Appendix A  Data

A.1 COVID-19 time series data

The model parameters $\Omega$, $\Psi$, $K_{\text{inf},\alpha\beta\gamma}$, $K_{\text{inf},\delta}$ and $A$ are calibrated using the 11 provincial time series for daily new hospitalisations (Fig. A1). 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. Fig. A2 provides a timeline of periods with severe preventive policies (lockdown) and their subsequent easing, along with an oversight of key events that influenced SARS-CoV-2 prevalence in Belgium during the 2020-2021 COVID-19 pandemic.

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 (Fig. A3). The seroprevalence time series is the estimated percentage of the population with SARS-CoV-2 antibodies in the blood, reflecting how many individuals have recovered from COVID-19. Demonstrating the model’s 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 [50], gathers and processes COVID-19-related hospitalisation time series at the provincial level from all 104 Belgian hospitals. This data set is updated daily, is exhaustive since March 15th 2020, and is 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. [49] 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 [49]). 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 [50] 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 individuals in need of medical attention and healthy individuals 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 the acquisition of natural immunity, causes the percentage of ‘immune’ individuals to approach 100% by the summer of 2021 (see Fig. A3).

### 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 [56]. 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) [50]. Daily data is available from March 15th 2020 onward. A grey background is used to indicate a holiday period.

| 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           |

**Table A1** All 10 provinces and Brussel-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.
**Fig. A2** Seven-day moving average of daily new COVID-19 hospitalisations in Belgium during 2020 and 2021 (solid black line). Vertical dashed lines are used to indicate events or policy changes with a possible impact on the number of daily new COVID-19 hospitalisations. Grey background colour is used to indicates school vacations. The horizontal arrows denote the periods with severe social restrictions, along with their subsequent release.

**Fig. A3** Timeline with seroprevalence data from randomly sampling individuals visiting the general practitioner (Herzog et al. [49], maroon), or Red Cross blood donors (Sciensano [50], 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 asymmetrical log scale on the y axis. A grey background is used to indicate a holiday period.
Fig. A4 Map of Belgium containing: The 10 Belgian provinces and Brussels bounded by solid black lines and labeled using red numbers (NUTS2). The 43 Belgian arrondissements bounded by grey lines and labeled in small script on the map (NUTS3).
Appendix B  Social contact model

Scaling prepandemic contacts to model pandemic contacts The pandemic social behaviour of the Belgian population must be translated into a linear combination of prepandemic interaction matrices, mathematically denoted as,

\[
\tilde{N}^g(t) = \alpha^g(t)N^{\text{home}} + \beta^g(t)N^{\text{schools}} + \gamma^g(t)N^{\text{work}}
+ \delta^g(t)N^{\text{transport}} + \epsilon^g(t)N^{\text{leisure}} + \zeta^g(t)N^{\text{other}}, \quad (B1)
\]

where \(\tilde{N}^g(t)\) is the pandemic social contact matrix in province \(g\) at time \(t\) and \(N^l\) is the prepandemic interaction matrix in location \(l\). These prepandemic matrices are available for six locations \(l\): at home, in schools, in workplaces, during leisure activities, on public transport and during other activities [32]. We have to find sensible time-dependent coefficients \(\alpha^g(t), \beta^g(t), \ldots, \zeta^g(t)\) so that the linear combination of prepandemic interaction matrices in Eq. (B1) is a good representation of macroscopic social behaviour throughout the pandemic. This supplementary read elaborates on the reasoning behind our choice of coefficients in Eq. (B1).

Ideally, pandemic contact matrices, gathered by performing surveys, are used as these are more likely to adequately represent mixing behaviour under lockdown measures. However, our models have been built upon prepandemic knowledge of social behaviour to make a prediction on pandemic social behaviour for two reasons. First, data on pandemic mixing were not available at the start of the pandemic, and setting up surveys requires a substantial investment of time and resources. Thus, the development of a readily available alternative may still be useful. Second, leveraging the general interest in COVID-19 to gather social contact data risks creating unrepresentative samples due to differential interest in the topic (selection bias) [54]. Unrepresentative sampling may skew data in the direction of more adherence to government measures, as it can be expected individuals adhering to government restrictions against COVID-19 are more likely to fill in a survey on their behavior. The effect of selection bias likely becomes larger as measures are prolonged, and public debate becomes more polarised. The use of aggregated mobility indicators does not suffer from such bias.

