Forecasting hospitalization and ICU rates of the COVID-19 outbreak: an efficient SEIR model

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ABSTRACT

Summary The severe acute respiratory syndrome-coronavirus (SARS-CoV-2) virus has caused a severe global pandemic of Corona virus disease 2019 (COVID-19) with major outbreaks in China, South Korea, Iran, US, Italy, the Netherlands and the remainder of Europe. Decisions for drastic measures for mitigation of spreading can be informed by monitoring techniques and model forecasts. These decisions are mainly driven by the capacity of the health care system. The Dutch National Corona Outbreak Team and individual hospitals request forecasts on hospitalization and intensive care unit (ICU) rates (both short and long term). They need this data in order to respond adequately to growth in number of patients with COVID-19 virus but also to maintain an adequate care system for other patients. Here we propose to use hospitalization and/or death rates as key monitoring data in conjunction with efficient and effective model forecasts in the early phase of the outbreak, complementary to testing results. Using this approach can overcome difficulties in assessing the scale of the outbreak and making forecasts for hospitalization rates, ICU usage and effectiveness of policy measures, in particular in face of limited testing capacity and under-registration as in the Netherlands and other countries.

Methods We used reported data from the outbreaks in China, South Korea, Italy from January 2020 to March 19, 2020 and for the Netherlands to March 26. We used a Monte Carlo Susceptible-Exposed-Infectious-Removed (SEIR) metapopulation model to simulate each of these outbreaks, as well as the effect of measures to reduce community spreading. The main aim was to calibrate the general model parameters, in spreading centers in advanced and intermediate stages, in order to be used subsequently in a currently active spreading center in an early stage in the Netherlands. This is particularly important in view of calibrating transmissibility and lag times between infection, hospital treatment and death, and their impact on understanding of critical effects of (delaying) particular mitigation measures. Monte Carlo forward modelling in combination with log-likelihood and ensemble smoother approaches are used for calibrating the model under uncertainty. The model is publicly available in python code.

Findings For the exponential growth of COVID-19 we propose a socalled data-based Aggregated Reproduction number (R_0^A) for the SEIR model with a value around 3.5, which is in agreement with rapid death and hospitalization rates at the onset of the outbreaks in most of the cases studied. The lag-times in the different outbreaks between registered cases is in line with earlier findings of around 2 weeks between exposure to the virus and hospitalization. Most deaths appear to occur relatively early, compared to long term treatment of 2-4 weeks of critical patients in Intensive Care Units (ICU). The long treatment time of ICU patients with COVID-19 allows to use the increase in hospitalization and ICU demand as an early warning for community spreading.

Interpretation COVID-19 is a pandemic, which can cause health care systems to collapse if further spreading of the virus is not contained at an early stage. As hospitalized patients mostly suffer from pneumonia, the rate of increase in COVID-19 related cases can be easily used as early indicator. Using models as presented here allow to make reliable forward predictions of ICU needs, even if testing capabilities are limited, and to evaluate the effects of a timely adaptive response.

INTRODUCTION

According to the World Health Organization (WHO), Corona virus disease 2019 (COVID-19) reached the pandemic phase on March 11, 2020. On March 27, 2020, the virus has spread to 199 countries worldwide, leading to 597,458 registered infections and 27,270 deceased[1]. Currently, COVID-19 is marked by community spreading in all European Union countries, with different governmental policies to prevent transmission of the severe acute respiratory syndrome-coronavirus (SARS-CoV-2) virus and its disease. The health care systems are being confronted with soaring numbers of registered infections, sickness and death in a matter of weeks. Especially, the care for critically ill patients (approximately 30-50% of admitted patients) puts a major constraint on hospital logistics.

During the major outbreak in the province of Hubei in China, a government-imposed lockdown has led to a decrease in the number of infected patients over the last weeks. Very stringent measures in the remainder of the country, such as the closing of schools, also appear to have been effective. Despite the apparent success of the China lockdown in terms of direct health benefits, many countries in Europe have chosen a less rigorous approach compared to China. A key challenge is to take the right measures at the right time, considering the trade-off of protecting the health of citizens on one hand and sustaining society, in view of reduced contacts and travel restrictions. There are effective models which allow to predict the evolution of an outbreak and effects of measures to reduce spreading[2], but these are marked by considerable uncertainty and are also dependent on social acceptance, lagging behind government measures[2,3].

Particularly challenging is the fact that COVID-19 is probably marked by a reproduction rate higher than the flu[4], COVID-19 can be contagious during the incubation period[5], and can survive on surfaces and in the air outside the body for hours or up to 3 days[6], while the initial symptoms of the disease are generally similar to flu symptoms. These factors pose major challenges to contain the virus through contact tracing and quarantine[7] and are in agreement with the observed failure to contain the virus around imported cases in many countries.

The aim of this paper is to predict hospitalization -in particular intensive care unit (ICU) admissions- in different age categories and the influence of different strategies (lockdown, control or limited control) We developed an effective tool for forecasting under uncertainties, constrained by various observed data. The model allows to study scenarios for the progress of community spreading. The open-access tool can be regularly updated to forecast and thus inform decision makers on the effect of measures and their timing. Key for the model calibration is to use the number of recorded death and hospitalized patients. General parameters for COVID-19 have been based on relatively progressed outbreaks in China, South Korea and Italy and the model has been subsequently tested in the Netherlands to forecast the needs for ICU care.

METHODS

We used data on registered infections, deceased and recovered patients in the period January, 15 2020 up to March 21, 2020. As a source, we used data from health agencies obtained from the John Hopkins data repository[8] for the outbreak centers in China and South Korea, whereas for Italy and the Netherlands we compiled data from national health agencies and data from news sources[1].

We used the data of China, South Korea and Italy focused towards testing and validation of parameters of the model, as these spreading centers are in relatively advanced stages. Subsequently, these have been used to model the incipient spreading center in an early stage in the Netherlands.

For the modelling we used a simplified Susceptible-Exposed-Infectious-Removed (SEIR) metapopulation model to simulate the epidemics[3,9], as well as the effect of measures to reduce community spreading[3,10] (Figure 1). Its underlying parameters are explained in detail in the appendix

(Table 1). This type of model is extensively used in other infectious disease research studies. Here, we included ensemble based techniques for calibration and forecast[11]. Our model stands out in its focus towards fitting hospitalization rates. The most important difference between our model and other used SEIR models[12] or epidemical models, is that our model is data-based and therefore giving an Aggregated Reproduction number (R_0^A) as output for the situation without measures. The Aggregated Reproduction number we inferred from the data is circa 20% higher than the Reproduction number (R_0=3) as used in most recent studies[12]. Our model is a fast deployable open access tool and usable worldwide at the beginning of outbreaks to give reliable predictions of the demand for hospital care. In the simulations, the initial day of introduction of the virus is at least 10-20 days prior to the first registered case, and the density of the virus introduced in the population is varied to obtain a first order fit with the observed number of registered infections, hospitalized and death. The simulation incorporates stages of control or lack thereof through the parameter $\alpha(t)$, which parameter represents the reduction of social contacts. Stages include contact tracing and quarantine, uncontrolled outbreaks, and government measures to restrict community transmission, at specified times in the simulation. We adopted representative values for various stages of control as listed in Table 2 in the appendix. These are tentative values marked by large uncertainty, which has been incorporated in the ensemble forecasts of the model. In the present study we neglected incorporation of time dependent effect of social acceptance in the measures[3].

