in Fig. 9(b) for scenario Mob. C. In scenario Mob. S, the only effect on the local number of daily hospitalisations in Brussels is to delay the onset (and peak). The timing of the hospitalisation peak logarithmically depends on the decrease of in- and outward mobility, at roughly 7 days per order of magnitude in $p^g$. In scenario Mob. C, a slight increase and advancement of the hospitalisation wave for decreasing mobility is forecasted in Brussels, while demonstrating a similar logarithmic dependence on the hospitalisation peak timing in Luxembourg (roughly 9 days per order of magnitude in $p^g$). These qualitative relations are of course not unique to Brussels and Luxembourg, but apply to all pairs of provinces.

During the first, very strict national lockdown, the corresponding value for $p^g$ was approximately 0.5, and certainly larger than $10^{-1}$ (see Fig. 4). At the same time, impact on local time series is only significant for very large mobility reductions, i.e. values $p^g < 10^{-1}$. Consequently, we may conclude that only reducing mobility as a means for postponing the wave, while leaving...
all other social behaviour unchanged, is therefore both very drastic and barely effective, and hence an undesirable mitigation policy. It should be noted that at very high levels of isolation (low $p^g$ values), the deterministic nature of the model results in an overprediction of the number of hospitalisations in the other province. At such levels of isolation, even a fractional person spillover can trigger an epidemic in the other province. A markov-chain stochastic version of the model, whose chains can go extinct, would be more appropriate to study low mobility cases. However, because such levels of isolation are not attainable in reality, the conclusions made above will still stand.

**Regulating local social contact**

Fig. 10(a) shows the result of introducing 100 exposed subjects in every age class in the province of Luxembourg, and demonstrates the effect of progressively enforcing stricter social restrictions in Brussels from the start of the simulation (scenario Soc. S.). A similar result is shown in Fig. 10(b) but now the 100 exposed subjects are released in Brussels (scenario Soc. C.).

Here we see that reducing social contact in Brussels does not influence the epidemic in Luxembourg, while strongly delaying and reducing the hospitalisation wave in Brussels. In the containment scenarios, a similar effect is seen for Brussels, but now we observe an additional effect of delaying the peak in Luxembourg. In both cases and for both effects (total amount of hospitalisations and peak delay), the effect is now roughly linear in $n_g^c$ rather than logarithmic, preventing hospitalisation of approximately 7000 Brussels residents per 10% reduction in $n_g^c$. This suggests that social contact reduction is a much more effective policy measure than mobility reduction. In reality, mobility and social contact will never be altered independently.

**4 Conclusion**

Starting from our previously developed national model [2], a spatially explicit variant was developed. The models were, over the past two years, extended to account for the emergence of VOCs, seasonality, and vaccines. These were critical model additions that were desired and required for the description, forecasting and understanding of the COVID-19 pandemic in Belgium. The spatially explicit and national models are equally capable of describing the hospitalisation data in the calibrated range. Beyond the calibrated range, the spatially explicit model was, at least qualitatively, able to forecast the emergence of a Delta hospitalisation wave in the autumn of 2021. The effective transmission was found to be significantly higher in the metropolitan Brussels-Capital region, arguably due to the much larger population density. The seasonal effect was found to be strong, with an estimated 60% transmissibility difference between summer and winter.
We demonstrate the model is deployable as a means to evaluate scenarios on the effects of non-pharmaceutical policy interventions, which can – and have been – applied to support the pandemic decision-making process. In addition, the model was used to study the effects of locally reducing mobility and of locally reducing social contact to shield or contain an epidemic. We found that reducing social contact is quasi-linearly correlated to reducing the sum of COVID-19 hospitalisations. Reducing mobility, on the other hand, only results in postponing a COVID-19 wave, and only does so for very high (and quasi unattainable) levels of isolation. We conclude that the reduction of social contact is a much more effective approach to slow SARS-CoV-2 spread. Generally, the presented model’s fidelity and applicability have been demonstrated. Generalising to a non-Belgian context or other infectious diseases is straightforward.
Supplementary information. This paper contains additional information on the geography of Belgium (Appendix A.1), details with regard to the data used in this work (Appendices A.1, A.2 and B), more details on the implementation of the VOCs, seasonality, and vaccines (Appendix C), an overview of the model equations, parameters and assumptions (Appendix D) and more details with regard to the model calibration (Appendix E).

Author contributions. Michiel Rollier: Conceptualisation, Methodology, Investigation, Data curation, Writing – original draft. Tijs W. Alleman: Conceptualisation, Software, Methodology, Investigation, Data curation, Writing – original draft. Both of the above authors have closely collaborated on the manuscripts contents and should both be regarded as the primary authors of the text. Jenna Vergeynst: Conceptualisation, Investigation, Project administration. Jan M. Baetens: Conceptualisation, Funding acquisition, Project administration, Writing – review & editing.

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Conflict of interest. None declared.

Ethics approval. All used data conform to GDPR standards.

Consent to participate. Not applicable

Consent for publication. All authors consent to publication in (to be determined), preceded by pre-print publication in an open-access archive.

Availability of data and materials. All data used in this research are publicly available [7, 31, 33].

Code availability. The source code for the presented spatially explicit SEIQRD model is freely available on GitHub in the public repository UGentBiomath/COVID19-Model. Note however that running the code requires access to data that is not publicly available.
Appendix A  Data

A.1 COVID-19 time series data

The model parameters $\beta^R$, $\beta^U$, $\beta^M$, $\Omega^{\text{schools}}$, $\Omega^{\text{work}}$, $\Omega^{\text{rest}}$, $\Omega^{\text{home}}$, $M_{\text{cal}}$, $K_{\text{inf},a\beta\gamma}$, $K_{\text{inf},\delta}$ and $A_s$ are calibrated using the 11 provincial time series for daily new hospitalisations. The motivation to use these data are fourfold. First, as long as the total hospital capacity is not surpassed, which has not happened in Belgium, the number of hospitalisations is a more objective measure than the daily number of newly detected cases. After all, the latter is highly dependent on the available test capacity. Second, pressure on hospitals is the most relevant measure when informing policy decisions. From a public health perspective, one primarily wants to avoid excess pressure on hospitals, which results in postponement of non-covid-19 care and eventually the collapse of the health care system. Third, these time series are preferred over data for ICU admissions or deaths, because due to the low number of counts, these data are very noisy, especially at the provincial level. Fourth, the daily number of hospitalisations does not depend on hospital dynamics, such as residence times and distributions between wards.

The model calibration secondarily relies on seroprevalence data, indicating the rate at which antibodies wane and thus the rate at which humoral immunity is lost. The seroprevalence time series is the estimated percentage of the population with SARS-CoV-2 antibodies in the blood, reflecting how many subjects have recovered from COVID-19. Demonstrating the models ability to match the seroprevalence in the Belgian population is an important gauge for overall model fidelity. In this way it is possible to demonstrate that the model captures the total number of asymptomatic infections. We assume that new VOCs and vaccines do not alter the seroreversion rate over the calibration period.

Sciensano hospitalisation data

Sciensano, the national public health institute of Belgium [7], gathers and processes COVID-19-related hospitalisation time series at the provincial level from all 104 Belgian hospitals. This data set is updated daily, exhaustive since March 15th 2020, and anonymous (aggregated over all ages). It contains the number of newly admitted lab-confirmed COVID-19 hospital patients in the last 24 hours, not referred from another hospital. This number excludes the patients that were admitted to the hospital for other reasons but tested positive for COVID-19 in a screening context. Seven-day moving-average time series for daily new hospitalisations are shown per province in Fig. A1. Provinces are denoted according to their NIS code (Table A1).

