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Estimating the effects of non-pharmaceutical interventions on **COVID-19 in Europe**

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Following the emergence of a novel coronavirus¹ (SARS-CoV-2) and its spread outside of China, Europe has experienced large epidemics. In response, many European countries have implemented unprecedented non-pharmaceutical interventions such as closure of schools and national lockdowns. We study the impact of major interventions across 11 European countries for the period from the start of COVID-19 until the 4th of May 2020 when lockdowns started to be lifted. Our model calculates backwards from observed deaths to estimate transmission that occurred several weeks prior, allowing for the time lag between infection and death. We use partial pooling of information between countries with both individual and shared effects on the reproduction number. Pooling allows more information to be used, helps overcome data idiosyncrasies, and enables more timely estimates. Our model relies on fixed estimates of some epidemiological parameters such as the infection fatality rate, does not include importation or subnational variation and assumes that changes in the reproduction number are an immediate response to interventions rather than gradual changes in behavior. Amidst the ongoing pandemic, we rely on death data that is incomplete, with systematic biases in reporting, and subject to future consolidation. We estimate that, for all the countries we consider, current interventions have been sufficient to drive the reproduction number R_t below 1 (probability R_t < 1.0 is 99.9%) and achieve epidemic control. We estimate that, across all 11 countries, between 12 and 15 million individuals have been infected with SARS-CoV-2 up to 4th May, representing between 3.2% and 4.0% of the population. Our results show that major non-pharmaceutical interventions and lockdown in particular have had a large effect on reducing transmission. Continued intervention should be considered to keep transmission of SARS-CoV-2 under control.

Following the identification of a novel coronavirus (SARS-CoV-2) in Wuhan, China in December 2019 and its global spread, large epidemics of the disease, COVID-19, have ensued in Europe. In response to the rising numbers of cases and deaths, and to preserve health systems, European countries, like those in Asia, have implemented measures to control their epidemics. These large-scale non-pharmaceutical interventions vary between countries but include social distancing (such as banning large gatherings), border closures, school closures, measures to isolate symptomatic individuals and their contacts, and large-scale lockdowns of populations with all but essential internal travel banned. Understanding firstly, whether these interventions have

had the desired impact of controlling the epidemic and secondly, which interventions are necessary to maintain control, is critical given their large economic and social costs. The key aim of these interventions is to reduce the effective reproduction number, R_t , of the infection, a fundamental epidemiological quantity representing the average number of infections generated, at time t, by each infected case over the course of their infection.

In China, strict movement restrictions and other measures including case isolation and quarantine began to be introduced from 23rd January, which achieved a downward trend in the number of confirmed new cases during February, resulting in zero new confirmed indigenous

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cases in Wuhan by March 19th. Studies have estimated how R, changed during this time in different areas of China from around 2-4 during the uncontrolled epidemic down to below 1, with an estimated 7-9 fold decrease in the number of daily contacts per person.^{1,2}

Estimating reproduction numbers for SARS-CoV-2 presents challenges due to the high proportion of infections not detected by health systems^{1,3,4} and regular changes in testing policies, resulting in different proportions of infections being detected over time and between countries. Most countries initially only had capacity to test a small proportion of suspected cases, reserving tests for severely ill patients or for high-risk groups (e.g. contacts of cases).

An alternative way to estimate the course of the epidemic is to back-calculate infections from observed deaths. We introduce a novel Bayesian mechanistic model of the infection cycle to observed deaths inferring the total populations infected (attack rates) and the reproduction number over time (R_t) . We assess whether there is evidence that interventions have so far been successful at reducing R_t below 1. We simulate a hypothetical counterfactual scenario where reproduction number remains at starting levels to estimate the deaths that would have occurred without interventions.

Reported deaths are likely to be far more reliable than case data, although this data still has limitations. First, early deaths attributable to COVID-19 may have been missed. Second, there is variation in reporting of deaths by country and over time. Third, reporting delays are expected and be both systematic and random in nature. We attempt to overcome these data limitations by using a consolidated data source, incorporating noise in our observational model, by partial pooling of information between countries, and by performing a sensitivity analysis under scenarios of underreporting to test our conclusions (see Supplementary Material).

Our model relies on fixed estimates of some epidemiological parameters such as the onset to death distribution, the infection fatality rate and the generation distribution based on previous work, and we perform a sensitivity analysis on these parameters. Our parametric form of R_t assumes that changes in the reproduction number are an immediate response to interventions rather than gradual changes in behavior and does not include importation or subnational variation. We make the strong assumption that individual interventions have a similar impact in different countries and that the efficacy of those interventions remains constant over time. Our framework infers R, from mortality data while accounting for time lags since infections occurred. As a result, even with perfect data and partial pooling, we cannot perfectly predict current R_t . However, the credible intervals on R_t show the self-consistent behaviour that is a hallmark of a fully Bayesian analysis throughout the entire period we study, exhibiting appropriate shrinkage as more data becomes available (see Supplementary Videos 1-3).

