Estimation of SARS-CoV-2 mortality during the early stages of an epidemic: a modelling study in Hubei, China and six areas of Europe

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**Background.** The epidemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that originated in Wuhan, China in late 2019 is now pandemic. Reliable estimates of mortality from SARS-CoV-2 infection are essential to guide control efforts and to plan health care system requirements. The objectives of this study are to: 1) simulate the transmission dynamics of SARS-CoV-2 using publicly available surveillance data; 2) infer estimates of SARS-CoV-2 symptomatic fatality rates (SFR) and infection fatality rates (IFR) adjusted for bias in the Hubei province of China and six areas of Europe: Austria, Bavaria (Germany), Baden-Württemberg (Germany), Lombardy (Italy), Spain and Switzerland.

**Method and Findings.** We developed an age-stratified susceptible-exposed-infected-removed (SEIR) compartmental model describing the dynamics of transmission and mortality during the SARS-CoV-2 epidemic. Our model accounts for two biases: preferential ascertainment of severe cases and delayed mortality (right-censoring). We fitted the transmission model to surveillance data from Hubei province, China and six regions in Europe. We found different estimates of IFR across regions, going from 0.5% (95% credible interval[CrI]: 0.4-0.6%) in Switzerland, to 2.9% (95%CrI: 2.4-3.5%) in Hubei province. Mortality increased with age; we estimate that among 80+ year olds infected with SARS-CoV-2, a proportion ranging between 20% (95%CrI: 16-26%) in Switzerland and 34% (95%CrI: 28-40%) in Spain eventually die. Limitations are that the model requires count data by date of onset.

**Conclusions.** We developed a mechanistic approach to correct the crude case fatality rate (CFR) for bias due to right-censoring and preferential ascertainment of severe cases and provide adjusted estimates of SFR and IFR by age group. We find substantial heterogeneity in the outcomes of SARS-CoV-2 infection across settings. These findings will help the mitigation efforts and planning of long-term strategies for overcoming the SARS-CoV-2 epidemic.

# Author summary

# Introduction

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has resulted in more than 2,800,000 confirmed cases and 193,000 deaths, as of 26 April 2020 . The infection emerged in late 2019 as a cluster of cases of pneumonia of unknown origin in Wuhan, Hubei province . Considering the number of reported deaths, the largest outbreaks to date are now in the United States and Western Europe . The epidemic appears to have originated from multiple zoonotic transmission events of a coronavirus, with the animal source remaining unknown . The causal agent, SARS-CoV-2, was identified in January 2020 . The transmission characteristics of SARS-CoV-2 appear to be similar to those of the 1918 pandemic influenza strain , but, at this early stage, its mortality rate is still unknown. During the early phase of the pandemic, reliable estimates of overall mortality, i.e. the proportion of all people with SARS-CoV-2 infection who will die from the disease are needed to plan health care capacity and for epidemic forecasting. Clinicians need to know age- and sex-specific mortality among symptomatic patients seeking care to assess prognosis and, in severe situations, prioritize patients with the best expected outcomes.

The crude case fatality rate (CFR), the number of reported deaths divided by the number of reported cases at a specific time point, is not a reliable indicator of overall mortality . The crude CFR can be misleading if used to assess the overall mortality because of two opposing biases . First, because of the delay of several weeks between disease onset and death, the number of confirmed and reported deaths at a certain time point does not consider the total number of deaths that will occur among already infected individuals (right-censoring). Second, surveillance-based SARS-CoV-2 infection case reports underestimate the total number of SARS-CoV-2-infected patients, because testing focuses on symptomatic individuals, and, among symptomatic cases, on patients with more severe manifestations (preferential ascertainment). Alternative indicators such as the symptomatic fatality rate (SFR) and the infection fatality rate (IFR) are more valuable. The SFR corresponds to the proportion of infected individuals showing symptoms that die over the course of their SARS-CoV-2 infection , and is of particular interest to physicians in assessing the prognosis of their patients. The IFR is the proportion of all SARS-CoV-2 infections that will eventually die from the disease, and is a central indicator to public health professionals and policy-makers in evaluating the overall impact of an epidemic affecting a given population. It is often assumed that the crude CFR overestimates the IFR , but it depends on the relative influence of the two opposing biases, so it could differ in different situations.

Estimates of real time SFR and IFR will rely on surveillance data and require statistical adjustment because longitudinal studies of representative samples of individuals with SARS-CoV-2 infection will take too long. The objectives of this study are to: 1) simulate the dynamics of transmission and mortality of SARS-CoV-2 using publicly available surveillance data; 2) give corrected age-specific estimates of SARS-CoV-2 SFR and IFR in Hubei province (China) and six areas in Europe: Austria, Bavaria (Germany), Baden-Württemberg (Germany), Lombardy (Italy), Spain and Switzerland.