The used hospitalisation time series are exhaustive and of high quality, but two limitations should be noted. First, there is a weekend effect in the raw time series. This is mainly due to fewer hospitals reporting data over the weekend.
and does not reflect viral dynamics; the effect is hence not captured by the model. Second, patients are recorded in the province they are hospitalised, not their province of residence. Thus, a patient residing in province \( g \) but hospitalised in province \( h \) is counted as a data point in province \( h \). Since there is no way to circumvent this problem without considerable privacy issues, we must assume that at the level of provinces this effect is negligible.

### Seroprevalence data

We consider two independent nationally aggregated time series containing information on the extrapolated number of Belgians that have a significant amount of anti-SARS-CoV-2 antibodies in residual serum samples (i.e. seroprevalence) – See Fig. A3. The first time series was gathered by Herzog et al. [40] between March 30th and October 17th 2020, and contains 7 data points from 3500 samples per collection period, spread over both sexes, all ages and all provinces (see Table 1 in [40]). Residual serum samples in this study originated from ambulatory patients (including people living in nursing homes) visiting their doctor (mainly general practitioners) for any reason including primary care, routine check-up or follow-up of pathology. The second time series was gathered by Sciensano [7] between March 30th 2020 and July 20th 2021, and contains 29 data points from 1000 samples per collection period, again homogeneously spread throughout Belgium. The blood samples originate from Red Cross blood donors. Combining both data sets is therefore interesting, as it contains both subjects in need of medical attention and healthy subjects capable of donating blood. The larger time period over which the latter study is conducted, implies that the data start to show the prevalence of anti-SARS-CoV-2 antibodies resulting from vaccination. This, combined with natural immunity, causes the percentage of ‘immune’ subjects to approach 100% by the summer of 2021.

### A.2 Mobility time series data

#### Origin and nature of the data

Proximus is Belgium’s largest telecommunication company with a market share of 30-40% in terms of active SIM cards [46]. Based on the connection between a user’s SIM card and the closest transmission tower, the approximate position of a SIM card is known at all times at which the device is operational. The amount of time that this device spends connected to a particular transmission tower is registered, on the condition that it has reconnected to a transmission tower and stays connected to this tower for over 15 minutes. Reconnecting occurs either by switching on a disabled device, or by travelling around – either within or outside a particular postal code. For any given Belgian province, the number of tracked SIM cards represents 25-50% of the province’s population. The extrapolation factor is calculated on a daily basis, based on the number of devices used by individuals living in
a particular postal code, and the total registered population there.

No data is available for times indicated by the hatched periods in Fig. 4, so we estimate $P_{gh}^t$ values at these times based on particular periods in the available data. For business days (resp. weekends) before February 10th 2020, we take the average $P_{gh}^t$ values over all business days (resp. weekends) between February 10th and March 1st 2020. For business days (resp. weekends) after August 31st 2021, we take the average over all business days (resp. weekends) between July 1st and August 31st 2021 (the summer holiday).

![Fig. A1](image_url)

**Fig. A1** Stacked area plot of all seven-day moving-averaged time series for daily new hospitalisations per province (denoted with NIS code, see Table A1) [7]. Daily data is available from March 15th 2020 onward.

**Table A1** All 10 provinces and Brussels-Capital Region (the “11th province” for convenience). We denote the population density classification, the systematic name (NIS code), and which region it is in (Flanders, Brussels-Capital, Wallonia). We also denote their registered population and the number of hospitals that report the daily number of new COVID-19 patients.

| Type      | NIS | Name             | Region | Population | # hospitals |
|-----------|-----|------------------|--------|------------|-------------|
| Metropolitan | 21000  | Brussels        | B      | 1 218 255  | 15          |
| Urban     | 10000  | Antwerpen       | F      | 1 869 730  | 14          |
|           | 20001  | Vlaams-Brabant  | F      | 1 155 843  | 6           |
|           | 40000  | Oost-Vlaanderen | F      | 1 525 255  | 14          |
| Rural     | 20002  | Brabant Wallon  | W      | 406 019    | 2           |
|           | 30000  | West-Vlaanderen | F      | 1 200 945  | 11          |
|           | 50000  | Hainaut         | W      | 1 346 840  | 14          |
|           | 60000  | Liège           | W      | 1 109 800  | 12          |
|           | 70000  | Limburg         | F      | 877 370    | 7           |
|           | 80000  | Luxembourg      | W      | 286 752    | 3           |
|           | 90000  | Namur           | W      | 495 832    | 6           |
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**Fig. A2** Map of the Belgian provinces indicated by their NIS code (Table A1). The average population density is indicated by the colour scheme and determines whether we consider a province to be rural, urban or metropolitan, with threshold values resp. 400 km$^{-2}$ and 4000 km$^{-2}$.

**Fig. A3** Timeline with seroprevalence data from randomly sampling subjects visiting the general practitioner (Herzog et al. [40], maroon), or Red Cross blood donors (Sciensano [7], green). The data is space- and age-aggregated and expressed as a percentage of the total population. The band around the data shows the 95% uncertainty interval. Note the symmetrical log scale on the y axis.
Appendix B  Social contact model

Google Community Mobility Reports
Social contact is rescaled daily based on data publicly provided in the Google Community Mobility Reports (GCMR) [33]. These data are available for (virtually) every day in 2020 since February 15th 2020, and are expressed as fractions of “activity” compared to the median value from the 5-week period between January 3rd and February 6th, 2020. This activity is quantified as an anonymous aggregated GPS-informed visitation frequency to six location types (retail & recreation, grocery, parks, transport, work, and residential). We call these unprocessed time series the GCMR indicators, or mathematically, \( G(t) \) with elements \( G_{g,k'}(t) \) for every province \( g \) and every activity type \( k' \). The time series \( G_k(t) \) as used in Eq. (3) are derived from \( G(t) \) as follows:

\[
\begin{cases}
G_{\text{home}}(t) = 1, \\
G_{\text{school}}(t) = H(t), \\
G_{\text{work}}(t) = G_{\text{work}}(t), \\
G_{\text{transport}}(t) = G_{\text{transport}}(t), \\
G_{\text{leisure}}(t) = G_{\text{retail & recreation}}(t), \\
G_{\text{other}}(t) = G_{\text{grocery}}(t).
\end{cases}
\]  

Here \( H(t) \) with elements \( H_g(t) \) is a function that is equal to 1 when schools are open, and 0 when schools are closed. All \( G_k(t) \) are equal to 1 before February 15th 2020. The resulting time series are shown in Fig. B4. The GCMRs are not age-stratified and do not correct for potential under-representation of older individuals in the data collection.

Scaling the social contact matrices with the GCMR indicators
The pandemic social behaviour of the Belgian population must be translated into a linear combination of pre-pandemic interaction matrices. These interaction matrices are available in different places, namely, at home, in schools, in workplaces, during leisure activities, on public transport and during other activities [31]. Mathematically, we must find tangible coefficients so that the combination of pre-pandemic interaction matrices, i.e.

\[
N_c(t) = \text{span} \left( N_{c,\text{home}}, N_{c,\text{schools}}, N_{c,\text{work}}, N_{c,\text{transport}}, N_{c,\text{leisure}}, N_{c,\text{others}} \right),
\]  

where all linear combination parameters are time-dependent, is a good representation of macroscopic social behaviour during the pandemic. Ideally, pandemic contact matrices are used as these will better represent mixing behaviour under lockdown measures. However, such matrices were not available at the start of the pandemic. Hence, our model was built upon pre-pandemic knowledge of social behaviour to make a prediction on pandemic social behaviour. First, the GCMR indicators for Workplaces, Transit stations,
Retail & recreation and Groceries & pharmacy are used as proxies to scale the work, transport, leisure and other social contact matrices.