Italy was the first European country to begin major NPI measures, and other countries followed soon afterwards (Extended Data Figure 4). The onset of interventions ranged between 2nd-29th March. We analyzed data on mortality from COVID-19 in 11 European countries up until the 4th May when lockdowns were relaxed in Italy and Spain. For each country, we model the number of infections, the number of deaths, and R_t (Figure 1). R_t is modelled as a piecewise constant function that changes only when an intervention occurs. Each country has its own individual starting reproduction number R_t before interventions take place. For all countries, interventions are assumed to have the same relative impact on R_t and are informed by mortality data across all countries. The only exception is that we use partial pooling to introduce country-specific effects of the effectiveness of the last intervention in a country, which is usually the lockdown.

Estimated true numbers of infections and current attack rates

In all countries, we estimate there are orders of magnitude fewer infections detected (Figure 1, Extended Data Figure 1, Extended Data Figure 2) than true infections, most likely due to mild and asymptomatic infections as well as limited testing capacity and changes in testing policy. In Italy, our results suggest that, cumulatively, 2.8 [2.2-3.5] million people have been infected as of May 4th, giving an attack rate of 4.6% [3.6%-5.8%] of the population (Table 1). In Spain, which has also experienced a large number of deaths we estimate 5.5% of the population (2.6 [2.1-3.3] million people) have been infected to date. Germany, the most populous country in our study, is estimated to have one of the lowest attack rates at 0.85% with 710,000 [550,000-930,000] people infected. Belgium has the highest estimated attack rates of 8% followed by Spain with 5.5%. While there have still been few reliable national serological studies⁵, initial small scale surveys in Austria⁶ and Denmark⁷ are closely aligned with our estimates. A much larger study in Spain is very closely aligned with our estimates⁸. These initial results, to some extent, validate our choice of infection fatality rate.

Averaged across all countries, we estimate initial reproduction numbers of around 3.8 [2.4-5.6], in line with other analyses. 1,9 These estimates are informed by our choice of generation interval distribution and the initial growth rate of observed deaths. A shorter assumed generation time results in lower starting reproduction numbers (Supplementary Discussion 3). The initial reproduction numbers are also uncertain due to (a) importation being the dominant source of new infections early in the epidemic, rather than local transmission (b) possible under-ascertainment in deaths particularly before testing became widespread. We perform sensitivity analysis around these parameters (Supplementary Discussions 10, 11).

We estimate large reductions in the reproduction number R_t in response to the combined non-pharmaceutical interventions. Our results, which are driven more by countries with advanced epidemics and larger numbers of deaths, suggest that these interventions have together had a substantial impact on transmission, as measured by changes in the estimated R_t . At the time of this study we find current estimates of R_t to range from a posterior mean of 0.44 [0.26 – 0.61] for Norway to a posterior mean of 0.82 [0.73 - 0.93] for Belgium, with an average of 0.66 across the 11 countries, an 82% reduction compared to the pre-intervention values. For all countries we find the current reproduction number significantly below 1. Overall, we can conclude that current interventions have been sufficient to drive the reproduction number R_t below 1 (probability $R_t < 1.0$ is 99.9% across all countries we consider) and achieve epidemic control. These conclusions are corroborated by individual country studies from a similar period see (France¹⁰, Spain¹¹, Germany¹² and the UK¹³), which arrive at very similar estimates despite different methodologies and data. For example Saljie et al 2020^{10} estimate an R_t of 0.67 (we estimate 0.68) for France using hospitalization records, and the Robert Koch Institute for Germany reports R_t of 0.76 (we estimate 0.71) using electronically notified cases¹². The retrospective stability of our model (see Supplementary Videos 1-3) is variable when the implementations of interventions are very dissimilar; an example of this is seen in Sweden, where interventions were dissimilar to other countries and led to large uncertainty initially. Our model uncertainty is also dependent on the magnitude of R_t ; this occurs because infections are a nonlinear function of R_t and are sensitive to small increases. Uncertainty shrinks greatly when R_t is reduced. Examples of this effect are seen in all countries but is most pronounced in Belgium and France which show large uncertainty in the number of infections in the early epidemic. Our choice of parameterizing R_t using piecewise constant functions means that we cannot capture fine scale variation that could be achieved by using additional covariates.

Lockdown has an identifiable large impact on transmission (81% [75% - 87%] reduction, see Figure 2). The close spacing of interventions in time (Extended Data Figure 4) mean the individual effects of the other interventions are not identifiable (Figure 2). Our partial pooling model requires only one country to provide a signal for the impact of a given intervention, and then this effect is shared across all countries. While this sharing can potentially lead to initial over/under estimation of intervention impact, it also means that a consistent signal for all countries can be estimated before that signal is presented in an individual countries data¹⁵. Therefore, this sharing is potentially useful for early warning by leveraging what happens in other countries with older data to inform those with newer data.

Estimated impact of interventions on deaths

Extended Data Table 1 shows total forecasted deaths since the beginning of the epidemic up to and including 4th May under our fitted model and under the counterfactual model, which predicts what would have happened if no interventions were implemented (and $R_t = R_0$ i.e. the initial reproduction number estimated before interventions).