For hospitalization and age dependent effects on ICU needs, we used data available from news sources and the health agencies of the corresponding countries, and recent study results. For Italy and the Netherlands reported hospitalization and ICU numbers are available in the public domain. Current statistics in the United Kingdom show age dependent numbers requiring hospitalization (ranging from 0.1-27.3%) and ICU admission (ranging from 5.0-70.9%)[10]. It is very likely that these rates are underestimating adequate numbers of real infections, in view of under registration and bias towards preferred testing of patients with symptoms or pneumonia.

In the Chinese cohort, 49% of the ICU patients (1023/2087) died[1,13] with a case fatality rate of 2.3%. At March 21,In Italy, ICU mortality was 7% (3631/53578)[1] and the case fatality rate was 9% (4825 death/53578 total cases)[1] However, from South Korea, marked by very intensive and unbiassed testing, we can infer a significantly lower case fatality rate of 1.1% (102 death/8799 total cases)[1]. In order to correct for under-registration, assuming the South Korean data to be more representative of true values, we adopted a default death-rate of 1.1%. The death rate ratio can then be taken as proxy for under registration but may be different due to demographic and health care conditions. Adopting a death rate of circa 1% implies that only 5% of infected persons predicted by the model are hospitalized in order to be consistent with ratios of hospitalization and deceased cases recorded in Italy and the Netherlands. In order to compare model predictions of infections to under-registered infections, we can impose a correction factor for the modelled numbers which is simply derived from the ratio of cumulative observed case fatality rates and the default death rate.

The calibration with past outbreaks is particularly important in view of transmissibility characteristics of the virus, and critical assessment of delay times between infection, subsequent hospital treatment, and death, as these have a major impact on calibration and the delayed effect of particular mitigation measures. The calibration of the parameters of the model is presented in the appendix (Figure 7). Subsequently, we tested if the inferred parameter settings from past outbreaks in China, South Korea, and Italy are consistent with the data in the Netherlands and evaluated the effects of using the model for prediction in view of needs for hospitalization and ICU demand during the course of the epidemic spreading. We made forecasts at different stages of the outbreak in the Netherlands. We tested and calibrated on the data reported up to March 21 and on data up to March 26.

Forecast initial stage, March 14 and 21

In the period March 14 to 21, the Netherlands was at the initial stage of the epidemic, in terms of pressure on the healthcare system. The timeline of measurements and governmental response is shown in Figure 2. On March 18, widespread community spreading was also suspected from 10 positive tests[14] of patients in 42 general practices representative for 0.7% of the Dutch population (Nivel sentinel stations[15]). In addition, cluster spreading has been identified earlier in the province of North Brabant of the Netherlands (population ≈2,5 million), including widespread infections in hospital personel and patients. The government responded with progressively stringent measures on March 15 with closure of schools, bars and restaurants and with no visits for elderly persons in homes on March 19.

In the modelling of hospitalization and ICU rates, we analyzed three scenarios: control scenario, lockdown, and 'limited' (uncontrolled) growth. The tentative $\alpha(t)$ values adopted at the time of modelling (March 21) were in line with the control scenario: 0.5 and 0.7 starting from March 12 and March 15 respectively. For the lockdown scenario these were 0.7 and 0.9 and for the 'limited' growth 0.23 and 0.5 respectively. The ensembles for these scenarios incorporated an uncertainty bandwidth on $\alpha(t)$ of ±10%, to illustrate the effect of uncertainty in the scenario.
Figure 3 shows the best fit curves of the model and ensembles of future forecasts for the control scenario using the log likelihood method for calibration with hospitalized data (see appendix for explanation). Figure 4 shows the effect of the control, lockdown and 'limited' growth fitted to the hospitalization and ICU data up to March 21. It is clear that the measures and underlying uncertainty in $\alpha(t)$ was not felt in the data until March 21, leaving major uncertainty on the effect of measures.
We also did an analysis if the data up to March 14 could be used to predict the observed data until March 21, and the effect of measures beyond that date. As the government measures are not yet felt in the data, the model predictions up to March 21 are in line with the inferred aggregated reproduction rate prior to 14th March and therefore show an excellent fit to the observed ICU and hospitalization data (Figure 4)..

Forecast March 26

In the week following March 21 the ICU rates steadily rose up to 761 beds in use at March 26 (Figure 5). The gradually climbing numbers suggested that the measures taken on March 12 had some, but limited effect. In addition, a major new measure was taken March 23 prohibiting gatherings larger than three people and included strict quarantine measures for family members of, or indivividuals with COVID-19 like symptoms. By now, we also had sufficient data to use ICU data directly and used the ensemble smoother to calibrate the effects of the measure (see appendix for explanation). We assumed in the model that 40% of hospitalized is ICU patients, and calibrated $\alpha(t)$ for the March 12 measure with the Ensemble Smoother approach (see appendix for explanation). In the process, we did rerun our model with updated settings in accordance with the measures. We adopted $\alpha(t)$= { 0.3, 0.5, 0.7} for March 12,15,23 and generated prior ensembles for these scenarios with an uncertainty bandwidth on $\alpha(t)$ of ±30%. The results of the ensemble smoother are shown in Figure 5. The results show an excellent fit with the data. Please note that the effectiveness of the measures taken March 15 and 23 cannot be calibrated to the data yet, leaving a very large uncertainty range as shown by the ensembles. In view of this, the predicted median value of the peak and duration of ICU needs are directly determined by the -not yet constrained- median values of $\alpha(t)$ of the measures taken March 15 and 23.

Age cohorts

For planning of ICU needs it is important to predict age cohorts of ICU patients which can be used to reserve enough ICU in specific age groups. For the different scenarios these hospitalized and ICU forecasts can be translated according to the expected age cohorts based on demographic build-up and knowledge of age dependent percentiles of COVID-19 cases in need for hospitalization and ICU from

the United Kingdom[10]. The resulting percentiles for the Netherlands are presented in Figure 6, weighted for the demographic distribution of the different age groups.