**Effectivity parameters and mentality**

Intuitively, the effectivity of a contact in a given location may not scale linearly with the observed mobility reductions. The net effectivity of the contacts under lockdown measures depends on a combination of the pre-pandemic physical proximity and duration of the contact, the effectivity of preventive measures and on behavioural changes when lockdown measures are taken. As an example, the effects of alcohol gel and face masks might be significant in workplaces and in grocery stores, but not at home or during leisure activities. To account for different effectivities of contacts in different places, we could introduce one additional parameter per contact matrix, denoted $\Omega_x$, bound between zero and one, and infer its distribution from the available hospitalisation data. However, estimating six effectivity parameters is unfeasible because of identifiability issues. We found that the effectivity parameters of public transport and other places could not be identified. This is most likely because few little contacts are made in those places [47]. Consequently, the effectivity parameters of public transport, other places and leisure contacts were aggregated to reduce the number of effectivity parameters from six to four. Another interpretation of these effectivity parameters is the degree of correlation between changes of the GCMR indicator and the effective number of social contacts. Thus, an effectivity value of zero indicates the GCMR indicator has no effect on the model dynamics, while an effectivity value of one indicates the GCMR indicator has a large effect on the model dynamics. Despite the attractive physical interpretation, the latter interpretation seems more scientifically defensible.

During model development, we observed that when strict social measures are taken, the number of effective social contacts becomes smaller than the number of contacts obtained after rescaling with the GCMR indicators and the effectivity parameters. Thus, one additional parameter was introduced to additionally downscale the number of social contacts when lockdown measures are taken. This parameter was naively introduced in the main text and explained further below. The so-called *mentality* ($M(t)$) parameter, is introduced over a two-week period in the social contact model every time lockdown measures were taken (2020-03-15 and 2020-10-19). Once the first lockdown measures were released (2020-05-01 and 2020-06-01), the mentality parameter was gradually eased out of the social contact model over a two month period. During the model calibration procedure, the value of mentality was inferred as $M_{cal} = 0.278^{\pm 0.006}$. The introduction of the mentality parameter adds a degree of freedom to the model that can be re-estimated when social context changes in the future. During August 2020, minor manual tweaks had to made to the mentality in certain provinces in order to adequately fit the second
After rescaling with the GCMR indicators and introducing the effectivity ($\Omega_x$) and mentality ($M(t)$) parameters, the combination of pre-pandemic interaction matrices used to model pandemic social contact becomes,

$$N_c(t) = \Omega_{\text{home}} N_{c,\text{home}} + M(t) \left\{ \Omega_{\text{schools}} G_{\text{schools}}(t) N_{c,\text{schools}} + \Omega_{\text{work}} G_{\text{work}}(t) N_{c,\text{work}} + \Omega_{\text{rest}} \left[ G_{\text{transport}}(t) N_{c,\text{transport}} + G_{\text{leisure}}(t) N_{c,\text{leisure}} + G_{\text{other}}(t) N_{c,\text{other}} \right] \right\},$$

where $M^g(t)$ of $M(t)$ are almost always identical, but not necessarily (see Fig. B5).

Fig. B4 Nationally averaged values of the GCMR indicators ($G^k(t)$) used for rescaling of the social contact matrices (Eq. (3)). The contact matrices for home and school contacts are not scaled with their respective GCMR indicator (motivated in [2]). The contact matrices for the other social environments (workplaces, transport, leisure and other places) are scaled with their appropriate GCMR indicator. The model uses such time series for every province.
Fig. B5  Top: time-dependent mentality factor varying between the values of one and $M_{\text{cal}} = 0.278^{+0.006}_{-0.008}$. Here, a value of one indicates people behave as if awareness for SARS-CoV-2 is low. The value of 0.278 represents the additional contact multiplier observed during lockdowns due to raised awareness for SARS-CoV-2 and was obtained during model calibration. The hatched area represents the period in August 2020 where mentality parameters had to be manually set for different provinces. Such ad-hoc change to the model were required to avoid mistakes over the summer period from propagating into the second 2020 COVID-19 wave (Oct. 2020). Bottom: Ad-hoc provincial differences in mentality $M^g(t)$ (close-up of hatched region). This is the only time at which some $M^g(t)$ differ between different $g$ values.
Appendix C  Variants of concern, vaccination, and seasonality

C.1 Variants of concern

VOCs are assumed to have three effects on the model dynamics: 1) VOCs are associated with an increase of the transmission coefficients \( \beta \) compared to the wild-type variant, denoted \( K_{\text{inf}} \). To this end, the infectivity parameters \( \beta^R \), \( \beta^U \) and \( \beta^M \) are rescaled with the prevalence-weighted average infectivity increase at time \( t \). 2) VOCs can alter the hospital admission propensity of infected individuals compared to the wild-type variant, this is denoted as \( K_{\text{hosp}} \). To this end, the hospital admission propensities (\( h \)) are rescaled with the prevalence-weighted average hospital admission propensity gain at every time \( t \). 3) Different VOC types are associated with different durations of the latent COVID-19 period \( \sigma \). The relevant parameter values are listed in Table C2 and graphically illustrated in Fig. C6. All values describe the “bare” effects of the VOCs irregardless of vaccination – it should be noted that as the pandemic progresses it becomes harder and harder to disentangle this bare effect.

| Parameter       | wild type | \( \alpha-\beta-\gamma \) | \( \delta \) |
|-----------------|-----------|---------------------------|-------------|
| \( K_{\text{inf}}, n \) (-) | 1.00      | 1.57                      | 1.79        |
| \( K_{\text{hosp}}, n \) (-)  | 1.00      | 1.00                      | 1.00        |
| \( \sigma, n \) (days)        | 4.5       | 4.5                       | 3.8         |

The VOC prevalence data (national level) were obtained from [37]. The increase in infectivity from the \( \alpha-\beta-\gamma \) and \( \delta \) VOCs compared to the wild-type were found during model calibration. The combination of the \( \alpha-\beta-\gamma \) VOCs were estimated to be 57% more infectious than the wild-type, while the \( \delta \) variant was estimated to be 79% more infectious than the wild-type. The combination of the \( \alpha-\beta-\gamma \) VOCs almost certainly increased the hospital admission propensity. For instance, Grint et al. [14] reported an average increase of 62%. However, we found that applying such multipliers to the model’s hospitalisation propensity did not yield satisfactory results. Hence, for the sake of simplicity, we assume no increase of the hospitalisation propensity. The \( \delta \) variant was shown to increase the hospital admission propensity for unvaccinated individuals with roughly 70% [15, 48]. On the other hand, a Norwegian study found no significant increase in hospital admission propensity [16].
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C.2 Seasonality

The introduction of seasonality rescales the infectivity parameters $\beta^R$, $\beta^U$, $\beta^M$. The effect of seasonality is incorporated in a cosine function with a period of one year (Eq. (6), based on [22]). Maximum infectivity is assumed at January 1st. The amplitude of the cosine was estimated at $A_s = 0.30$ during model calibration. The seasonality influences viral transmission in ways considered out of this work’s scope for this work, hence the simplicity of the seasonal relationship.