By comparing the deaths predicted under the model with no interventions to the deaths predicted in our intervention model, we calculated the total deaths averted in our study period. We find that, across 11 countries, since the beginning of the epidemic, 3,100,000 [2,800,000 - 3,500,000] deaths have been averted due to interventions (see Extended Data Figure 5 comparing the actual total deaths to the counterfactual). The counterfactual model without interventions is illustrative only and reflects our model assumptions. We do not account for changes in behavior; in reality even in the absence of government interventions we would expect R_r to decrease and therefore would overestimate deaths in the no-intervention model. Conversely, we do not consider the impact on the infection fatality rate as a result of an overwhelmed health system in which patients may not be able to access critical care facilities, which would underestimate the number of counterfactual deaths. In the Supplementary Material we show counterfactuals under differing assumptions of the generation distribution and onset-to-death distribution and all scenarios broadly show the same trends. Given this agreement in differing scenarios we believe our estimates for the counterfactual deaths averted to be plausible.

Discussion

During ongoing transmission of coronavirus in Europe, we analyze trends in numbers of deaths to assess the extent to which transmission has been reduced. Representing the COVID-19 infection process using a semi-mechanistic, joint, Bayesian hierarchical model, we can reproduce trends observed in the data on deaths and produce empirically driven predictions which are valid over short time horizons.

We estimate that there have been many more infections than are currently reported. The high level of under-ascertainment of infections that we estimate here is likely due to the focus on testing in hospital settings which misses milder or asymptomatic cases in the community. Despite this, we estimate that only a relatively small minority of individuals in each country have been infected (Table 1). Our estimates imply that the populations in Europe are not close to herd immunity $(70\% \text{ if } R_0 \text{ is } 3.8^{14})$. Further, with R_t values below 1 in all countries, the rate of acquisition of herd immunity will slow down rapidly. Our estimates for attack rates during our study period are in line with those reported from national serological studies⁵. Similarly, comparable studies estimating R_t all agree that that the number as of 4^{th} of May 2020 is less than 1.

Our modelling approach is unique in pooling information from multiple countries at once. Using this approach means we require a central consolidated data source (such as ECDC data) and it also means that trends in some countries will be affected by those with more data. We argue that this effect is beneficial in that it helps minimise idiosyncrasies in the data¹⁵, as well as improve consistency of estimates over time. Whilst our qualitative conclusions surrounding impact of interventions and the value of Rt under control are robust to our choice of whether to incorporate pooling or not, the ability to utilise a greater extent of available data and share information across countries in a statistically principled manner dramatically improves the consistency of model predictions across the study period (see Videos 1-3 in the Supplementary Material).

Most interventions were implemented in rapid succession in many countries, and as such it is difficult to disentangle individual effect sizes of each intervention. In our analysis we find that only the effect of lockdown is identifiable, and that it has a substantial effect (81% [75% - 87%] reduction in Rt). Even when we allow lockdowns to have fully independent effect sizes in different countries in our model, effects remain large across all countries in this study (Figure 3.4).

We acknowledge limitations of existing COVID-19 mortality data, in particular deaths outside hospitals may go underreported. However, by using the ECDC data we rely on a comprehensive data source refined and updated each day by a systematic process. Our sensitivity analysis on underreporting and statistical measurement noise identifies that we may slightly underestimate the attack rates in some countries, but this does not change our overall conclusions on R_t . However, even if the data were complete, our method cannot surmount the time lag between infections and deaths and can only fully identify trends in infections 2-3 weeks before. Extensions of our model could use case, hospitalization or intensive care data, but reconciling the different biases inherent in these sources while ensuring parsimony is challenging and would require additional strong assumptions.

Modern understanding of infectious disease with a global publicized response has meant that nationwide interventions could be implemented with widespread adherence and support. Given observed infection fatality ratios and the epidemiology of COVID-19, major non-pharmaceutical interventions have had an impact in reducing transmission in all the countries we have observed. In all countries in this study we find that these interventions have reduced the reproduction number below one and have contained their epidemics at the current time. When looking at simplistic counterfactuals over the whole epidemic the number of potential deaths averted is substantial. We cannot say for certain that the current measures will continue to control the epidemic in Europe; however, if current trends continue, there is reason for optimism.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information. acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-020-2405-7.

- Li, R. et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2). Science (2020) https://doi.org/10.1126/science. abb3221.
- Zhang, J. et al. Patterns of human social contact and contact with animals in Shanghai. China, Sci. Rep. 9, 1-11 (2019).
- Zhao, A. J. et al. Title: Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019 Brief Title: Antibody responses in COVID-19 patients. (2020).
- Jombart, T, et al. Inferring the number of COVID-19 cases from recently reported deaths. medRxiv 2020.03.10.20033761 (2020) https://doi.org/10.1101/2020.03.10.20033761
- Bobrovitz, N. et al. Lessons from a rapid systematic review of early SARS-CoV-2 serosurveys, medRxiv (2020) https://doi.org/10.1101/2020.05.10.20097451.
- Austria, S. COVID-19 prevalence study: maximum 0.15% of Austrian population infected with SARS-CoV-2. (2020).
- Erikstrup, C. et al. Estimation of SARS-CoV-2 infection fatality rate by real-time antibody screening of blood donors. medRxiv (2020) https://doi.org/10.1101/2020.04.24.20075291.
- Estudio ENE-Covid19: Primera Ronda Estudio Nacional de Sero-Epidemiologica de la Infeccion por SARS-COV-2 en Espana. (2020).
- Zhang, J. et al. Age profile of susceptibility, mixing, and social distancing shape the dynamics of the novel coronavirus disease 2019 outbreak in China. (2020) https://doi.org /10.1101/2020.03.19.20039107
- Salje, H. et al. Estimating the burden of SARS-CoV-2 in France. Science (2020) https://doi.
- Hyafil, A. & Morina, D. Analysis of the impact of lockdown on the evolution Covid-19 epidemics in Spain. medRxiv (2020) https://doi.org/10.1101/2020.04.18.20070862.
- Institut, R. K. Coronavirus Disease 2019 (COVID-19) Daily Situation Report of the Robert Koch Institute. (2020).