Google Community Mobility Reports Social contact is rescaled daily based on data publicly provided in the GCMR. These data are available (virtually) every day 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 activity types \(l'\): retail & recreation, grocery, parks, transport, work, and residential, which differ slightly from the locations/activities used in the prepandemic contact matrices. We
call these unprocessed time series the GCMR indicators, or mathematically, \( G(t) \) with elements \( G^{g,l'}(t) \) for every province \( g \) and every activity type \( l' \). The time series \( G^l(t) \), with elements \( G^{g,l}(t) \), used to rescale the prepanademic contact matrices \( N^l \), are derived from \( G(t) \) as follows,

\[
\begin{align*}
G^{\text{home}}(t) &= 1, \\
G^{\text{school}}(t) &= H(t), \\
G^{\text{work}}(t) &= G^{\text{work}}(t), \\
G^{\text{transport}}(t) &= G^{\text{transport}}(t), \\
G^{\text{leisure}}(t) &= G^{\text{retail & recreation}}(t), \\
G^{\text{other}}(t) &= G^{\text{grocery}}(t).
\end{align*}
\] (B2)

The GCMR includes an indicator for residential mobility as well. During lockdowns, residential mobility increases and this is indicative of decreased community mobility. Although the mobility figures indicate people spend more time at home during lockdown (see Fig. 2 in Alleman et al. [2]), this does not mean people have more contacts at home. Increasing the fraction of household contacts under lockdown measures would increase the intergenerational mixing of the population and this is not realistic or desired when modeling social restrictions. Hence, we assume home mobility remains the same throughout the entire pandemic, and thus \( G^{\text{home}}(t) = 1 \). \( H(t) \) with elements \( H^g(t) \) equals 1 when schools are open in province \( g \), and 0 otherwise. All \( G^l(t) \) are assumed equal to 1 before the start of the dataset on February 15th 2020. The resulting time series \( G^l(t) \) are shown in Fig. B5.

**Fig. B5** Nationally averaged values of the GCMR indicators \( G^l(t) \), used for rescaling of the social contact matrices (Eq. (B1)). A grey background is used to indicate a holiday period.

**Effectivity parameters** Intuitively, the effectivity of a social contact to spread SARS-CoV-2 in a given location \( l \) may not scale linearly with the observed mobility reductions. The net effectivity of the contacts under lockdown depends on a combination of the prepanademic physical proximity and duration of the contact, the effectivity of preventive measures and on behavioural changes during lockdown. 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 location \( l \), denoted \( \Omega_l \), but this would require inferring six additional parameters based on the hospitalisation data, which is not possible because of both practical and structural unidentifiability. Simplifications were thus made, reducing the number of effectivity parameters from six to two identifiable parameters. However, as the posterior distributions of these parameters had similar means, significant overlap and little correlation, we could further reduce the number of effectivity parameters to only one.

First, we found that the effectivity parameters of public transport and other places could not be identified. Likely because too few contacts are made in these places [57]. Consequently, the effectivity parameters of public transport, other places and leisure contacts were aggregated, as such reducing the number of effectivity parameters from six to four. Second, as previously mentioned, the home contacts are not scaled with the residential GCMR indicator but rather it is assumed that \( G_{\text{home}} = 1 \). The analytical expression of the basic reproduction number \( R_0 \) of the (equivalent) national model is [2],

\[
R_0 = \beta(ad_a + \omega)N
\]