C.3 Vaccination

Figs. C8 and C9 show the percentages of the population, resp. per province and per age class, that have had their first vaccination dose (‘partial’ vaccination), their second vaccination dose (‘full’ vaccination), or their booster shot (‘boosted’). These time series were taken from Ref. [39] and have been smoothed by an exponential moving average. This procedure incidentally resulted in a two-week delay, which we adopted to represent vaccine immunity onset. Table C3 shows the vaccine’s efficacies with which the SARS-CoV-2-related susceptibility, infectiousness, and hospitalisation are rescaled in the model. The efficacies $E_{\text{full,n,w}}$ are used to calculate the dynamic vaccine waning after full vaccination.

Vaccine efficacies

As previously mentioned, Tartof et al. [19] demonstrated that, for an individual fully vaccinated with the mRNA-1273 (Pfizer) vaccine, protection against hospitalisation wanes at a lower rate than protection against symptoms (proxy
Similar findings were reported by Braeye et al. [49]. The efficacies $E_{v,n,\text{susc}}$ and $E_{v,n,\text{inf}}$, for the vaccination stages ‘full’ and ‘boosted’ under the $\alpha$-$\beta$-$\gamma$ and $\delta$ VOCs were derived from an updated version of Braeye et al. [20] (informal communication). For the vaccination stage ‘full’, the efficacies 150 days post-vaccination were extracted. From Ref. [49], the efficacies $E_{\text{full,}\delta,\text{hosp}}$ were extracted both 25 and 225 days post vaccination. It was assumed that the vaccines offer the same protection against hospitalisation under the $\alpha$-$\beta$-$\gamma$ VOCs. It is assumed that all efficacies under the the wild type are the same as under the $\alpha$-$\beta$-$\gamma$ variant. The efficacy reductions reported for the Pfizer vaccine in [20] are assumed to apply to all vaccines and all ages. This simplifying assumption is motivated by the fact that over 72% of vaccines administered by the end of the period considered during the model calibration (2021-10-01) were Pfizer’s. We further assume that partial vaccination offers half the protection a full vaccination offers. The vaccine efficacies used in this study are summarised in Table C3.

**Table C3** Efficacies of the vaccines in lowering the susceptibility to SARS-CoV-2, lowering the infectiousness of SARS-CoV-2, and the efficacies of the vaccines in lowering the hospitalisation propensity. Partial vaccination is assumed to result in half the efficacy of a full vaccination. The first vaccines were not administered during wild-type VOC dominance, and booster shots were not administered under the $\alpha$-$\beta$-$\gamma$ VOC dominance, so these data are omitted and irrelevant. Protection against hospitalisation is retrieved for the $\delta$ VOC from Ref. [49] but assumed to same for the $\alpha$-$\beta$-$\gamma$ VOC. All $E_{\text{none},n}$ are 0.

|          | $E_{\text{partial},n}$ | $E_{\text{full},n,0}$ | $E_{\text{full},n,w}$ | $E_{\text{booster},n,0}$ |
|----------|-------------------------|------------------------|------------------------|---------------------------|
| **Susceptibility** |                         |                        |                        |                           |
| $\alpha$-$\beta$-$\gamma$ | 0.44                     | 0.87                   | 0.64                   | NA                        |
| $\delta$ | 0.40                     | 0.79                   | 0.54                   | 0.80                      |
| **Infectiousness** |                         |                        |                        |                           |
| $\alpha$-$\beta$-$\gamma$ | 0.31                     | 0.62                   | 0.43                   | NA                        |
| $\delta$ | 0.19                     | 0.38                   | 0.25                   | 0.34                      |
| **Hospitalisation** |                         |                        |                        |                           |
| $\alpha$-$\beta$-$\gamma$ | 0.47                     | 0.93                   | 0.81                   | NA                        |
| $\delta$ | 0.47                     | 0.93                   | 0.81                   | 0.93                      |

**Exponential vaccine waning**

Vaccine waning is incorporated by dynamically altering the average vaccine efficacies after full vaccination. Waning for partial or boosted vaccination were not included because data were not readily available at the time of writing. Mathematically, we rely on 1) the past vaccine incidence, available per province, age group and vaccination stage [39]; 2) the vaccine efficacies for every protective mechanism and every VOC, both 25 and 175 days after vaccination [20], and 3) the assumption that waning occurs exponentially, asymptotically
approaching a null efficacy for large $t$. The latter assumption is expressed by

$$
\tilde{E}_{\text{full}, n, \text{susc}}(t) = E_{\text{full}, n, 0, \text{susc}} \exp \left(-t/\tau\right),
$$

where,

$$
\tau = \frac{150 \text{ d}}{\ln \left(\frac{E_{\text{full}, n, 0, \text{susc}}}{E_{\text{full}, n, w, \text{susc}}}\right)} > 0,
$$

and similarly for $\tilde{E}_{\text{full}, n, \text{inf}}(t)$ and $\tilde{E}_{\text{full}, n, \text{hosp}}(t)$ (see Fig. C7). These values are used in a weighted sum to find the current average vaccine efficacy in province $g$ and age class $i$, as follows:

$$
E_{\text{full}, n, \text{susc}}(t) = \frac{1}{\int_{-\infty}^{t} \tilde{\phi}_v(t')dt'} \int_{-\infty}^{t} \tilde{\phi}_v(t') \tilde{E}_{\text{full}, n, \text{susc}}(t-t')dt',
$$

where

$$
\int_{t}^{t+\epsilon} \tilde{\phi}_{v,i}^{g}(t')dt' = \text{the fraction of the total population in province } g \text{ and age class } i \text{ entering vaccination state } v \text{ between times } t \text{ and } t + \epsilon, \text{ i.e. the vaccination incidence over } [t, t + \epsilon]. \text{ So, } \tilde{\phi}_{v,i}^{g}(t) \text{ is the incidence rather than the cumulative data. Further note that this does not equal } \phi_{v,i}^{g}(t), \text{ because the latter also takes into account subjects leaving the vaccination stage } v \text{ due to a new vaccination. Consequently, we may write}
$$

$$
\tilde{\phi}_v(t) = \max (0, \frac{d\phi_v(t)}{dt}).
$$

Hence, when a large amount of newly-vaccinated individuals enter the metapopulation, the average $E_{\text{full}, n}(t)$ increases. Also note that now the efficacy $E_{\text{full}, n, \text{susc}}$ has a spatial and an age dimension. This implies that the transmission coefficient becomes

$$
\beta_{vw}^{g} \rightarrow \bar{\beta}_{vw}^{g} \text{ with elements } \bar{\beta}_{ij,vw}^{g} = \bar{\beta}^{g} \sum_{n} \alpha_{n}(t)(1 - E_{v,n,\text{susc},i}^{g})(1 - E_{w,n,\text{inf},j}^{h}),
$$

where indices $g$, $i$ and $v$ indicate the susceptible person, and indices $h$, $j$ and $w$ indicate the infectious person. The vaccine efficacies with waning are computed once beforehand.
**Fig. C7** Evolution of the vaccine efficacy associated with infectivity $E_{\text{inf}}(t)$, susceptibility $E_{\text{susc}}(t)$, and hospitalisation propensity $E_{\text{hosp}}(t)$ under the $\alpha$-$\beta$-$\gamma$ VOCs and over a two year period. The observations extracted from literature (see Table C3) were used to inform the half-life of the exponential decay function.