DISCUSSION

During the outbreak, there is a strong need to make planning on hospitalization and ICU needs. With data flowing in on the rising number of hospitalized patients, the model can be used on a daily basis to forecast the future rise of hospitalization and ICU needs and can be used to predict age cohorts flowing in. The results highlight that predictions are marked by a large range of uncertainty when measures to mitigate further spread become effective. Due to underestimation in the delay in social acceptance, the effect of measures may come later or less strong than anticipated. In the control scenario this effect is very pronounced, where even with a relatively small uncertainty of 10% in $\alpha(t)$, the hospitalized and ICU numbers can in the forecasts exceed planned numbers based on the median values by a factor of 2 for a considerable time. For a control scenario, this advocates for applying measures which are on the safe side, i.e. close to lockdown conditions may be necessary at identification of cluster and community spreading, and to step to less constrictive measures at a later stage, once the measures have proved to be effective.

The adopted $\alpha(t)$ values which have been chosen in this paper are based on expert judgement and are in range of values used in literature[3], based on the logic of contact reduction and social distancing[3,10]. They serve to illustrate the large variability in uncertainty regarding the effect of measures and it should be stressed that these have not and cannot yet be validated from the data. The results also illustrate that the future outcome of the measures is still uncertain.

CONCLUSIONS

In this study we demonstrated for the Netherlands that the ensemble based SEIR model, with an Aggregated Reproduction number (R_0^A) calibrated to data in China, South Korea and Italy, is well capable to predict hospitalization, ICU rates and deaths during a COVID-19 outbreak. The model is fast and effective, and can be based on data collected through news data and national and international repositories.

Key in the model approach is the use of reported hospitalization rates of ICU rates complemented with death rates for calibration of the models. This is an earlier and denser signal than death rates, assuming hospitalization case fatality rates of circa 20%. Furthermore, hospitalization is a very reliable signal compared to test rates, which is often under registrated.

The capability to visualize and calibrate the effects of the different strategies enforced by the government (lockdown, control, 'limited growth') allows hospital staff and policy makers to plan, prepare and adapt, and can be used to raise awareness of the importance of adhering to these measures. It facilitates hospital staff to forecast capacity needs and underlying uncertainty and incorporates the effect of age on the burden of our hospital capacity. All these factors assist in prevention of further spread of the SARS-CoV-2 virus and risk for collapse of the health care system.

Research in context

Evidence before this study

COVID-19 is a pandemic, which in case of community spreading can easily make health care systems collapse if further spreading of the virus is not controlled at the early stages of the outbreak. A large number of approaches are available for prediction, but most have been calibrated on test case or death rates, not hospitalization rates, are often more complex and do not take an empirically defined aggregated reproduction rate as proposed here, resulting in underestimation of the exponential growth of infections.

Added value of this study
We present an open access modeling tool which can predict the near future number of hospital and ICU beds needed during the present SARS-CoV-2 pandemic. Use of hospitalization and ICU rates for calibration allows to make reliable forward prediction of ICU needs during the outbreak when the effects of government measures are not yet effective, and it easily allows to evaluate the effects of a timely adaptive response. It can also help to evaluate the effectiveness and impact of policy measures that has been taken to control and the COVID-19 virus outbreak, through calibrating the effects to incoming data on a daily basis.

Implications of all the available evidence
The potential of immediate application and value for hospital staff or policy makers makes the research paper and open access tools important. Worldwide, the number of patients is still rising dramatically.

Contributors
JDW, SO, OL and MP developed the model. LB, MT, and MTF collected and modelled data. JDW, MH, MK, JZ and MTF, interpreted the results and wrote the manuscript.
Declaration of interests
We declare no competing interests.
Data and model sharing
We collected the data from publicly available data sources (news articles, press releases, and published reports from public health agencies) and used the John Hopkins data repository[8].The modelling code and data used for our analysis of Italy and the Netherlands is available under github https://github.com/TNO/Covid-SEIR for use by scientists and governmental agencies.

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References

1. worldometer. 2020; Available at: https://www.worldometers.info/coronavirus/. Accessed 3/2 and 3/27, 2020.

2. Kucharski AJ, Russell TW, Diamond C, et al. Early dynamics of transmission and control of COVID-19: a mathematical modelling study. *The Lancet Infectious Diseases* 2020; .

3. Lin Q, Zhao S, Gao D, et al. A conceptual model for the coronavirus disease 2019 (COVID-19) outbreak in Wuhan, China with individual reaction and governmental action. *International Journal of Infectious Diseases* 2020; **93**: 211-6.

4. Coburn BJ, Wagner BG, Blower S. Modeling influenza epidemics and pandemics: insights into the future of swine flu (H1N1). *BMC Medicine* 2009; **7**(1): 30. doi:10.1186/1741-7015-7-30.

5. Li P, Fu J, Li K, et al. Transmission of COVID-19 in the terminal stage of incubation period: a familial cluster. *International Journal of Infectious Diseases* 2020; .

6. van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. *N Engl J Med* 2020; . doi:10.1056/NEJMc2004973.

7. Hellewell J, Abbott S, Gimma A, et al. Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. *The Lancet Global Health* 2020; **8**: e488-96.

8. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *The Lancet Infectious Diseases* 2020; .

9. Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. *The Lancet* 2020; **395**: 689-97.

10. N.M. Ferguson ea. Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand. 2020; Available at: https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-NPI-modelling-16-03-2020.pdf. Accessed 03/22, 2020.

11. Yang, Z., Zeng, Z., Wang, K., Wong, S., Liang, W., Zanin, M., Liu, P., Cao, X., Gao, Z., Mai, Z., Liang, J., Liu, X., Li, S., Li, Y., Ye, F., Guan, W., Yang, Y., Li, F., Luo, S., Xie, Y., Liu, B., Wang, Z., Zhang, S., Wang, Y., Zhong, N., He,J. Modified SEIR and AI prediction of the epidemics trend of COVID-19 in China under public health interventions. *Journal of Thoracic Disease* 2020; **12**(2).

12. Walker PGT, Whittaker C, Watson O. The Global Impact of COVID-19 and Strategies for Mitigation and Suppression. WHO Collaborating Centre for Infectious Disease Modelling, MRC Centre for Global Infectious Disease Analysis, Abdul Latif Jameel Institute for Disease and Emergency Analytics, Imperial College London. 2020; Available at: https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-Global-Impact-26-03-2020.pdf. Accessed 02/27, 2020.

13. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020; . doi:10.1001/jama.2020.2648.

14. RIVM. current information about novel coronavirus covid-19. 2020; Available at: https://www.rivm.nl/en/news/current-information-about-novel-coronavirus-covid-19. Accessed 02/22, 2020.

15. Nivel. Nivel Primary Care Database – Sentinel Practices. 2020; Available at: https://www.nivel.nl/en/nivel-primary-care-database-sentinel-practices. Accessed 03/22, 2020.

16. Anderson RM, Heesterbeek H, Klinkenberg D, Hollingsworth TD. How will country-based mitigation measures influence the course of the COVID-19 epidemic? *The Lancet* 2020; **395**: 931-4.

17. Emerick AA, Reynolds AC. Ensemble smoother with multiple data assimilation. *Computers & Geosciences* 2013; **55**: 3-15.