where \( \beta \) is the per contact chance of SARS-COV-2 transmission, \( a \) is the fraction of asymptomatic individuals, \( d_a \) the length of the asymptomatic infectious period, \( \omega \) the length of the presymptomatic infectious period and \( N \) the total number of social contacts. A constant contribution of home contacts during the pandemic (constituent of \( N \)) strongly correlates with the infectivity parameters in the model \( \beta \), which makes \( \Omega_{\text{home}} \) (structurally) unidentifiable. We thus assume \( \Omega_{\text{home}} = 1 \), and the remaining effectivities are thus expressed relatively to the effectivity of home contacts. Third, when calibrating the remaining three effectivity parameters \( \Omega_{\text{schools}} \), \( \Omega_{\text{work}} \) and \( \Omega_{\text{leisure}} \) from March 15th, 2020 until October 14th, 2021, effectivities in schools close to zero are inferred. Changes in school and work contacts often coincide, during holidays schools are closed and workplace mobility is lower. This results in practical unidentifiability between the effectivities of contacts in schools and workplaces. So, we had to assume that \( \Omega_{\text{schools}} = \Omega_{\text{work}} = \Omega_{\{\text{work, schools}\}} \). In this way, only two effectivity parameters remained, \( \Omega_{\{\text{work, schools}\}} \) and \( \Omega_{\text{leisure}} \). When inferring the distributions of these remaining two parameters, we found highly similar average values (\( \Omega_{\{\text{work, schools}\}} = \Omega_{\text{leisure}} \approx 0.5 \)) and overlapping distributions. Thus, we could assume that only one effectivity parameter \( \Omega \) is needed to describe the relevant trends in the data. Its physical meaning is the relative effectivity of social contacts in workplaces, schools and during leisure activities for the transmission of SARS-COV-2 as compared to contacts at home. It’s value should be smaller than one to be consistent with literature [43], which suggests secondary attack rates are higher for household contacts.
**Intervention parameter** During model development, we observed that the number of effective social contacts becomes smaller than the number of contacts obtained after rescaling with the GCMR indicators and the effectivity parameters when strict social measures are taken. Thus, one additional parameter was introduced to additionally downscale the number of social contacts when lockdown measures are taken. The so-called *intervention* parameter $\Psi(t)$, with entries $\Psi^g(t)$ for province $g$, is gradually introduced during a two-week period using a ramp function when lockdown measures are taken (2020-03-15 and 2020-10-19) and kept in place throughout lockdowns. Once the lockdown measures are released, it is gradually released from the social contact model over a two-month period using a ramp function. The entries $\Psi^g(t)$ for province $g$ of $\Psi(t)$ are always identical, except during a brief period four week period in August 2020, when ad-hoc values were used in order to prevent mistakes during the summer of 2020 from propagating into the second 2020 COVID-19 wave (see Fig. B6). First, the COVID-19 hospitalisation incidence per 100 000 inhabitants at the peak of the second COVID-19 wave were extracted from the hospitalisation data and expressed relative to Antwerp (Table B2). These values were then rescaled with three parameters: one for Flemish provinces (0.65, 95 %CI : 0.60 – 0.70), one for Walloon provinces (0.38, 95 %CI : 0.29 – 0.49) and one for Brussels (0.73, 95 %CI : 0.14 – 0.124). Because no correlation with other model parameters was observed, the values of these parameters were kept constant during the calibrations detailed in this work. Aside from August 2020, the value of the intervention parameter was found to be $\Psi^g(t) = 0.65$ (95 %CI : 0.60 – 0.70) for all provinces $g$. The introduction of the intervention parameter adds a degree of freedom to the model that can be re-estimated when social context changes in the future or when different measures are taken in different spatial patches of the model.

**Pandemic contact model** Combining all of the above, the linear combination of prepandemic interaction matrices used to model pandemic social contact is,

$$
\tilde{N}^g(t) = N^\text{home} + \Psi^g(t) \Omega \left\{ N^\text{schools}(t) N^\text{schools} + G^g, \text{work}(t) N^\text{work} \\
G^g, \text{transport}(t) N^\text{transport} + G^g, \text{leisure}(t) N^\text{leisure} + G^g, \text{other}(t) N^\text{other} \right\}.
$$

(B3)

where $\tilde{N}^g(t)$ is the pandemic social contact matrix in province $g$ at time $t$. $N^\text{home}$, $N^\text{schools}$, $N^\text{work}$, $N^\text{transport}$, $N^\text{leisure}$, and $N^\text{other}$ are the prepandemic social contact matrices. $\Psi^g(t)$ is the intervention parameter in province $g$ at time $t$. $\Omega$ is the relative effectivity of social contacts in workplaces, schools, and during leisure activities to the spread of SARS-COV-2 as compared to social contacts at home ($\Omega^\text{home} = 1$). $G^g, \text{schools}$, $G^g, \text{work}$, $G^g, \text{transport}$, $G^g, \text{leisure}$, and $G^g, \text{other}$ represent the mobility reductions retrieved from the GCMRs. Alternatively,
\[ \tilde{N}^g(t) = \alpha^g(t) N^{\text{home}} + \beta^g(t) N^{\text{schools}} + \gamma^g(t) N^{\text{work}} + \delta^g(t) N^{\text{transport}} + \epsilon^g(t) N^{\text{leisure}} + \zeta(t)^g N^{\text{other}}, \quad (B4) \]