**Fig. C8** Vaccination time series in terms of the fraction (%) of the total population in the province (indicated by NIS code, see Table A1), aggregated for all ages. From top to bottom: first dose only (all vaccine types except Janssen), full dose only (second dose and Janssen vaccine), booster shot.
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**Fig. C9** Vaccination time series in terms of the fraction (%) of the total number of individuals in the age group, aggregated for all provinces. From top to bottom: first dose only (all vaccine types except Janssen), full dose only (second dose and Janssen vaccine), booster shot.
Appendix D  Model equations, parameters, and assumptions

D.1 Model equations and parameters

The model is governed by a first-order, ordinary coupled differential equation per model compartment, per age class $i$, and per province $g$:

$$
\dot{S_{i,v}}^g = - \sum_{h=1}^{G} P_{i,v}^{gh} S_{i,v}^g \sum_{w} \sum_{j=1}^{N} \sum_{j=1}^{N} \beta_{ij,vw}^g N_{c,ij} (I_{\text{presy}})^{h}_{j,w,\text{eff}} + (I_{\text{asy}})^{h}_{j,w,\text{eff}} \frac{T_{j,w,\text{eff}}^g}{T_{j,w,\text{eff}}^g} + \zeta R_{i,v}^g,
$$

$$
\dot{E_{i,v}}^g = \sum_{h=1}^{G} P_{i,v}^{gh} S_{i,v}^g \sum_{w} \sum_{j=1}^{N} \sum_{j=1}^{N} \beta_{ij,vw}^g N_{c,ij} (I_{\text{presy}})^{h}_{j,w,\text{eff}} + (I_{\text{asy}})^{h}_{j,w,\text{eff}} \frac{T_{j,w,\text{eff}}^g}{T_{j,w,\text{eff}}^g} - \frac{1}{\sigma} E_{i,v},
$$

$$
(I_{\text{presy}})^{g}_{i,v} = \frac{1}{\sigma} E_{i,v}^g - \frac{1}{\omega} (I_{\text{presy}})^{g}_{i,v},
$$

$$
(I_{\text{asy}})^{g}_{i,v} = \frac{a_i}{\omega} (I_{\text{presy}})^{g}_{i,v} - \frac{1}{d_a} (I_{\text{asy}})^{g}_{i,v},
$$

$$
(Q_{\text{mild}})^{g}_{i,v} = 1 - \frac{a_i}{\omega} (I_{\text{presy}})^{g}_{i,v} - \left( \frac{1 - \bar{h}_{i,v}}{d_m} + \frac{\bar{h}_{i,v}}{d_{\text{hospital}}} \right) (Q_{\text{mild}})^{g}_{i,v},
$$

$$
(Q_{\text{hosp}})^{g}_{i,v} = \bar{h}_{i,v,c_{i}}^{g}_{i,v} (Q_{\text{mild}})^{g}_{i,v} - \frac{1 - m_{C,i}}{d_{C,R,i}^{g}} C_{i,v}^{g} - \frac{m_{C,i}}{d_{C,D,i}^{g}} C_{i,v}^{g},
$$

$$
(Q_{\text{ICU}})^{g}_{i,v} = \bar{h}_{i,v,r_{i}}^{g}_{i,v} (Q_{\text{mild}})^{g}_{i,v} - \frac{1 - m_{\text{ICU},i}}{d_{\text{ICU},R,i} - d_{\text{ICU},\text{rec},i}} (Q_{\text{ICU}})^{g}_{i,v} - \frac{m_{\text{ICU}}}{d_{\text{ICU},D,i}^{g}} (Q_{\text{ICU}})^{g}_{i,v},
$$

$$
(Q_{\text{ICU},\text{rec}})^{g}_{i,v} = \frac{1 - m_{\text{ICU},i}}{d_{\text{ICU},R,i}} (Q_{\text{ICU}})^{g}_{i,v} - \frac{1}{d_{\text{ICU},\text{rec}}} (Q_{\text{ICU},\text{rec}})^{g}_{i,v},
$$

$$
\dot{D_{i,v}} = \frac{m_{I_{\text{asy}}}}{d_{\text{ICU},D,i}^{g}} (Q_{\text{ICU}})^{g}_{i,v} + \frac{m_{C,i}}{d_{C,D,i}^{g}} (Q_{\text{hosp}})^{g}_{i,v},
$$

$$
\dot{R_{i,v}} = \frac{1}{d_a} (I_{\text{asy}})^{g}_{i,v} + \frac{1 - \bar{h}_{i,v}}{d_m} (Q_{\text{mild}})^{g}_{i,v} + \frac{1 - m_{C,i}}{d_{C,R,i}^{g}} (Q_{\text{hosp}})^{g}_{i,v} + \frac{1}{d_{\text{ICU},\text{rec}}} (Q_{\text{ICU},\text{rec}})^{g}_{i,v} - \zeta R_{i,v}^g,
$$

which results in a system of $10 \times 10 \times 11 \times 4 = 4400$ coupled differential equations. All variables representing a model compartment are time-dependent. The social contact matrix $N_c(t)$, the mobility matrix $P(t)$, and (therefore) the effective populations $I_{\text{presy},\text{eff}}(t)$, $I_{\text{asy},\text{eff}}(t)$ and $T_{\text{eff}}(t)$ are time-dependent as well (see Subsection 2.2 and Appendices B and A.2). Additionally, the introduction of VOCs, seasonality and vaccination makes the parameters $\beta(t)$, $\bar{h}(t)$, and $\sigma(t)$ time dependent as well (see Subsection 2.3 and Appendix C). For simplicity, this explicit time dependence and its
associated parameters are not shown below, however, all information can be found in the relevant appendices. The meaning and value of the parameters are listed in Tables D6 and the associated Tables D4, D5 and D7.

Table D4 Fraction of asymptomatic subjects $a_i$ (based on [50]), and hospitalisation propensity $h_i$ for symptomatic infections per age class (inferred, see [2]). The hospitalisation propensity $h$ is dynamically and spatially rescaled in the model to account for the combined effects of VOCs and vaccination. The baseline values without VOCs or vaccines are shown here.

| Age class $i$ (years) | $a_i$ (%) | $h_i$ (%) |
|-----------------------|-----------|-----------|
| [0, 12]               | 98.3      | 1.5       |
| [12, 18]              | 97.8      | 2.0       |
| [18, 25]              | 90.4      | 2.7       |
| [25, 35]              | 78.5      | 3.0       |
| [35, 45]              | 64.2      | 3.0       |
| [45, 55]              | 48.9      | 4.5       |
| [55, 65]              | 26.8      | 10.3      |
| [65, 75]              | 10.3      | 24.3      |
| [75, 85]              | 4.4       | 55.7      |
| [85, ∞]               | 1.2       | 80.0      |
| **Population average**| 57.0      | 11.2      |

Table D5 Average fraction $c_i$ of hospitalised subjects admitted in a cohort ward (as opposed to an ICU), average mortality in cohort wards ($m_{C,i}$) and average mortality in ICU ($m_{ICU,i}$) per age class. These estimates were obtained by analysing a dataset of 22 136 patients in all 133 Belgian hospitals (see [2] for details).

| Age class $i$ (years) | $c_i$ (%) | $m_{C,i}$ (%) | $m_{ICU,i}$ (%) |
|-----------------------|-----------|--------------|-----------------|
| [0, 12]               | 97.4      | 0.0          | 0.0             |
| [12, 18]              | 88.8      | 0.0          | 9.0             |
| [18, 25]              | 90.3      | 0.4          | 17.4            |
| [25, 35]              | 91.5      | 1.0          | 11.8            |
| [35, 45]              | 87.1      | 1.5          | 16.0            |
| [45, 55]              | 83.0      | 2.7          | 19.3            |
| [55, 65]              | 78.3      | 5.1          | 35.4            |
| [65, 75]              | 76.3      | 11.4         | 51.6            |
| [75, 85]              | 83.6      | 26.4         | 70.0            |
| [85, ∞]               | 95.3      | 42.3         | 78.6            |
| **Population average**| 83.8      | 16.6         | 46.4            |
Table D6  Parameters used for calculating the dynamics between the various SEIQRD compartments shown in Fig. 2. Note that all symbols in boldface are non-scalar (vector or matrix), and the values of their elements are provided in separate tables.