- Davies, N. G., Kucharski, A. J., Eggo, R. M., Gimma, A. & Edmunds, W. J. The effect of non-pharmaceutical interventions on COVID-19 cases, deaths and demand for hospital services in the UK: a modelling study. medRxiv (2020) https://doi.org/10.1101/2020.04.01. 20049908.
- Miller, J. C. A Note on the Derivation of Epidemic Final Sizes. Bull. Math. Biol. 74, 2125–2141 (2012)
- Gelman, A. & Hill, J. Data analysis using regression and multilevel/hierarchical models. (Cambridge university press, 2006).

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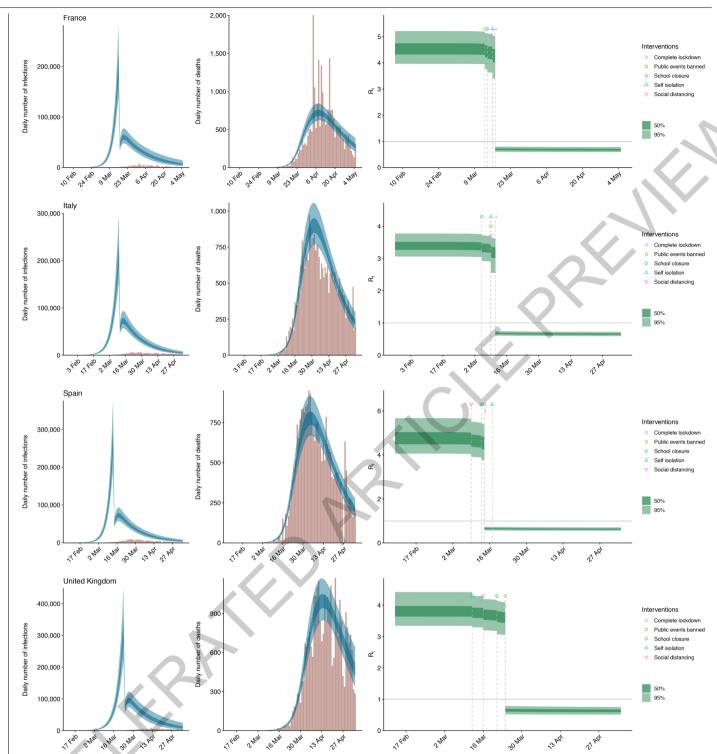
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 $Fig. 1 | Country-level \, estimates \, of \, in fections, \, deaths \, and \, R_t for \, France, \,$ Italy, Spain and UK. Left: daily number of infections, brown bars are reported infections, blue bands are predicted infections, dark blue 50% credible interval (CI), light blue 95% CI. The number of daily infections estimated by our model drops immediately after an intervention, as we assume that all infected $people \, become \, immediately \, less \, infectious \, through \, the \, intervention.$

 $Afterwards, if the \, R_t is above \, 1, the \, number \, of infections \, will \, start \, growing \,$ again. Middle: daily number of deaths, brown bars are reported deaths, blue bands are predicted deaths, CI as in left plot. Right: time-varying reproduction number R_t, dark green 50% CI, light green 95% CI. Icons are interventions shown at the time they occurred.

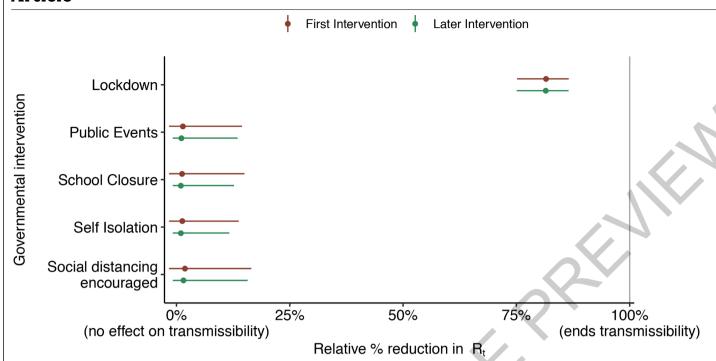


Fig. 2 | Effectiveness of interventions on R_t . Our model includes five covariates for governmental interventions, adjusting for whether the intervention was the first one undertaken by the government in response to COVID-19 (red) or was subsequent to other interventions (green). Mean relative percentage reduction in R_t is shown with 95% posterior credible intervals. If 100% reduction is achieved, $R_t = 0$ and there is no more

transmission of COVID-19. Lockdown is significantly different from the other interventions; the other interventions are not significantly different from each other, probably due to the fact that many interventions occurred on the same $day \, or \, within \, days \, of \, each \, other \, as \, shown \, in \, Extended \, Data \, Figure \, 4. \, Results \, are \,$ $derived from a model \, representing \, 11 \, countries \, with a \, total \, population \, of \, 375 \,$ million with 128,928 reported COVID-19-related deaths up to 4th May 2020.