where,
\[
\begin{align*}
\alpha^g(t) &= \Psi^g(t), \\
\beta^g(t) &= \Psi^g(t) \Omega^g, \text{schools}(t), \\
\gamma^g(t) &= \Psi^g(t) \Omega^g, \text{work}(t), \\
\delta^g(t) &= \Psi^g(t) \Omega^g, \text{transport}(t), \\
\epsilon^g(t) &= \Psi^g(t) \Omega^g, \text{leisure}(t), \\
\zeta(t)^g &= \Psi^g(t) \Omega^g, \text{other}(t).
\end{align*}
\] (B5)

**Fig. B6** *Top*: time-dependent intervention parameter varying between the values of one when no lockdown is imposed, and \( \Psi^g(t) = 0.65 \) (95% CI: 0.60 – 0.70) for all provinces \( g \) under lockdown. The hatched area represents the period in August 2020 where the magnitude of the intervention parameters had to be derived from the peak COVID-19 hospitalisation incidence during the second COVID-19 wave. A grey background is used to indicate a holiday period.

**Table B2** Incidence per 100 000 inhabitants at peak of second COVID-19 wave, expressed relative to Antwerpen.

| NIS | Name               | Region | Incidence |
|-----|--------------------|--------|-----------|
| 10000 | Antwerpen             | F      | 1.00      |
| 20001 | Vlaams-Brabant       | F      | 1.12      |
| 20002 | Brabant Wallon       | W      | 1.12      |
| 21000 | Brussels            | B      | 1.12      |
| 30000 | West-Vlaanderen    | F      | 1.45      |
| 40000 | Oost-Vlaanderen    | F      | 1.13      |
| 50000 | Hainaut             | W      | 2.15      |
| 60000 | Liège               | W      | 1.93      |
| 70000 | Limburg            | F      | 1.43      |
| 80000 | Luxembourg         | W      | 1.16      |
| 90000 | Namur               | W      | 1.30      |
C.1 Variants of concern

VOCs are assumed to influence the model dynamics in three ways: 1) VOCs are associated with an increase of the transmission coefficient $\beta$ compared to the wild-type variant, denoted $K_{\text{inf}}$, 2) VOCs can alter the hospital admission propensity of infected individuals compared to the wild-type variant, this is denoted as $K_{\text{hosp}}$, 3) VOCs are associated with different durations of the latent COVID-19 period $\sigma$. To account for 1) and 2) respectively, the transmission coefficient $\beta$ is rescaled with the prevalence-weighted average infectivity increase at time $t$, and the hospital admission propensities ($h$) are rescaled with the prevalence-weighted average hospital admission propensity gain at every time $t$. The relevant parameter values are listed in Table C3 and graphically illustrated in Fig. C7.

\textbf{Table C3} VOC prevalence and VOC-dependent variables: infectivity increase of VOC type $n$ compared to the wild type ($K_{\text{inf},n}$), hospitalisation propensity increase, and duration of the latent period. The values of $K_{\text{inf},n}$ were found during model calibration. Values of $K_{\text{hosp},n}$ and $\sigma_n$ were extracted from [12–14, 47].

| Parameter          | wild type | Alpha-Beta-Gamma | Delta         |
|--------------------|-----------|------------------|---------------|
| $K_{\text{inf},n}$ (-) | 1.00      | $1.40 \pm 0.10$ | $2.00 \pm 0.18$ |
| $K_{\text{hosp},n}$ (-) | 1.00      | 1.00             | 1.00          |
| $\sigma_n$ (days)  | 4.5       | 4.5              | 3.8           |

The VOC prevalence data (on the national level) were obtained from Tom Wenseleers [46]. The increase in infectivity from the Alpha-Beta-Gamma and Delta VOCs compared to the wild-type was found during model calibration. The combination of the Alpha-Beta-Gamma VOCs were estimated to be 40 ± 10% more infectious than the wild-type, while the Delta variant was estimated to be 100 ± 18% 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. [12] 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% [13, 58]. On the other hand, a Norwegian study found no significant increase in hospital admission propensity [14]. We thus model no hospitalisation propensity increase in this work, as evidence appears to be conflicting.
C.2 Seasonality