18. wikipedia. 2020 coronavirus pandemic in South Korea. 2020; Available at: https://en.wikipedia.org/wiki/2020_coronavirus_pandemic_in_South_Korea. Accessed 03/22, 2020.

19. Jia L, Li K, Jiang Y, Guo X, zhao T. Prediction and analysis of Coronavirus Disease 2019. 2020; **Available at: https://arxiv.org/pdf/2003.05447.pdf**.

FIGURES

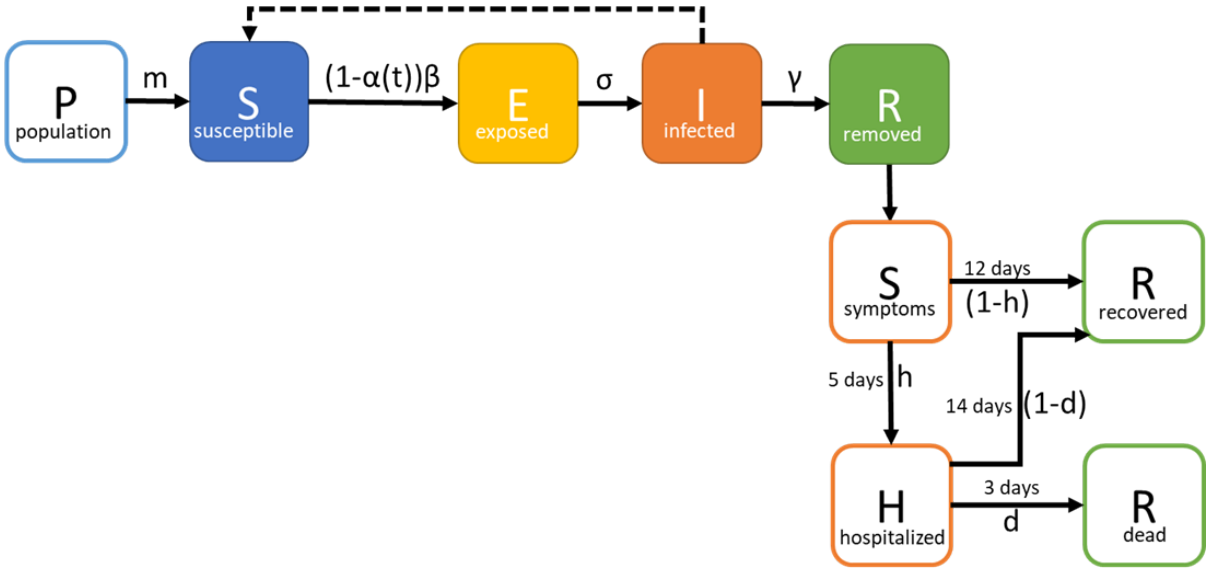


Figure 1 Schematic diagram of the SEIR model, extended for R with delay times and fractions h and d for hospitalization and death respectively.

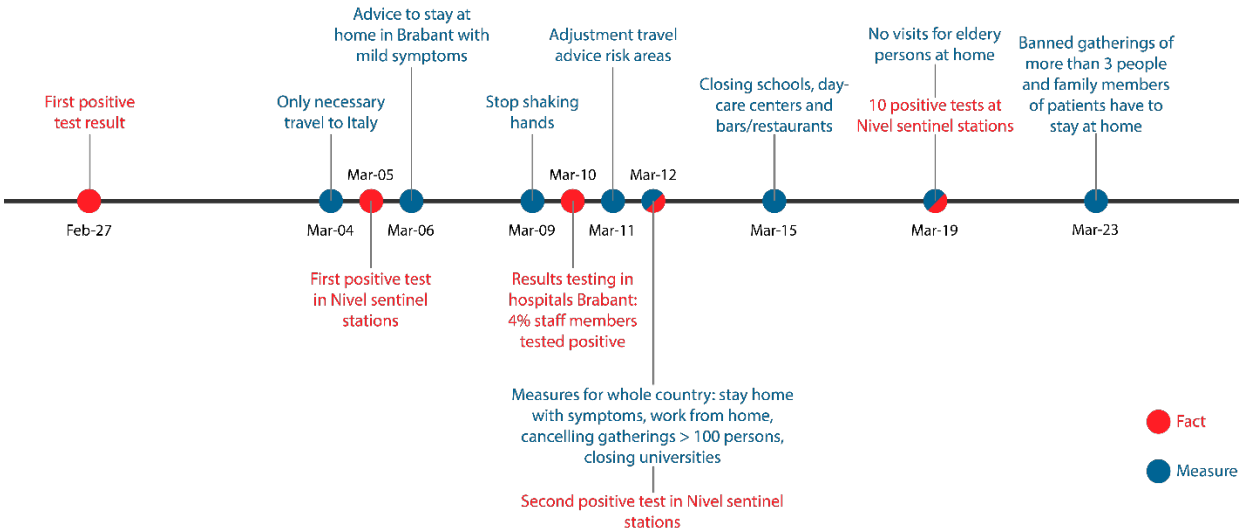


Figure 2 Timeline of events, and measures related to the COVID-19 outbreak in The Netherlands.

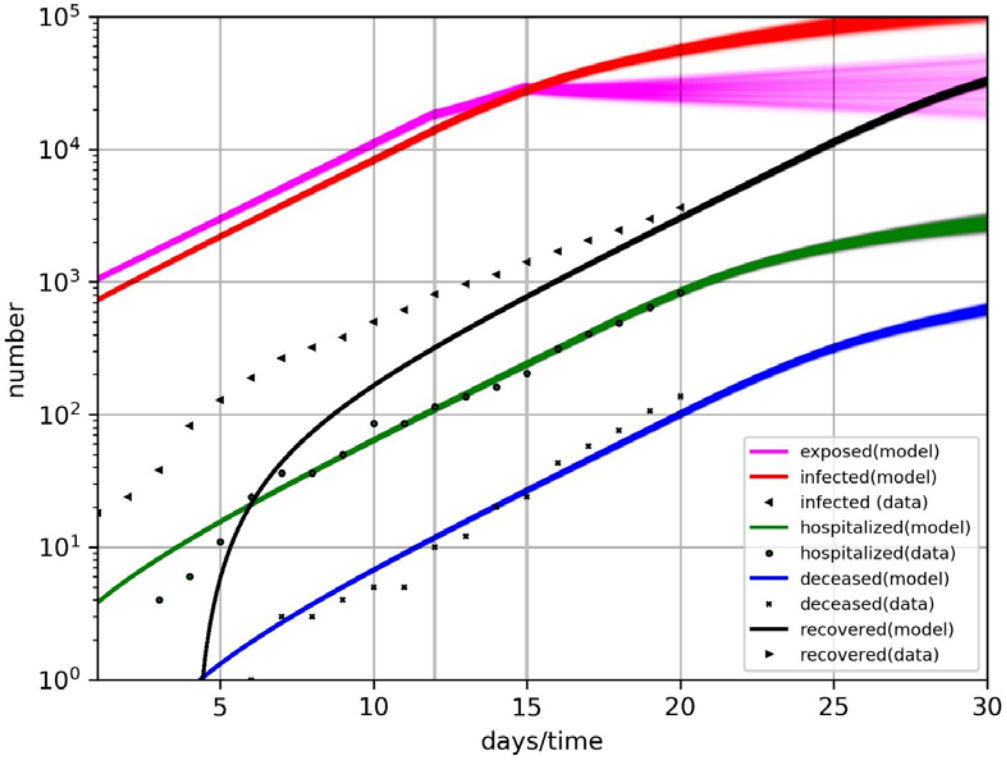


Figure 3 Ensemble forecast of the Netherlands made March 21, based on data reported up to March 20. Uncertainty is largely related to uncertainties in the future effect of mitigating measures. The model has been calibrated on the hospitalized data. The grey vertical lines are the transitions of different values of $\alpha(t)$ of {0.5, 0.7} at March 12 and 15, respectively. Same convention as in Figure 1.