Table 1 | Total population infected by county

Country	% of total population infected (mean [95% credible interval])
Austria	0.76% [0.59% - 0.98%]
Belgium	8% [6.1% - 11%]
Denmark	1.0% [0.81% - 1.4%]
France	3.4% [2.7% - 4.3%]
Germany	0.85% [0.66% - 1.1%]
Italy	4.6% [3.6% - 5.8%]
Norway	0.46% [0.34% - 0.61%]
Spain	5.5% [4.4% - 7.0%]
Sweden	3.7% [2.8% - 5.1%]
Switzerland	1.9% [1.5% - 2.4%]
United Kingdom	5.1% [4.0% - 6.5%]

 $Posterior\ model\ estimates\ of\ the\ attack\ rate\ by\ country\ (percentage\ of\ total\ population$ infected) as of 4th May 2020. Results are derived from a model representing 11 countries with a total population of 375 million with 128,928 reported COVID-19-related deaths up to 4th May

Methods

Data

Our model utilizes daily consolidated death data from the ECDC (European Centre of Disease Control), for 11 European countries currently experiencing the epidemic: Austria, Belgium, Denmark, France, Germany, Italy, Norway, Spain, Sweden, Switzerland and the United Kingdom. The ECDC provides information on confirmed cases and deaths attributable to COVID-19. For population counts, we use UNPOP age-stratified counts. ¹⁶

We also catalogue data on the nature and type of major non-pharmaceutical interventions. We looked at the government webpages from each country as well as their official public health division/information webpages to identify the latest advice/laws being issued by the government and public health authorities. We collected the following: School closure ordered, case-based measures, public events banned, social distancing encouraged, lock down decreed, and the time of the first and last intervention. A full list of the timing of these interventions and the sources we have used can be found in Supplementary Notes and in Supplementary Table 2.

By using the ECDC data we rely on a consolidated data source undertaken by ECDC, who inloude many sources of data each day, constantly refining and updating data using a comprehensive and systematic process. However, despite the rigorous protocols, countries may still vary in the specifics of the data that they report to the ECDC. For example, there is variation in reporting (i.e. community vs hospital) and time lags. Despite these issues, we use ECDC data to ensure as much consistency across all countries as possible.

Model

A visual summary of our model is presented in Extended Data Figure 3 (details in Supplementary Methods). Replication code is available at https://github.com/ImperialCollegeLondon/covid19model/

We fit our model to observed deaths according to ECDC data from 11 European countries. The modelled deaths are informed by an infection-to-death distribution (Supplementary Fig. 1, derived from assumption about the time from infection to the onset of symptoms and about the time from the onset of symptoms to death), and the population-averaged infection fatality ratio (adjusted for the age structure and contact patterns of each country, see Supplementary Methods and Supplementary Table 3).

Given these distributions and ratios, modelled deaths are a function of the number of infections. The number of infections is modelled as the product of the effective reproduction number (R_t) with a discrete convolution of the previous infections. Individual components of this convolution sum are weighted by the generation time distribution (the average time from infection of one person to the time at which they infect another, Supplementary Fig. 2). In our work we approximate the generation time distribution using the serial interval distribution. The time-varying reproduction number is a function of the initial reproduction number before interventions and the effect sizes from interventions, where interventions are modelled as piecewise constant functions

Following the Bayesian hierarchy from bottom to top gives us a full framework to see how interventions affect infections, which can result in deaths. A schematic description of our model is shown in Extended Data Figure 3. To maximize the ability to observe intervention impact on deaths, we fit our model jointly for all 11 European countries, and use partial pooling of information between countries with both individual and shared effects on R_t . Partial pooling operates on the last intervention, which is in most cases lockdown. The effect of partial pooling can be seen in Supplementary Discussion 12 and in Supplementary Figure 29. We chose a balanced prior that encodes the prior belief that interventions have an equal chance of having an impact or not and ensure a uniform prior on the joint effect of all interventions

(Supplementary Fig. 3). We evaluate the effect of our Bayesian prior distribution choices and evaluate our Bayesian posterior calibration to ensure our results are statistically robust.