The effect of seasonality on SARS-CoV-2 transmissibility is incorporated in a cosine function with a period of one year (Eq. (6), based on [20]). The introduction of seasonality rescales the transmission coefficient $\beta(t)$. Maximum transmissibility is assumed at January 1st and minimum transmissibility is assumed at July 1st. The amplitude of the cosine was estimated at $A = 0.18 \pm 0.03$ 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

Our model uses vaccine incidence data to transfer individuals between the considered vaccination metapopulations (see Section 2.2). In every vaccine metapopulation, the vaccine offers protection through three mechanisms, each associated with its own efficacy and waning rate. By dynamically rescaling the efficacies of every vaccine metapopulation, the impact of vaccine waning is accounted for in a computationally inexpensive way (see Section 2.4).
Vaccine efficacies Tartof et al. [17] demonstrated that, for an individual fully vaccinated with the mRNA-1273 (Pfizer) vaccine, protection against hospitalisation wanes slower than protection against symptoms. Similar findings were reported by Braeye et al. [59]. From an updated version of Braeye et al. [18] (informal communication), for every relevant VOC, the three vaccine efficacies of a partial vaccination (one dose), full vaccination (two doses) and boosted vaccination (three doses) with mRNA-1273 could be extracted. In addition, the vaccine efficacies 200 days after a full vaccination (two doses) with mRNA-1273 could be extracted (Table C4). All vaccine efficacies are assumed equal to those of mRNA-1273 because 72% of vaccines administered by the end of the period considered during the model calibration (2021-10-01) were Pfizer’s. We assume that partial vaccination offers half the protection a full vaccination offers, both 25 days and 175 days post-vaccination. No data was available on the waning of booster immunity at the time of writing, so we assumed the immunity of only partially and fully vaccinated individuals to wane. This assumption does not alter any of the results in this work. We assume that the vaccine efficacies for the wild-type variant are the same as the vaccine efficacies of the Alpha-Beta-Gamma variant. This assumption has no impact on the results in this work because an appreciable amount of individuals had only been vaccinated when the Alpha-Beta-Gamma variant became dominant.

Table C4 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 (both 25 days and 175 days post-vaccination). We assume that the vaccine efficacies for the wild-type variant are the same as the vaccine efficacies of the Alpha-Beta-Gamma variant. Booster shots were not administered under the Alpha-Beta-Gamma VOC. Protection against hospitalisation is retrieved for the Delta VOC from Ref. [59] 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                  |
A Stochastic Mobility-Driven Spatially Explicit SEIQRD COVID-19 Model with VOCs, Seas

Fig. C8  Dynamics of the vaccine efficacy associated with infectivity $\bar{E}_{\text{full}, \alpha\beta\gamma, \text{inf}}(t)$, susceptibility $\bar{E}_{\text{full}, \alpha\beta\gamma, \text{susc}}(t)$, and hospitalisation propensity $\bar{E}_{\text{full}, \alpha\beta\gamma, \text{hosp}}(t)$ under the Alpha-Beta-Gamma VOCs and for a full vaccination. The observations extracted from literature (see Table C4) were used to inform the half-life of the fitted exponential decay function.

Fig. C9  Dynamics of the vaccination efficacy associated with susceptibility $E_{v,\text{susc}}$, infectivity $E_{v,\text{inf}}$, and hospitalisation propensity $E_{v,\text{hosp}}$ for $v \in \{\text{partial, full, boosted}\}$. VOC-weighted efficacy. Average of all age groups and provinces. Values closer to one denote better protection. A grey background is used to indicate a holiday period.
Fig. C10 Fraction of individuals in every province in the partially, fully and boosted vaccine metapopulations (indicated by NIS code, see Table A1). From top to bottom: first dose only (all vaccine types except Janssen), full dose only (second dose and Janssen vaccine), booster shot. A grey background is used to indicate a holiday period.