| Symbol | Parameter | Migration | Value |
|--------|-----------|-----------|-------|
| $a$    | Fraction of infected subjects remaining asymptomatic | $I_{\text{presy}} \rightarrow I_{\text{asy}}$ | Table D4, [50] |
| $h(t)$ | Fraction of mildly symptomatic subjects requiring hospitalisation. Time-dependent due to VOCs and vaccination. | $Q_{\text{mild}} \rightarrow Q_{\text{hosp}}$ or $Q_{\text{ICU}}$ | inferred, see [2] |
| $c$    | Fraction of hospitalisations admitted in regular cohort hospital ward | $Q_{\text{mild}} \rightarrow Q_{\text{hosp}}$ | Table D4, inferred, see [2] |
| $m_C$  | Mortality of patients in a cohort hospital ward | $Q_{\text{hosp}} \rightarrow D$ | Table D5, [2] |
| $m_{ICU}$ | Mortality of patients in an IC unit | $Q_{\text{ICU}} \rightarrow D$ | Table D5, [2] |
| $d_{C,R}$ | Length-of-stay in hospital cohort ward (outcome: recovered) | $Q_{\text{hosp}} \rightarrow R$ | Table D7, [2] |
| $d_{C,D}$ | Length-of-stay in hospital cohort ward (outcome: deceased) | $Q_{\text{hosp}} \rightarrow D$ | Table D7, [2] |
| $d_{ICU,R}$ | Length-of-stay in an IC unit (outcome: recovered) | $Q_{\text{ICU}} \rightarrow Q_{\text{ICU, rec}}$ | Table D7, [2] |
| $d_{ICU,D}$ | Length-of-stay in an IC unit (outcome: deceased) | $Q_{\text{ICU}} \rightarrow D$ | Table D7, [2] |
| $d_{ICU,rec}$ | Average recovery stay in a cohort ward after ICU | $Q_{\text{ICU,rec}} \rightarrow R$ | Table D7, [2] |
| $d_a$  | Average duration of asymptomatic infection | $I_{\text{asy}} \rightarrow R$ | 7.0 d, assumed |
| $d_m$  | Average duration of mild infection before recovery | $Q_{\text{mild}} \rightarrow R$ | 7.0 d, assumed |
| $d_{hosp}$ | Average duration between symptom onset and hospitalisation | $Q_{\text{mild}} \rightarrow Q_{C}$ or $Q_{\text{ICU}}$ | 6.4 d, [2] |
| $\sigma(t)$ | Average duration of latent period. Time-dependent due to VOC prevalence. | $E \rightarrow I_{\text{presy}}$ | Table C2, [38] |
| $\omega$ | Average duration of presymptomatic infectious period | $I_{\text{presy}} \rightarrow I_{\text{asy}}$ or $Q_{\text{mild}}$ | 0.7 d, [25, 51] |
| $\zeta$ | Average seroreversion rate | $R \rightarrow S$ | $\ln(2)/365$ d$^{-1}$, assumed |
| $\beta(t)$ | Probability of infection upon contact with an infectious individual (if the infectee is 100% susceptible), elements $\beta^g$ and three degrees of freedom $\beta^R, \beta^U, \beta^M$. Time-dependent due to seasonality, VOC prevalence, and vaccination. | $S \rightarrow E$ | inferred |
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Table D7 Hospital length-of-stay in a cohort ward (C) or intensive care unit (ICU) in case of recovery or death. NA denotes no deaths were recorded in that particular age class. These estimates were obtained by analysing a dataset of 22,136 patients in all 133 Belgian hospitals (see [2] for details).

| Age class i (years) | \(d_{C,R,i}\) (days) | \(d_{C,D,i}\) (days) | \(d_{ICU,R,i}\) (days) | \(d_{ICU,D,i}\) (days) | \(d_{ICU,rec,i}\) (days) |
|---------------------|----------------------|----------------------|------------------------|------------------------|------------------------|
| [0, 12]             | 3.5                  | NA                   | 5.9                    | NA                     | 3.0                    |
| [12, 18]            | 6.8                  | NA                   | 3.2                    | 16.0                   | 4.0                    |
| [18, 25]            | 5.7                  | 2.0                  | 5.3                    | 3.0                    | 4.0                    |
| [25, 35]            | 4.8                  | 8.1                  | 9.3                    | 12.6                   | 4.5                    |
| [35, 45]            | 5.9                  | 6.0                  | 10.9                   | 16.3                   | 5.0                    |
| [45, 55]            | 6.9                  | 8.8                  | 11.4                   | 20.6                   | 6.0                    |
| [55, 65]            | 8.5                  | 8.7                  | 12.7                   | 17.3                   | 6.0                    |
| [65, 75]            | 11.2                 | 13.2                 | 13.8                   | 16.3                   | 8.0                    |
| [75, 85]            | 15.2                 | 12.1                 | 11.9                   | 13.6                   | 11.0                   |
| [85, ∞]             | 18.9                 | 11.8                 | 5.0                    | 9.1                    | 10.0                   |
| Population average  | 10.8                 | 11.8                 | 12.0                   | 15.2                   | 5.6                    |

D.2 Model assumptions and simplifications

Here, we list the main assumptions and simplifications underlying our model. While we consider these to not alter the paper’s conclusions, we choose to explicitly mention them below as good scientific practice.

1. Cross-border mobility is not included in this model, the mobility matrix, \( P \), is not age-stratified, and the elements \( P_{gh}^{\text{tot}}(t) \) were estimated when no data was available at time \( t \) (see Appendix A.2).

2. We assume that, on average, one only has work-related contacts in visited provinces, whereas all other types of contact are possible within the home province.

3. The GCMR indicators, which are used to inform the degree of social interaction in the model, are not age-stratified. The GCMR indicators thus present a more coarse-grained alternative to social-epidemiological contact studies under lockdown measures.

4. The average vaccine efficacies and information on vaccine waning used in the model were those of the Pfizer vaccine. The model does not explicitly distinguish between the different vaccines.

5. We aggregate the \( \alpha, \beta \) and \( \gamma \) VOCs because the effect of their epidemiological properties are comparable in our model, and the aggregation decreases
6. Our models do not include age-specific increases for transmissibility and disease severity for the VOCs. The emergence of the variants was implemented on the national level, thus, the geographic spread of the $\alpha$-$\beta$-$\gamma$ and $\delta$ variant was not included in the simulations.

7. Implementing seasonality using a cosine function is a high-level mathematical abstraction of several factors such as, but not limited to, the effects of humidity and temperature on viral survival in the environment.

8. In order for the negative binomial distribution loglikelihood function to apply to all $G \times n$ data points, the data points should strictly speaking be independent of each other, which they are not.

9. The model does not explicitly account for testing and tracing. These effects are implicitly accounted for in the calibrated parameters, however.

10. The model is based on ordinary differential equations (ODEs) and is thus deterministic in nature. This implies that epidemiological chain extinction is not possible and thus, at low SARS-CoV-2 prevalences, the model may overpredict the number of observed daily hospitalisations.