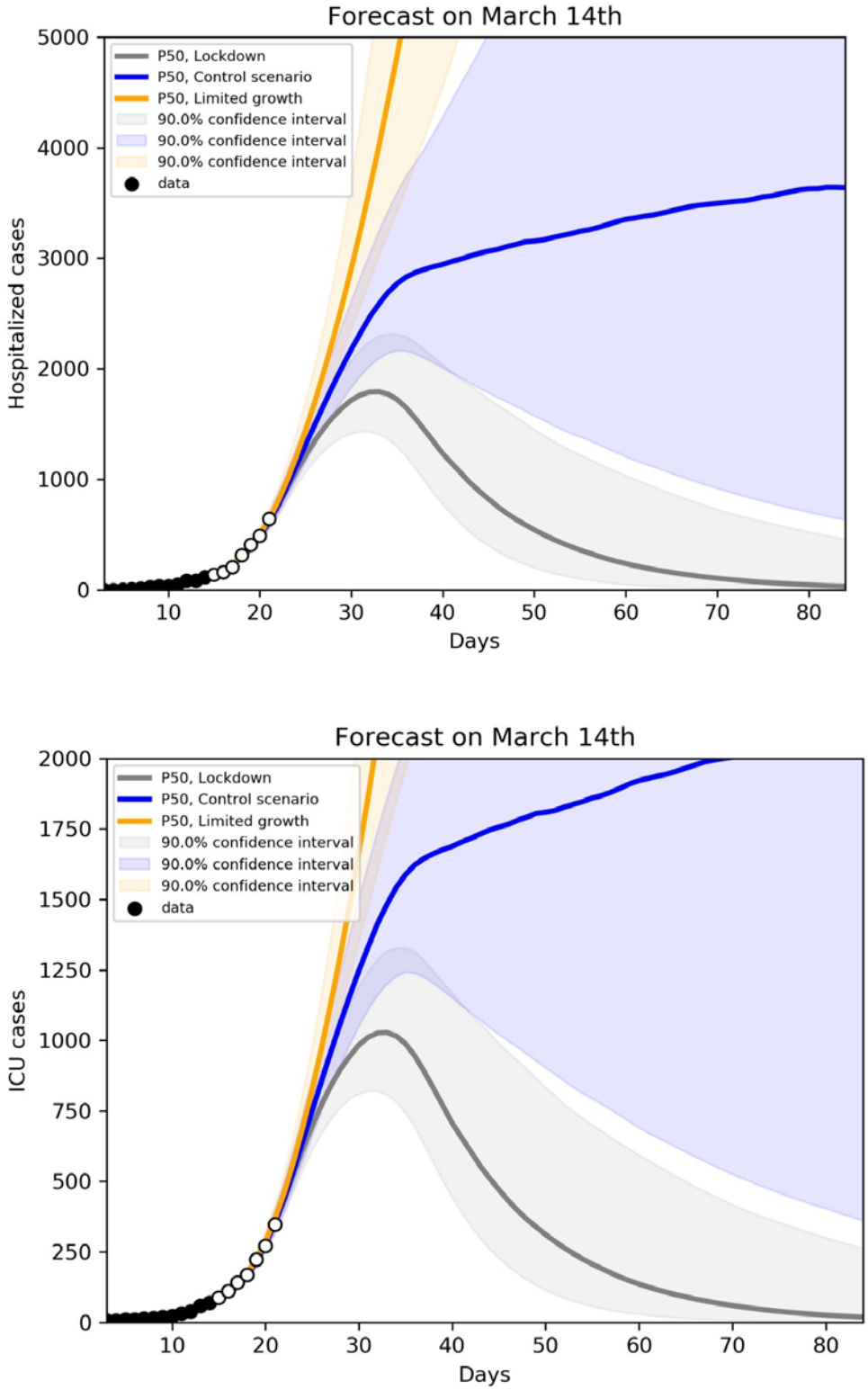
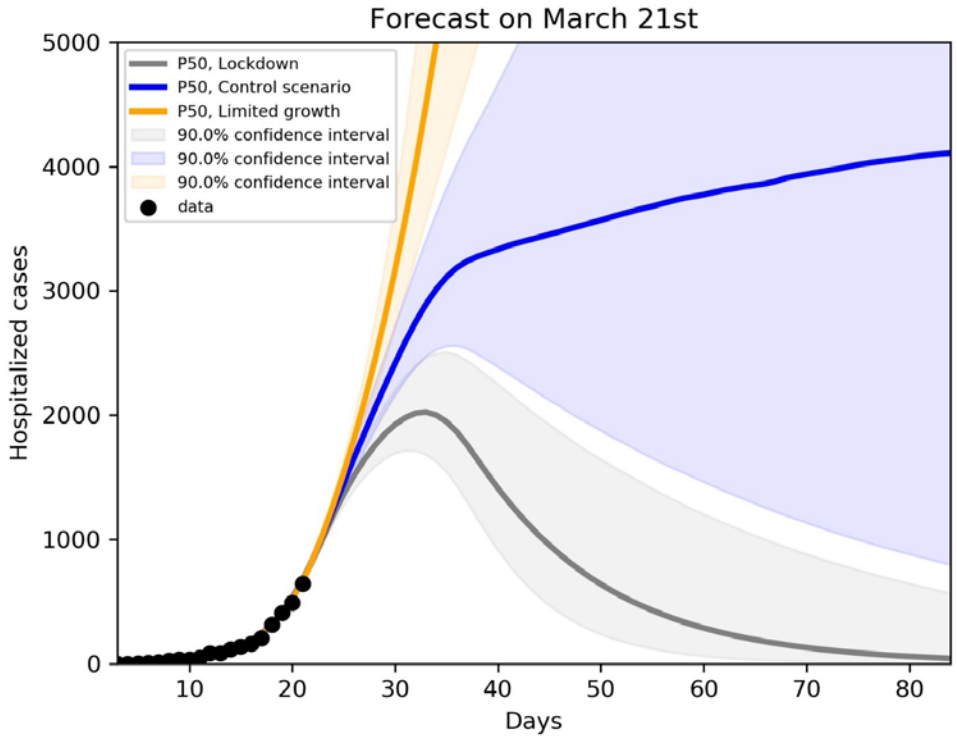