Fig. C11 Fraction of individuals in every age group in the partially, fully and boosted vaccine metapopulations. From top to bottom: first dose only (all vaccine types except Janssen), full dose only (second dose and Janssen vaccine), booster shot. A grey background is used to indicate a holiday period.
Appendix D  Model parameters and assumptions

D.1 Model parameters

Table D5  Fraction of asymptomatic individuals $a_i$ (based on [30]), and hospitalisation propensity $h_i$ for symptomatic infections per age class (inferred, see Alleman et al. [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]               | 81.9      | 1.0       |
| [12, 18]              | 81.9      | 1.0       |
| [18, 25]              | 78.8      | 1.5       |
| [25, 35]              | 77.6      | 2.5       |
| [35, 45]              | 73.6      | 3.0       |
| [45, 55]              | 69.5      | 6.0       |
| [55, 65]              | 67.1      | 12.0      |
| [65, 75]              | 64.5      | 40.0      |
| [75, 85]              | 51.1      | 70.0      |
| [85, $\infty$]       | 35.4      | 99.0      |
| Population average    | 71.4      | 14.7      |

Table D6  Average fraction $c_i$ of hospitalised individuals admitted in a cohort ward (as opposed to an Intensive Care Unit), 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 Alleman et al. [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, $\infty$]       | 95.3      | 42.3          | 78.6            |
| Population average    | 83.8      | 16.6          | 46.4            |
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 Alleman et al. [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, \( \infty \)]      | 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 assumptions and simplifications underpinning 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. The Tau-Leaping method [23] assumes the model’s rates of transitions remain constant during one leap. Because some of our model’s parameters and populations change over the course of one leap, due to time dependency, we expect the introduction of a small numerical error. By contrasting the stochastic model with a deterministic (ODE) variant, it was verified that the error was small and did not alter any of the manuscript’s in a significant way. We suspect the deviation is not noticeable because the changes to the parameters (f.i. due to seasonality) and populations (due to vaccinations) are small during the Tau-leap of \( \tau = 0.5 \ d \).

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

3. The GCMR indicators, which are used to inform the degree of social interaction in the model, are not age-stratified. Because the pandemic contact matrices are made by scaling prepandemic contact matrices with the GCMR indicators, our model preserves prepandemic mixing of the population under pandemic circumstances. Our method is thus a more coarse-grained alternative to social-epidemiological contact studies under lockdown measures.
4. The intervention parameter, $\Psi(t)$, is a phenomenological parameter downscaling the number of social contacts when lockdown measures are taken. It is introduced into the model when lockdown measures are taken and gradually eased out of the model when lockdown measures are released. Its value under lockdown measures is determined by fitting to the available hospitalisation data. Alternatively, $\Psi(t)$ could be a function (linear, logistic, etc.) of SARS-CoV-2 spread and the function's parameters could be determined during the calibration procedure (similar to [60]).

5. 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.

6. We aggregate the Alpha, Beta and Gamma VOCs because the effect of their epidemiological properties are comparable in our model, and the aggregation decreases the overall complexity.

7. Our model does not include age-specific increases for transmissibility and disease severity for the VOCs.

8. VOC strains are modeled by rescaling the transmission coefficient ($\beta$), hospitalisation propensity ($h$) and length of the latent phase ($\sigma$) with the weighted prevalence of VOCs, as obtained from data. The model does not accommodate VOCs explicitly by adding compartments and can thus not be used to model competition between strains. We used the former approach because it is computationally cheaper.

9. 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.

10. We assume that new VOCs and vaccines do not alter the seroreversion rate ($\zeta$).

11. 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.

12. In order for the negative binomial distribution log-likelihood function to apply to all $G \times n$ data points in the model calibration, the data points should strictly speaking be independent of each other, which they are not.

13. The model does not explicitly account for testing and tracing. These effects are implicitly accounted for in the calibrated parameters, however.
14. 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.

15. Vaccinated people are assumed to have the same number of contacts and the same mobility patterns as non-vaccinated people. Vaccinated people come into contact with the same fraction of vaccinated and non-vaccinated people as the national average, while some degree of segregation between vaccinated and non-vaccinated individuals could be expected.