11. Raw vaccination data is only communicated for minors 0-17 years. There is no distinction for 0-12 or 12-17. In our current implementation, all vaccinations are distributed between 0-12 and 12-17 year olds based on demographics.

12. A number of assumptions are made when implementing the vaccination into the model. In (8) it is assumed that vaccinations are given homogeneously to subjects in all vaccine-eligible compartments, while e.g. in reality people that had only recently recovered were not immediately invited for vaccination. It is assumed that vaccinated people have the same number of contacts and the same mobility patterns as non-vaccinated people, and that they on average come into contact with the same fraction of vaccinated and non-vaccinated people as the global average.
Appendix E  Model calibration

11 model parameters are considered to be a priori unknown and must be calibrated using the available data. Here we elaborate on the calibration procedure and the resulting parameter values and uncertainties.

E.1 Statistical model

Given a time series $x^g$ for every province $g \in \{1, ..., G\}$ with $n$ observations $x^g_t$ for $t \in \{1, ..., n\}$ corresponding to times $\{t_1, ..., t_n\}$, any choice for model parameters $\theta$ combined with an initial condition (IC) will produce a continuous time series $\tilde{x}^g(t)$ for every province $g$. This time series may be sampled to produce a set of model-based values $\{\tilde{x}^g(t_1), ..., \tilde{x}^g(t_n)\}$ that we will denote as $\{\tilde{x}^g_1, ..., \tilde{x}^g_n\}$. The aim is to find the model setup for which it is most likely that the $x^g$ are observations of the modelled time series $\tilde{x}^g$, considering a particular error.

We have estimated the variance in all provincial time series as a function of their rolling exponential mean. Next, the most appropriate statistical model was chosen by fitting the mean-variance of several candidate models – the Gaussian model ($\sigma^2 = c$), Poisson model ($\sigma^2 = \mu$), quasi-Poisson model ($\sigma^2 = \alpha\mu$) and negative binomial model ($\sigma^2 = \mu + \alpha\mu^2$) – and using the AIC to determine what model fits best. The negative binomial model best described the variance in the data in all but two provinces, in which the quasi-Poisson model had the lowest AIC score. However, for the sake of simplicity, it was assumed that all eleven provincial time series variance are described by the negative binomial model. In this way, we assume that a single observation $x^g_t$ is the result of a counting experiment with an additional unknown error for every province $g$, captured by the estimated overdispersion parameter $\alpha^g$ per province $g$ [41, 52] (see Table E8). The values of which were obtained by fitting the negative binomial mean-variance relationship to our estimated mean-variance couple. In general, the overdispersion in the data becomes larger when the population in a province decreases. The associated negative binomial likelihood for every observation $t$ is

$$L(\tilde{x}^g_t | x^g_t) = \frac{\Gamma(x^g_t + 1/\alpha^g)}{x^g_t! \Gamma(1/\alpha^g)} \left( \frac{1/\alpha^g}{1/\alpha^g + \tilde{x}^g_t} \right)^{1/\alpha^g} \left( \frac{\tilde{x}^g_t}{1/\alpha^g + \tilde{x}^g_t} \right)^{x^g_t},$$

(E9)

with $\Gamma$ the gamma function. The negative binomial distribution has mean value $\tilde{x}^g_t$ and variance $\tilde{x}^g_t (1 + \alpha^g \tilde{x}^g_t)$; it is maximised for $\tilde{x}_t = x_t$ and reduces to the Poisson likelihood for $\alpha^g \to 0$. Adding more observations over time and regions, individual likelihood functions can be multiplied:

$$L(\tilde{x} | x) = \prod_{g=1}^{G} \prod_{t=1}^{n} L(\tilde{x}^g_t | x^g_t).$$
Again, this value $L(\tilde{x}|x)$ is maximised if $\forall g, t : \tilde{x}^g_t = x^g_t$, but this is generally not possible: the values $\tilde{x}^g_t$ must be samples of the simulated local time series $\tilde{x}^g_t$, for particular $\theta$ values. Since the logarithmic function is monotonically increasing, the maximum value for $L(\tilde{x}|x)$ occurs at the same location in parameter space as for $\log L(\tilde{x}|x)$, so we may as well consider:

$$
\log L(\tilde{x}|x) = - \sum_{g=1}^{G} \sum_{t=1}^{n} \left( \log \left[ \frac{\Gamma(x^g_t + 1/\alpha^g)}{\Gamma(1/\alpha^g)} \right] + 1/\alpha^g \log \left[ \frac{1/\alpha^g}{1/\alpha^g + \tilde{x}^g_t} \right] + x^g_t \log \left[ \frac{\tilde{x}^g_t}{1/\alpha^g + \tilde{x}^g_t} \right] - \log(x^g_t!) \right).
$$

The result is the loglikelihood in Eq. (12). The parameter choice $\theta = \hat{\theta}$ that maximises Eq. (12) for particular values of $\alpha^g$ is considered the ‘best-fit’ choice. A large collection of such sampled $\hat{\theta}$ make up the posterior. The posterior distributions resulting from the calibration MCMC also provide a quantitative measure for the calibrated value’s uncertainty interval [53], which together with the overdispersion values ($\alpha^g$) determines the uncertainty on the simulated time series. Note that large $\tilde{x}^g_t$ and $x^g_t$ values will contribute more to the total sum in Eq. (12) than small such values, which means that time series of large provinces will have a larger weight in the overall sum. This effect is further amplified by the fact that less densely populated provinces generally have noisier data and thus larger overdispersion factors $\alpha^g$. In our calibration procedure, we use three sources of data and thus, we optimise the weighted sum of three such loglikelihoods,

$$
\log L(\tilde{x}_{Hin}|x_{Hin}) + \epsilon[\log L(\tilde{x}_{R}|x_{R,Herzog}) + \log L(\tilde{x}_{R}|x_{R,Sciensano})],
$$

where the weighting factor $\epsilon$ is fixed at $10^{-4}$ and was found through trial and error. The time series $\tilde{x}_{Hin}$ and $\tilde{x}_{R}$ correspond to the simulated daily new hospitalisations and the total number of recovered subjects, respectively. The observed time series are $x_{Hin}$, $x_{R,H}$ and $x_{R,S}$: observed daily new hospitalisations per province [7], national seroprevalence data from general practitioners by Herzog et al. [40], and national seroprevalence data from Red Cross by Sciensano [7], respectively (see Appendix A.1).

| Province       | $\alpha^g$ | Province       | $\alpha^g$ | Province       | $\alpha^g$ |
|----------------|------------|----------------|------------|----------------|------------|
| Antwerpen      | 0.031      | Vlaams-Brabant | 0.035      | Limburg        | 0.060      |
| Vlaams-Brabant | 0.035      | Oost-Vlaanderen | 0.027      | Luxembourg     | 0.003      |
| Brabant Wallon | 0.059      | Hainaut        | 0.029      | Namur          | 0.007      |
| Brussels       | 0.037      | Liège          | 0.039      |                |            |

Table E8: Values per province of the inferred overdispersion parameter of the negative binomial distribution associated with the time series of daily COVID-19 hospitalisations, used in the loglikelihood function (12). The average overdispersion coefficient of 0.034 (population-size weighted) was used for all simulations presented in this work.
E.2 Results of model calibration

Calibrated values of all a priori unknown model parameters, including their interpretation, are listed in Table E9. The posterior distributions of the estimated parameters and their potential correlations are shown in Fig. E10. Simulations of the daily number of new hospitalisations for every province are shown in Figs E11 and E12. The negligible difference in goodness-of-fit between the spatially explicit and the national models is demonstrated in Fig. E13.