We perform extensive model validation and sensitivity analyses. We validate our model by cross-validation over a 14-day period (Supplementary Discussion 1, Supplementary Table 1) and we show the fits for hold out samples in Supplementary Figs. 5-15. We check the convergence of the MCMC sampler (Supplementary Fig. 4). We consider the sensitivity of our estimates of the reproduction numbers to the mean of the generation distribution (Supplementary Discussion 3, Supplementary Figs. 16, 17). We further show that the choice of generation distribution does not change our counterfactual conclusions (Supplementary Fig. 18). Using univariate analyses and uninformative priors, we find (Supplementary Fig. 19) that all effects on their own serve to decrease R_t (Supplementary Discussion 4). We compare our model to a non-parametric Gaussian model (Supplementary Discussion 5). To assess the effect of individual countries on the results, we perform a "leave one country out" sensitivity analysis (Supplementary Discussion 6, Supplementary Figs. 20, 21). To validate our starting reproduction numbers, we compare our model against an exponential growth linear model (Supplementary Discussion 7, Supplementary Fig. 22). Instead of a joint analysis, we consider fits of our model to individual countries (Supplementary Discussion 8, Supplementary Figs. 23-26). We perform a sensitivity analysis with respect to the onset-to-death distribution (Supplementary Discussion 9, Supplementary Fig 27). We validate our probabilistic seeding scheme through an importance-sampling leave-one-out cross-validation (Supplementary Discussion 10). We consider a model extension with a constant, probabilistic under-reporting (Supplementary Discussion 11), finding that reproduction numbers do not change substantially (Supplementary Fig. 28).

Our model is different to other approaches employing the discrete renewal equation such as EpiEstim¹⁷. We employ the renewal equation as a latent process to model infections and propose a generative mechanism to connect these infections to death data. Simply applying the renewal equation directly to death data requires a challenging mechanism where deaths in the past can cause future deaths (see for example¹⁸). In addition, for R_t , we are able to use a functional relationship where non pharmaceutical interventions can have a direct effect on R_t .

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this paper.

Data availability

Death counts for the 11 European countries for the time period in our study and the full set of posterior draws from our model are available at https://reshare.ukdataservice.ac.uk/cgi/users/home?screen=EPrint::View&eprintid=854380.

Code availability

All source code and data necessary for the replication of our results and figures is available at https://github.com/ImperialCollegeLondon/covid19model.

- United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects 2019: Data Booket. ST/ESA/SER.A/424. (2019).
- Cori, A., Ferguson, N. M., Fraser, C. & Cauchemez, S. A New Framework and Software to Estimate Time-Varying Reproduction Numbers During Epidemics. Am. J. Epidemiol. 178, 1505–1512 (2013).
- Goldstein, E. et al. Reconstructing influenza incidence by deconvolution of daily mortality time series. Proc. Natl. Acad. Sci. 106, 21825–21829 (2009).

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Author contributions SB, SF, SM and AG conceived and designed the study. SB, SF, SM, AG, HC, HJTU, TM, MC, JE, NF performed analysis. LO, SB, SF, AG, CD, SR and

NF wrote the first draft of the paper. SB, SF, HC, CW, PW, TB, PNPG, NS, LC, MV, HC collected data. All authors discussed the results and contributed to the revision of the final manuscript.

Competing interests The authors declare no competing interests.

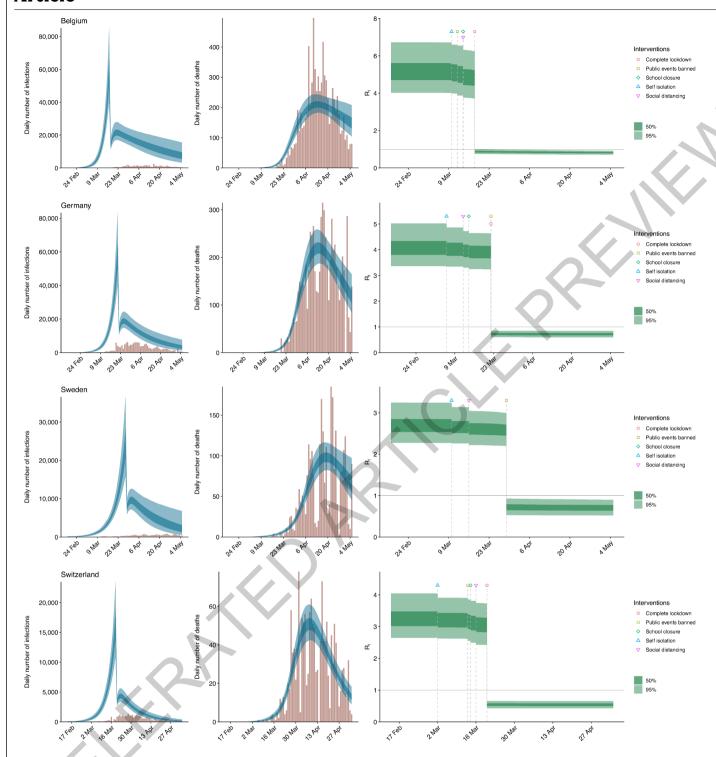
Additional information

Supplementary information is available for this paper at https://doi.org/10.1038/s41586-020-2405-7.

Correspondence and requests for materials should be addressed to S.B.