16. The rate of transfer from the recovered to the susceptible pool, which influences the average duration of protection against reinfection does not depend on the vaccine stage.
Appendix E  Model calibration

Eight 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  Choosing an appropriate observational model

Given a time series of daily hospitalisations \( x^g \) for every province \( g \in \{1, \ldots, G\} \) with \( n \) observations \( x^g_t \) for \( t \in \{1, \ldots, n\} \) corresponding to times \( \{t_1, \ldots, t_n\} \), 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 \( g \) (after summing over all age groups and vaccination stages). This time series may be sampled to produce a set of model-based values \( \{\tilde{x}^g(t_1), \ldots, \tilde{x}^g(t_n)\} \) that we will denote as \( \{\tilde{x}_1^g, \ldots, \tilde{x}_n^g\} \). The aim is to find the model parameters for which it is most likely that the \( x^g \) are observations of the modelled time series \( \tilde{x}^g \). An appropriate statistical distribution must be chosen to assess what deviations between \( x^g \) and \( \tilde{x}^g \) are tolerable. To find the most appropriate statistical distribution, the relationship between the mean and variance of the time series \( x^g \) must be studied. The time series for the daily number of hospitalisations consist of one observation per day without information on the variance. Mean-variance couples were approximated for all provincial time series using the following procedure,

1. Compute the (7-day) exponential moving average of the time series \( x^g \) (solid red line in Figure E12). Assume it represents the underlying truth.
2. Subdivide the time series \( x^g \) into discrete windows of length \( n \) days. Window lengths \( n \) of 7, 14 and 31 days were used with consistent results.
3. In every window, compute the mean observation and the variance between the exponential moving average and the observations.

Next, the most appropriate statistical model was chosen by fitting the mean-variance of several candidate distributions – the Gaussian model (\( \sigma^2 = \)
A Stochastic Mobility-Driven Spatially Explicit SEIQRD covid-19 Model with VOCs, 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 Akaike Information Criterion (AIC) to determine what model fits best. As an example, the result of the above analysis is shown for the national time series of daily hospitalisations in Figure E13. At the provincial level, 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. 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 \( g \) [51, 61] (see Table E8). The values of which were obtained by fitting the negative binomial mean-variance relationship to our estimated mean-variance couples. 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

\[
L(\tilde{x}_t^g | x_t^g) = \frac{\Gamma(x_t^g + 1/\alpha^g)}{\Gamma(x_t^g + 1)\Gamma(1/\alpha^g)} \left( \frac{1/\alpha^g}{1/\alpha^g + \tilde{x}_t^g} \right)^{1/\alpha^g} \left( \frac{\tilde{x}_t^g}{1/\alpha^g + \tilde{x}_t^g} \right)^{x_t^g},
\]

with \( \Gamma \) the gamma function. The negative binomial distribution has mean value \( \tilde{x}_t^g \) and variance \( \tilde{x}_t^g(1 + \alpha^g \tilde{x}_t^g) \); 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:

\[
L(\tilde{x} | x) = \prod_{g=1}^G \prod_{t=1}^n L(\tilde{x}_t^g | x_t^g).
\]

Again, this value \( L(\tilde{x} | x) \) is maximised if \( \forall g, t : \tilde{x}_t^g = x_t^g \), but this is generally not possible: the values \( \tilde{x}_t^g \) 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:

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

The result is the log-likelihood in Eq. (11). The parameter choice \( \theta = \hat{\theta} \) that maximises Eq. (11) for the obtained values of \( \alpha^g \) is considered the best-fitting 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 [62], which
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Fig. E13 Estimated mean-variance couples of the national time series of daily new hospitalisations, shown together with the fitted mean-variance models and their respective AIC scores.

together with the overdispersion values ($\alpha^g$) determines the uncertainty on the simulated time series. Note that large $\tilde{x}_t^g$ and $x_t^g$ values will contribute more to the total sum in Eq. (11) 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 log-likelihoods,

$$
\log \mathcal{L}(\tilde{x}_{H\text{in}} | x_{H\text{in}}) + \log \mathcal{L}(\tilde{x}_{R} | x_{R,\text{Herzog}}) + \log \mathcal{L}(\tilde{x}_{R} | x_{R,\text{Sciensano}}),
$$

The time series $\tilde{x}_{H\text{in}}$ and $\tilde{x}_{R}$ correspond to the simulated daily new hospitalisations per province (summed over age groups and vaccine doses) and the total number of recovered individuals (summed over provinces, age groups, and vaccine doses), respectively. The observed time series are $x_{H\text{in}}, x_{R,H}$ and $x_{R,S}$: observed daily new hospitalisations per province [50], national seroprevalence data from general practitioners by Herzog et al. [49], and national seroprevalence data from Red Cross by Sciensano [50], respectively (see Appendix A.1).