Figure 4 Forecasts for hospitalized and ICU patients, based on data reported for the period until March 14 and 21 respectively



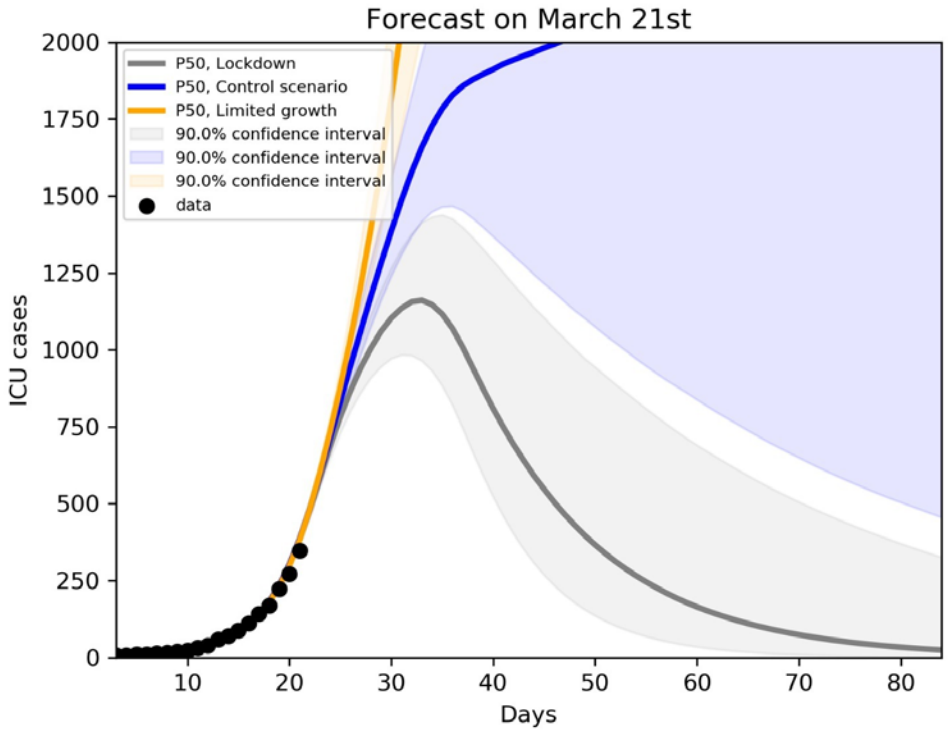


Figure 4 (continued from previous page)

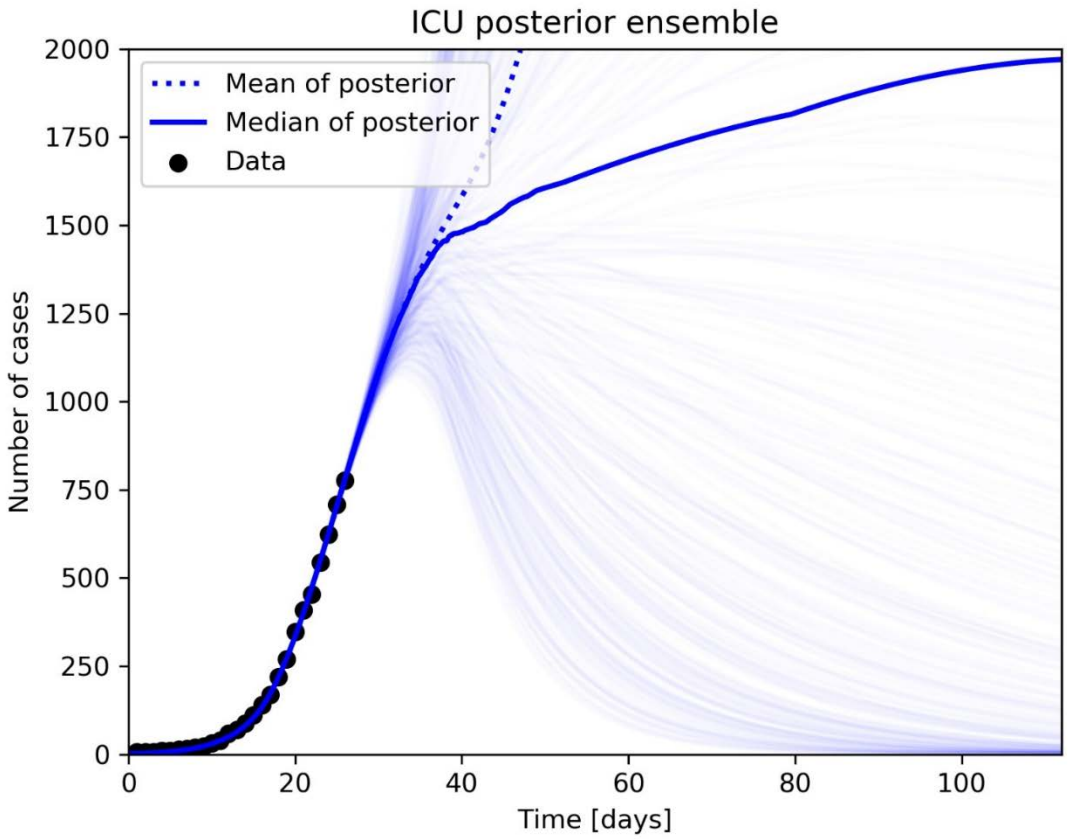


Figure 5 Forecast based on reported data of actual ICU occupation for the period until March 26.