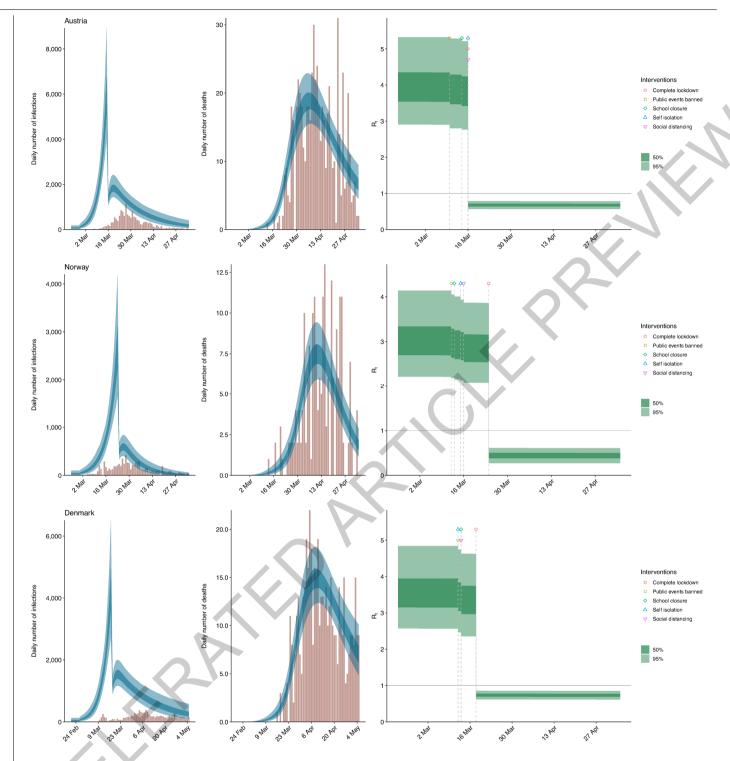
Peer review information Nature thanks David Earn and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available.

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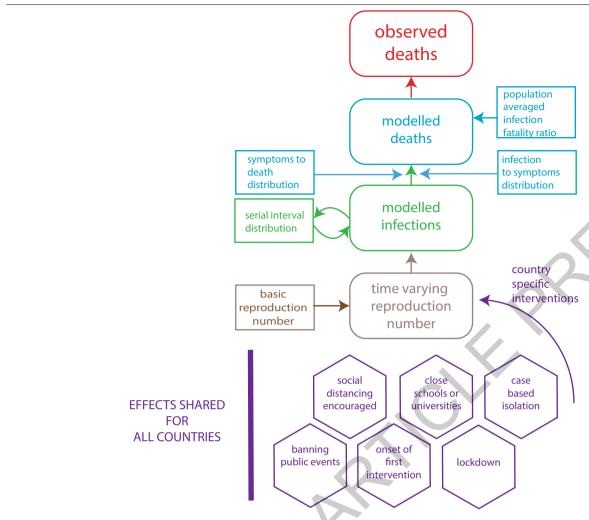
 $\label{lem:extended Data Fig. 1 | Country-level estimates of infections, deaths and R_t for Belgium, Germany, Sweden and Switzerland. Left: daily number of infections, brown bars are reported infections, blue bands are predicted infections, dark blue 50% credible interval (CI), light blue 95% CI. The number of daily infections estimated by our model drops immediately after an intervention, as we assume that all infected people become immediately less$

infectious through the intervention. Afterwards, if the R_t is above 1, the number of infections will starts growing again. Middle: daily number of deaths, brown bars are reported deaths, blue bands are predicted deaths, Clas in left plot. Right: time-varying reproduction number R_t , dark green 50% Cl, light green 95% Cl. Icons are interventions shown at the time they occurred.

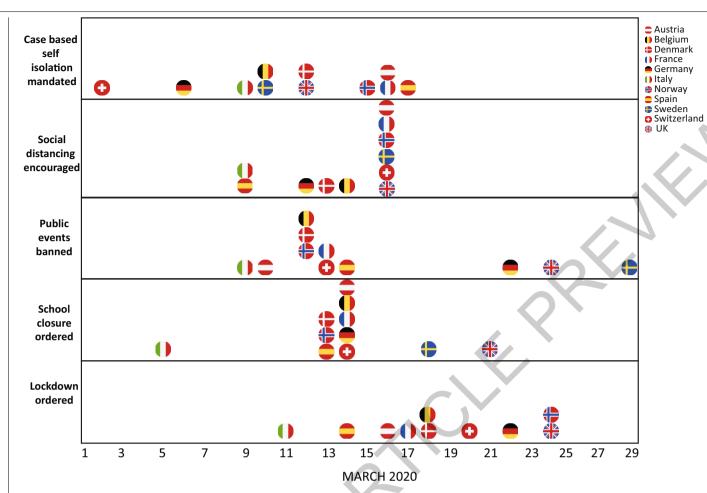


Extended Data Fig. 2 | Country-level estimates of infections, deaths and R_t for Austria, Sweden and Denmark. Left: daily number of infections, brown bars are reported infections, blue bands are predicted infections, dark blue 50% credible interval (CI), light blue 95% CI. The number of daily infections estimated by our model drops immediately after an intervention, as we assume that all infected people become immediately less infectious through the