Due to the stochastic nature of the model, the simulated time series $\tilde{x}^g(t)$ will differ slightly for every choice of model parameters and IC. To assess the robustness of the sampled parameter distributions to this stochasticity, the model was calibrated using the mean of 2, 5 and 10 stochastic realisations as $\tilde{x}^g(t)$. No noticeable changes in the distributions were observed, however, the calibration procedure had become respectively 2,5 and 10 times slower. A single stochastic realisation was thus used as $\tilde{x}^g(t)$. 

Table E8  Values per province of the estimated overdispersion parameter of the negative binomial distribution associated with the time series of daily COVID-19 hospitalisations, used in the log-likelihood function (11). The average overdispersion coefficient of 0.034 (population-size weighted) was used for all simulations presented in this work.

| Province          | $\alpha^g$ | Province          | $\alpha^g$ | Province          | $\alpha^g$ |
|-------------------|------------|-------------------|------------|-------------------|------------|
| Antwerpen         | 0.031      | West-Vlaanderen   | 0.041      | 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      |                   |            |

Fig. E14  Corner plot showing the posterior distributions of the five calibrated parameters. Provincial model. Created with the corner package [63].

E.2 Results of Model calibration

Calibrated values of all a priori unknown model parameters, including their interpretation, are listed in Table 3. The posterior distributions of the estimated parameters and their potential correlations are shown in Fig. E15. Simulations of the daily number of new hospitalisations for every province are shown in Figs E16 and E17. The small difference in goodness-of-fit between the spatially explicit and the national models is demonstrated in Fig. E18.
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![Corner plot showing the posterior distributions of the five calibrated parameters.](image)

**Fig. E15** Corner plot showing the posterior distributions of the five calibrated parameters. Equivalent national model. Created with the `corner` package [63].

![100 model realisations of the daily new hospitalisations between March 15th 2020 and January 1st 2022](image)

**Fig. E16** 100 model realisations of the daily new hospitalisations between March 15th 2020 and January 1st 2022 (solid lines) with a negative binomial 95% confidence region (transparent band). Black crosses signify raw data from Sciensano [50] were used in the calibration procedure while red crosses signify data were not used during the calibration procedure. From top to bottom: Antwerpen (10000), Brussels, Brabant Wallon and Vlaams Brabant (20001, 20002, 21000), West-Vlaanderen (30000) and Oost-Vlaanderen (40000). (see Table A1 and Fig. A4). A grey background is used to indicate a holiday period.
Fig. E17 100 model realisations of the daily new hospitalisations between March 15th 2020 and January 1st 2022 (solid lines) with a negative binomial 95% confidence region (transparent band). Black crosses signify raw data from Sciensano [50] 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. A4). A grey background is used to indicate a holiday period.

Fig. E18 (a) 100 realisations of the equivalent national model and (b) 100 realisations of the spatially explicit model (nationally aggregated) of the daily new hospitalisations between March 15th 2020 and January 1st 2022 (solid lines) with a negative binomial 95% confidence region (transparent band). The accompanying negative binomial log-likelihood score of the model predictions is given in black on the right hand axis. (c) Boxplot of the log-likelihood values at every time $t$ of the national and spatially explicit model. No difference in log-likelihood was found between the national model and the spatially-explicit model (Mann-Whitney U test; $p = 0.81$) Despite morphological differences, the goodness of fit of both models behaves in a similar manner: when SARS-COV-2 prevalence is low, both models have difficulties being accurate. A grey background is used to indicate a holiday period.
Fig. E19 (a) 100 realisations of the estimated fraction of seropositive individuals, as proxied by the Recovered (R) state of the model (solid lines), along with the negative binomial 95% confidence region (transparent band) versus the fraction of seropositive individuals as measured by Herzog et al. [49] and the Belgian Scientific Institute of Public Health [50]. The dashed vertical line indicates the start of the nation-wide vaccination campaign (2020-12-28). After the start of the vaccination campaign, the Recovered (R) state no longer is a valid proxy for seroprevalence. A grey background is used to indicate a holiday period.