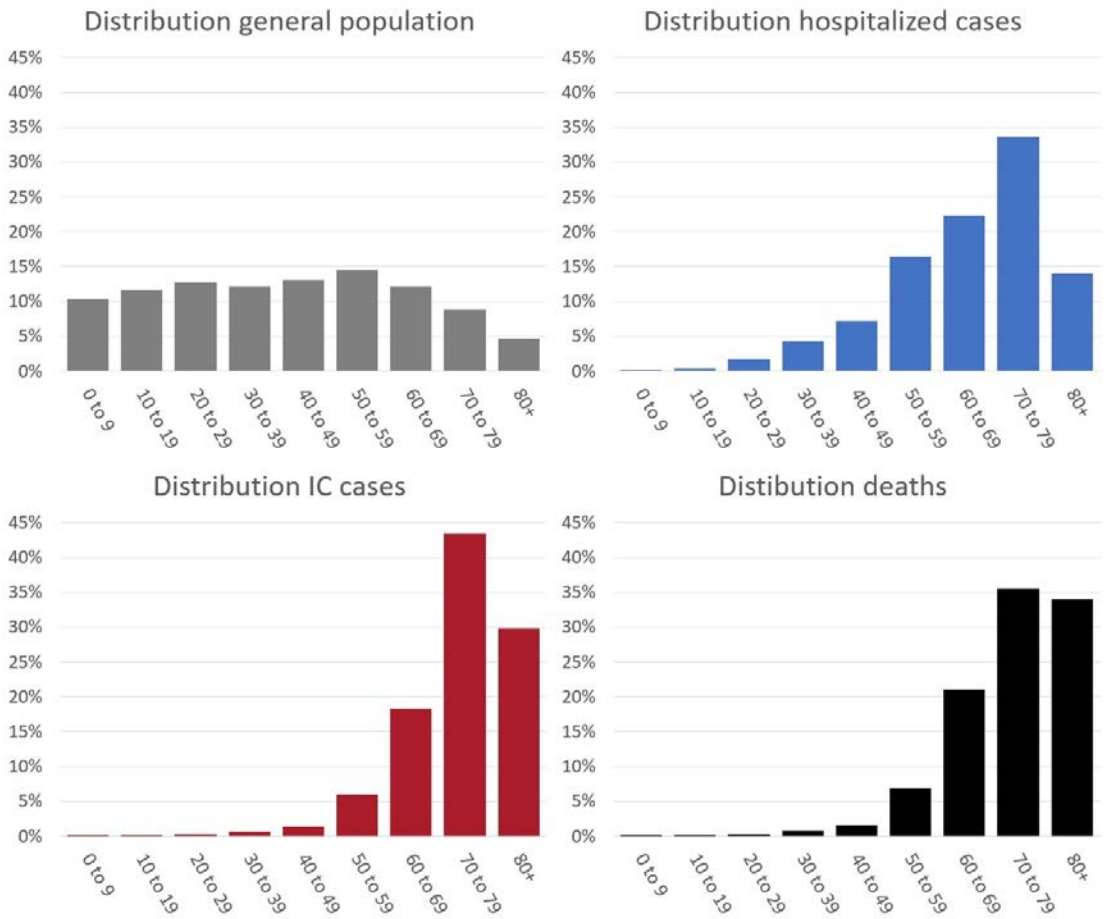


Figure 6 Demographic buildup of population, expected age distribution for hospitalized cases, ICU cases, and deceased based thereon.

Appendix Model description

In The SEIR model: **S**usceptible part of the population, **E**xposed part carries the virus, and **I**nfected shows first mild symptoms. **R**emoved has recovered or died. We simplified the model based on Lin et al.[3] which includes the effect of time dependent social distancing through the paramer $\alpha(t)$. $\alpha(0)$ is 0 when no measures are in place.

Mathematically the S,E,I,R components are modelled as fractions of the population, initially susceptible to the virus. Subsequently, we solve the following differential equations starting from initial values for S=1-1/N,E=1/N and setting I,R to 0. N is ratio of population size and exposed persons introduced at the start of the simulation. The initial day of introduction of the virus is at least 10-20 days prior to the first registered case, and the density of the virus per N is varied to obtain a first order fit with the observed number of registered infections, hospitalized, death. The simulation can incorporate stages of containment by contact tracing and quarantine, uncontrolled outbreaks and government measures to restrict community transmission, at specified times in the simulation. We adopted discrete values for various stages of control as listed in Table 2.

The differential model is formulated as follows :

$$S' = -\big(1-\alpha(t)\big)\beta(t)SI$$
$$E' = \big(1-\alpha(t)\big)\beta(t)SI - \sigma E$$
$$I' = \sigma E - \gamma I$$
$$R' = \gamma I$$

Table 1 default parameters for the SEIR model

Parameter	Value	Unit	Description
m	0.9	-	Fraction of total population Susceptible to COVID-19[3]
β	1.75	day^{-1}	Transfer coefficient
σ	0.2	day^{-1}	Incubation time of 5 days (source WHO)
γ	0.5	day^{-1}	Removal rate of infected people in self quarantine
delayREC	12	days	Days required for recovery of mild cases (guidelines WHO for reporting)
delayHOS	5	days	Days of illness before hospitalization[16]
delayHOSREC	14	days	Days of hospitalization for recoverable cases[3]
delayHOSD	3	days	Days of hospitalization for death cases (estimated from data fit)
h	0.05		Fraction of hospitalized cases (source: estimated from under-registration and data)
d	0.22		Mortality of hospitalized cases
ICfrac	0.33-0.5		Fraction of hospitalized patients in need for IC treatment (fitted on reported rates from hospitalization and ICU of past five days)

Table 2 stages of the development of the outbreak

$\alpha(t)$value	Stage	Effect on daily rate of infections
>0.8	Containment (Lockdown)	Active reduction
0.6–0.8	Control	Arrest growth
<0.6	'Limited' (uncontrolled) growth	Slow down growth
0.6–0.9	Contact tracing & quarantine	Very limited growth, or containment

Calibration and Forecasting

For Calibration and forecasting we use two ensemble based approaches: the Log Likelyhood approach and the Esemble smoother. The Log likelihood method performs well at the start when the measures are not having a large effect on the ICU growth yet, whereas the ensemble smoother is well capable to calibrate $\alpha(t)$.

To calibrate the model, we define a prior distribution for all model parameters of interest, assuming all parameters to be independent (i.e. we do not define a prior covariance). We apply a Monte Carlo approach, randomly sampling from each distribution, and running the model repeatedly in multiple forward model runs. In principle, any variable can be modified, but in practice we vary mostly N and β with uniform distributions at the onset of the outbreak, when measures are not yet active, and at later stages main focus is towards calibration of $\alpha(t)$.

In the Netherlands, for the forecasts March 21, the measures were taken too recently to have an effect on the number of hospitalizations or deaths, due to the delay between infection and the development of symptoms, therefore for these forecasts we used the Log likelihood approach. However, for the forecasts made March 27, we used the ensemble smoother.

Log likelihood approach

Model calibration:

Each run is assigned a performance score (i.e. a posterior probability) by comparing the model results to the observed data (hospitalized cases or deaths) in a log-likelihood function:

$$\ell = \sum_{i=1}^{N_{obs}} \log \lambda_i - N_{modelled}$$

where Nobs is the observed number of data points, λ_i is the modelled rate (of hospitalization (ICU usage) or death) at day i occurring, and $N_{modelled}$ is the total number of days modelled over the calibration period. This function is based on Poissonian probability, and implicitly assumes that cases are independent. This is justified since although the underlying cause (the spread of a viral infection) makes cases of COVID-19 highly dependent, the occurrence of individual events (hospitalization or death) is independent (i.e. the death of person A does not affect the death of person B). Note that this assumption is only valid in a properly functioning healthcare system, which is not overloaded.

Forecasting:

For forecasting, we select the model with the best performance over the calibration period up to the "present day". We then account for uncertainty in the effectiveness of mitigation measures by Monte Carlo sampling a value for from the prior range. This leads to a divergence of the models after the time at which mitigation measures take effect.