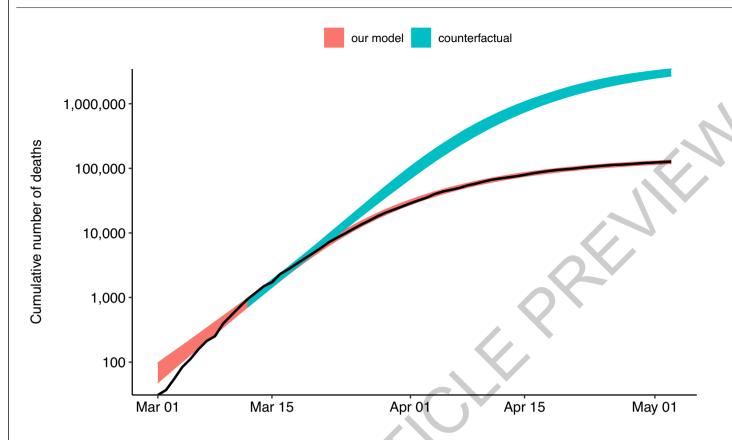
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 $Extended\,Data\,Fig.\,3\,|\,Summary\,of\,model\,components.$



 $\textbf{Extended Data Fig. 4} | \textbf{Intervention timings.} Intervention timings for the 11 European countries included in the analysis. For further details see the Supplementary Material.}$



Extended Data Fig. 5 | **Deaths averted due to interventions.** Lower and upper credible interval for cumulative number of deaths for 11 countries in Europe from our model with interventions (pink) and the no-interventions counterfactual model (blue). Reported deaths are shown as a thick black line.

Extended Data Table 1 | Total forecasted deaths since the beginning of the epidemic up to 4th May in our model and in a counterfactual model (assuming no intervention had taken place)

Forecasted deaths since the beginning of the epidemic up to 4th May in our model vs. a counterfactual model assuming no interventions had taken place

Country	Observed Deaths up to 4th May	Model estimated deaths up to 4th May	Model estimated deaths up to 4th May	Model deaths averted up to 4th May
Country	(observed)	(our model)	(counterfactual model assuming no interventions have occurred)	(difference between counterfactual and actual)
Austria	600	620 [520 - 720]	66,000 [40,000 - 86,000]	65,000 [40,000 - 85,000]
Belgium	7,924	7,300 [6,400 - 8,400]	120,000 [93,000 – 140,000]	110,000 [86,000 – 130,000]
Denmark	493	500 [430 - 590]	34,000 [17,000 - 50,000]	34,000 [17,000 - 49,000]
France	25,201	23,000 [21,000 - 27,000]	720,000 [590,000 - 850,000]	690,000 [570,000 - 820,000]
Germany	6,831	6,800 [6,000 - 7,900]	570,000 [370,000 - 780,000]	560,000 [370,000 - 770,000]
Italy	29,079	31,000 [27,000 - 35,000]	670,000 [540,000 - 800,000]	630,000 [510,000 - 760,000]
Norway	208	210 [170 - 250]	12,000 [3,400 - 24,000]	12,000 [3,200 - 23,000]
Spain	25,613	25,000 [22,000 - 28,000]	470,000 [390,000 - 560,000]	450,000 [360,000 – 540,000]
Sweden	2,769	2,800 [2,500 - 3,300]	28,000 [15,000 - 49,000]	26,000 [12,000 - 46,000]
Switzerland	1,476	1,500 [1,300 - 1,800]	54,000 [36,000 - 73,000]	52,000 [34,000 - 71,000]
United Kingdom	28,734	29,000 [25,000 - 34,000]	500,000 [400,000 - 610,000]	470,000 [370,000 – 580,000]
All	128,928	130,000 [120,000 - 140,000]	3,200,000 [2,900,000 - 3,600,000]	3,100,000 [2,800,000 - 3,500,000]

Estimated averted deaths over this time period as a result of the interventions. Numbers in brackets are 95% credible intervals.

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For	all statistical ar	nalyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.		
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	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)			
\boxtimes	For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>			
	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings			
	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes			
\boxtimes	\boxtimes Estimates of effect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated			
Our web collection on <u>statistics for biologists</u> contains articles on many of the points above.				
So	ftware an	d code		
Poli	cy information	about availability of computer code		
Da	ata collection	No such software was used		
Da	ata analysis	RStan version 2.19.3 was used within R version 3.6.3		
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- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data $% \left(1\right) =\left(1\right) \left(1\right) \left($
- A description of any restrictions on data availability

All source code and data necessary for the replication of our results is available at https://github.com/ImperialCollegeLondon/covid19model
The full set of posterior draws from our model are available at https://reshare.ukdataservice.ac.uk/cgi/users/home?screen=EPrint::View&eprintid=854380

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All studies must dis	sclose on these points even when t	the disclosure is negative.	
Sample size	No samples were collected; data on	the count of COVID-19-related deaths over time in 11 European countries was used.	
Data exclusions	No data was excluded.		
Replication	n/a		
Randomization			
Randomization	n/a		
Blinding	n/a		
Reportin	g for specific m	aterials, systems and methods	
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