Table E9 All calibrated parameters in the spatially explicit SEIQRD model, with their physical interpretation and the equation that shows their mathematical definition. The values and confidence intervals of these parameters are determined in the MCMC procedure constructed around the loglikelihood function given by Eq. (12).

| Param. | Interpretation | Eq.     | Value  | Error     |
|--------|----------------|---------|--------|-----------|
| $\beta^R$ | Transmission coefficient associated with rural provinces. | Eq. (4) | 0.040 | $+0.002$ $-0.002$ |
| $\beta^U$ | Transmission coefficient associated with urban provinces. | Eq. (4) | 0.041 | $+0.002$ $-0.002$ |
| $\beta^M$ | Transmission coefficient associated with metropolitan provinces. | Eq. (4) | 0.053 | $+0.003$ $-0.003$ |
| $\Omega^\text{home}$ | Effectivity parameter in a home environment. | Eq. (2) | 0.16 | $+0.01$ $-0.01$ |
| $\Omega^\text{school}$ | Effectivity parameter in a school environment. | Eq. (2) | 0.02 | $+0.01$ $-0.01$ |
| $\Omega^\text{work}$ | Effectivity parameter in a work environment. | Eq. (2) | 0.69 | $+0.04$ $-0.05$ |
| $\Omega^\text{rest}$ | Effectivity parameter in transport, leisure and other environments. | Eq. (2) | 0.13 | $+0.02$ $-0.01$ |
| $K_{\text{inf},\alpha\beta\gamma}$ | Increased infectivity of the $\alpha$-$\beta$-$\gamma$ VOCs compared to the wild type for non-vaccinated subjects. | Eq. (5) | 1.57 | $+0.02$ $-0.02$ |
| $K_{\text{inf},\delta}$ | Increased infectivity of the $\delta$ VOC compared to the wild type for non-vaccinated subjects. | Eq. (5) | 1.79 | $+0.03$ $-0.04$ |
| $A_s$ | Amplitude of changing transmission coefficient due to seasonality of SARS-CoV-2. | Eq. (6) | 0.30 | $+0.01$ $-0.01$ |
| $M_{\text{cal}}$ | National mentality factor | Eq. (2) | 0.36 | $+0.01$ $-0.01$ |
Fig. E10 Corner plot showing the posterior distributions of all 11 free parameters. Created with the corner package [54].
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**Fig. E11** 100 model realisations of the daily new hospitalisations between March 17th 2020 and January 1st 2022 (solid lines) with a negative binomial 95% confidence region (transparent band). Black crosses signify raw data from Sciensano [7] were used in the calibration procedure while red crosses signify data were not used during the calibration procedure. From top to bottom: Antwerpen (10000), Vlaams Brabant (20001), Brabant Wallon (20002), Brussels (21000), West-Vlaanderen (30000) and Oost-Vlaanderen (40000). (see Table A1 and Fig. A2).

**Fig. E12** 100 model realisations of the daily new hospitalisations between March 17th 2020 and January 1st 2022 (solid lines) with a negative binomial 95% confidence region (transparent band). Black crosses signify raw data from Sciensano [7] were used in the calibration procedure while red crosses signify data were not used during the calibration procedure. From top to bottom: Hainaut (50000), Liège (60000), Limburg (70000), Luxembourg (80000), Namur province (90000) (see Table A1 and Fig. A2).
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Fig. E13 (a) 100 realisations of the national model (see Ref. [2]) and (b) 100 realisations of the spatially explicit model (nationally aggregated) of the daily new hospitalisations between March 17th 2020 and January 1st 2022 (solid lines) with a negative binomial 95% confidence region (transparent band). The accompanying normalised root mean square error (RMSE) of the model predictions is given in black on the right hand axis. (c) Boxplot of the normalised RMSE values of the national and spatially explicit model. The RMSE time series of both models have a similar morphology, and no statistically significant difference in RMSE values was found.

Fig. E14 (a) 100 realisations of the model estimated fraction of seropositive individuals (solid lines) with negative binomial 95% confidence region (transparent band) versus the fraction of seropositive individuals as measured by Refs. [40] and [7].
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Thomas Stanton, Stephen Michell, Claire Bewshea, Ben Temperton, Michelle Michelsen, Joanna Warwick-Dugdale, Robin Manley, Audrey Farbos, James Harrison, Christine Sambles, David Studholme, Aaron Jeffries, Leigh Jackson, Alistair Darby, Julian Hiscox, Steve Paterson, Miren Iturriza-Gomara, Kathryn Jackson, Anita Lucaci, Edith Vamos, Margaret Hughes, Lucille Rainbow, Richard Eccles, Charlotte Nelson, Mark Whitehead, Lance Turtle, Sam Haldenby, Richard Gregory, Matthew Gemmell, Claudia Wierzbicki, Hermione Webster, Thushan de Silva, Nikki Smith, Adrienn Angyal, Benjimin Lindsey, Danielle Groves, Luke Green, Dennis Wang, Timothy Freeman, Matthew Parker, Alexander Keeley, Paul Parsons, Rachel Tucker, Rebecca Brown, Matthew Wyles, Max Whiteley, Peijun Zhang, Marta Gallis, Stavroula Louka, Chrystala Constantinidou, Meera Unnikrishnan, Sascha Ott, Jeffrey Cheng, Hannah Bridgewater, Lucy Frost, Grace Taylor-Joyce, Richard Stark, Laura Baxter, Mohammad Alam, Paul Brown, Dinesh Aggarwal, Alberto Cerda, Tammy Merrill, Rebekah Wilson, Patrick McClure, Joseph Chappell, Theocharis Tsoleridis, Jonathan Ball, David Buck, John Todd, Angie Green, Amy Trebes, George MacIntyre-Cockett, Mariateresa de Cesare, Alex Alderton, Roberto Amato, Cristina Ariani, Mathew Beale, Charlotte Beaver, Katherine Bellis, Emma Betteridge, James Bonfield, John Danesh, Matthew Dorman, Eleanor Drury, Ben Farr, Luke Foulser, Sonia Goncalves, Scott Goodwin, Marina Gourtovaia, Ewan Harrison, David Jackson, Dorota Jamrozy, Ian Johnston, Leanne Kane, Sally Kay, Jon-Paul Keatley, Dominic Kwiatkowski, Cordelia Langford, Mara Lawniczak, Laura Letchford, Rich Livett, Stephanie Lo, Inigo Martincorena, Samantha McGuigan, Rachel Nelson, Steve Palmer, Naomi Park, Minal Patel, Liam Prestwood, Christoph Puethe, Michael Quail, Shavanthi Rajatileka, Carol Scott, Lesley Shirley, John Sillitoe, Michael Spencer Chapman, Scott Thurston, Gerry Tonkin-Hill, Danni Weldon, Diana Rajan, Iraad Bronner, Louise Aigrain, Nicholas Redshaw, Stefanie Lensing, Robert Davies, Andrew Whitwham, Jennifer Liddle, Kevin Lewis, Jaime Tovar-Corona, Steven Leonard, Jillian Durham, Andrew Bassett, Shane McCarthy, Robin Moll, Keith James, Karen Oliver, Alex Makunin, Jeff Barrett, and Rory Gunson. Hospital admission and emergency care attendance risk for SARS-CoV-2 Delta (B.1.617.2) compared with Alpha (b.1.1.7) variants of concern: a cohort study. *The Lancet Infectious Diseases*, 22(1):35–42, Jan 2022.

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