Ensemble Smoother

For data assimilation of all parameters in conjuction with calibration of $\alpha(t)$, we use the Ensemble Smoother with Multiple Data Assimilation (ES-MDA) which is a computationally efficient method for ensembles of non-linear forward models[17]. The data assimilation is performed by matching modeled hospitalization or ICU usage to reported usage. We assumed a value of 5 for the error standard deviation in reported bed count.

Model Calibration to data of China, South Korea and Lombardy (Italy)

Figure 7 shows the log likelihood calibration results for China, South Korea, and Italy. China is marked by a relatively long period of free spreading of the COVID-19 prior to the discovery of the spread end of January 2020[2]. In the following week, the government imposed very stringent containment measures, through a lockdown, which proved effective[3]. In South Korea, after a period of successful contact tracing and quarantine of imported cases starting January 20, 2020, an outbreak occurred most likely around day 8 through members of the Shincheonji Church of Jesus travelling around the country, which went undetected. After 3 weeks authorities got alarmed by rising numbers of positive tests and subsequently aggressive measures were taken. Massive testing contact tracing and quarantine has successfully helped in containment of the virus[18]. For Italy, we focused on the data of the region of Lombardy in the beginning of March up to March 17. The Lombardy region initially managed to contain the virus in a limited area closed off from the remainder of the region, but eventually the virus started spreading through Lombardy, the North of Italy and the remainder of Italy. In response, progress measures have been taken in the North of Italy, closing schools end of February, prohibiting gathering of large groups on March 4 and finally on March 7 close to lockdown conditions for the whole of Italy in an attempt to arrest the outbreak.

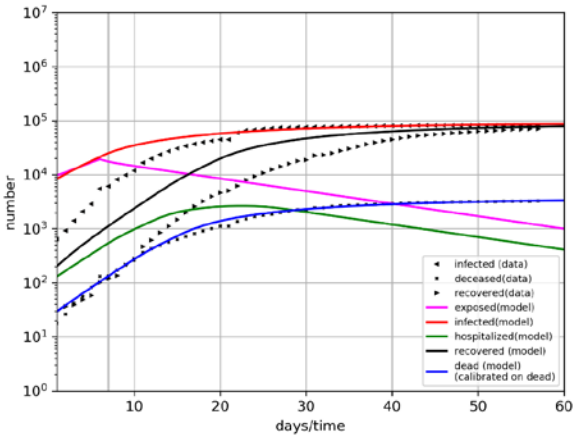
From the results of China in view of the close model fit of deaths and for Italy in view of numbers on both deaths and hospitalized patients, we can clearly see that transmissibility of COVID-19 behaves very similar in both tested regions. This can be inferred from the slope of increase in cumulative deaths (and patients) in the outbreak stage, which is consistent in all cases.

The adopted lag-times in the different outbreak centers between registered cases and deaths is in line with earlier findings of around 2 weeks between exposure to the virus and hospitalization[16]. Interestingly, we find a good fit with the data if most deaths appear to occur relatively early, compared to long term treatment of 2-3 weeks of critical patients in the ICU. This suggests that the long treatment time required to ICU patients with COVID-19 allows to use the steady rate increase in hospitalization and ICU usage as early warning for spreading.

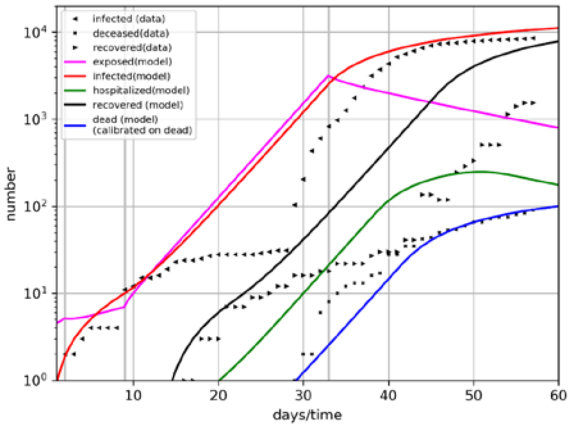
The model showed a very consistent fit with data sets from COVID-19 outbreaks in different countries. The best fit β value in all model runs which are very close to the value of 1.75 listed in Table 2 in the appendix. This is a relatively high value, suggesting an Aggregated Reproduction number (R_0^A) of 3.5 ($\beta = R_0^A * \gamma$), which is significantly higher than estimates of R_0 made at the early stages of the COVID-19 outbreak in Wuhan[9]. This suggests a significant spread due to asymptomatic infected persons or indirect infections. The Aggregated Reproduction number is in perfect agreement with doubling times of registered infections and hospitalization which can be as short as two to four days, and recent findings in literature on R_0[19]. The relatively high Aggregated R_0^A is very challenging in view of both managing to avoid collapse of the health care system and for controlling the outbreak.

The presented models highlight the strong variability in recorded death rates as a function of registered infections. Here we adopted circa 1% based of the South Korean data, but such numbers are subject to discussion, as the gender and age group in Korea has been different from other country average, as most cases were related to the Shincheonji Church of Jesus.

a) China



b) South Korea



c) Lombardy (Italy)

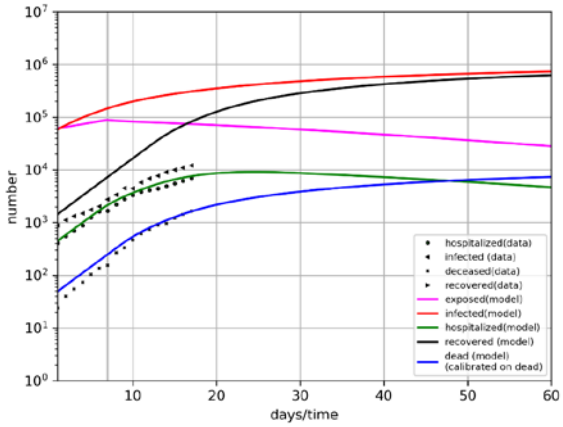


Figure 7 Best fit models calibrated on death cases for (a) China and (b) South Korea, and (c) Italy-Lombardy. Starting day in China and Republic of Korea is registration of first COVID-19 infections in the Johns Hopkins repository[8], which is respectively January 20 and 22. The grey vertical lines are the transitions of different values of $\alpha(t)$ starting from t=0 at the starting day in the graphs: China $\alpha(t)$ = {0.5,0.85} after days {1,7}; South Korea $\alpha(t)$ = {0.6,0,0.85} after days {2,8,33}; Italy $\alpha(t)$ = {0.7,0.85} after days {0,7}. The modelled infected and exposed have been scaled to observed death rates to the reference death rate of 1.1%. Please note that most of the observed recoveries are 14 days after testing, as according to WHO registered cases with mild symptoms can be considered recovered at that time. The best fit curves represent mean values of normal distributions marked by a standard deviation equal to the square root of the modelled value.