# Methods

## Setting and data, Hubei province, China

The first known case of SARS-CoV-2 infection has been traced back to December 1st, 2019 in Wuhan, the main city of the Hubei province of China . The first death was reported on 11 January 2020. Most early cases were linked to the Huanan Seafood Wholesale Market in Wuhan, which was closed on 1 January. From this point, human-to-human transmission of SARS-CoV-2 occurred at a high rate in Wuhan and other areas of Hubei, leading to exponential growth of the reported incidence of cases (Figure [fig:desc]A). On 20 January 2020, Chinese authorities implemented extensive control measures in Hubei: early identification and isolation of clinical cases, tracing and quarantining of contacts, temperature checks before accessing public areas, extension of the lunar new year holiday period, and extreme social distancing, including cancellation of mass gatherings . Three days later, a cordon sanitaire was imposed, with strict traffic restrictions. From 27 January, the daily incidence of cases, by date of disease onset, started to plateau, then decreased. The number of reported deaths started to increase after the increase in incidence, with a delay of a few weeks.

The Chinese Center for Disease Control and Prevention (China CDC) reported the number of cases by date of disease onset, and the age distribution of cases and deaths up 11 February 2020 in China (Figure [fig:desc]B) . We extracted these data, together with the age distribution of the Chinese population. Deaths counts were obtained from a repository aggregating data from Chinese public data sources . We used data about the daily number of potentially infectious contacts by age group in Shanghai . We extracted data about the age-specific prevalence of diabetes, chronic respiratory diseases, cardiovascular diseases and hypertension in China from the Institute for Health Metrics and Evaluation (IHME) website . We assumed that all data sources were applicable to the population of Hubei.

As of 11 February, after which information about date of disease onset was no longer available, there were 41,092 cases and 979 deaths; crude CFR 2.4%.

![(A) Reported number of confirmed cases of SARS-CoV-2 infection by date of disease onset in Hubei, China until 11 February 2020. (B) Age distribution of the Chinese population and of the reported cases and deaths in Hubei, China. (C) Reported number of deaths associated with SARS-CoV-2 infection in in Hubei, China until 11 February 2020. (D) Age-specific contact matrix from a 2018 survey conducted in Shanghai, China  that was applied to Hubei province.](data:application/pdf;base64,)

(A) Reported number of confirmed cases of SARS-CoV-2 infection by date of disease onset in Hubei, China until 11 February 2020. (B) Age distribution of the Chinese population and of the reported cases and deaths in Hubei, China. (C) Reported number of deaths associated with SARS-CoV-2 infection in in Hubei, China until 11 February 2020. (D) Age-specific contact matrix from a 2018 survey conducted in Shanghai, China that was applied to Hubei province.

## Setting and data, six areas in Europe

The first cases of SARS-CoV-2 infection in Europe have been reported at the end of January 2020. Italy was the first country in Europe affected by the epidemic, after a cluster of cases has emerged in Lombardy at the end of February. During this period, the first deaths due to SARS-CoV-2 infection were also observed in Italy. The outbreak then spread in all Europe. As of 6 May 2020, Europe is the continent having reported the highest number of cases and deaths (more than 1,500,000 cases and 147,000 deaths) .

We selected European countries that reported the daily number of cases of confirmed SARS-CoV-2 infection by date of symptom onset. In countries where this information was available at a regional level, we selected the regions that have been worst affected by the epidemic. We thus considered the following six areas: Austria, Bavaria (Germany), Baden-Württemberg (Germany), Lombardy (Italy), Spain and Switzerland. In addition to the number of cases by symptom onset, we also collected the daily number of deaths, and the distribution of cases and deaths across age classes for each of these six areas.

In Austria, we collected the number of daily cases and deaths from 11 March to 14 April, as well their age distribution, based on a report from the Austria authorities . On 14 April, they reported 14,151 cases (all assumed with date of onset) and 399 deaths, leading to a crude CFR of 2.8%. For the two German regions Baden-Württemberg and Bavaria, we used data collected by the Robert Koch Institute from 3 March to 16 April . Age distributions of cases and deaths were only available at the country level and were applied to both regions. As of 16 April, there were 31,196 cases (56% with date of onset) and 802 deaths in Baden-Württemberg and 36,538 cases (62% with date of onset) and 1,049 deaths in Bavaria; crude CFR 2.6% and 2.9% respectively. We collected data for Lombardy, Italy from reports from the Instituto Superiore di Sanita and the Dipartimento della Protezione Civile, from 11 February to 25 April . Age distribution of deaths were collected at the national level. As of 25 April, Lombardy has reported 74,346 cases (77% with date of onset) and 13,263 deaths; crude CFR 17.8%. We directly received data from Switzerland from the Federal Office of Public Health, from 2 March to 23 April . On this date, there were 33,228 cases (11% with date of onset) and 1302 deaths; crude CFR 3.9%. Finally, we used data from Spain from 2 March to 16 April, as reported by the Ministerio de Sanidad . On 16 April, 188,068 cases (79% with date of onset) and 19,478 deaths were reported; crude CFR 10.4%. Further details about the data sources are available in S1 Text, section 1.

## Age-structured model of SARS-CoV-2 transmission and mortality

We used an age-stratified susceptible-exposed-infected-removed (SEIR) compartmental model, with a distinction between incubating, pre-symptomatic, asymptomatic and symptomatic infections. We stratified the population into nine 10-year groups (0-9 up to 80+ years for all areas except Austria where the 9 age groups were 0-4, 5-14, up to 75+ years). We assumed that susceptibility to SARS-CoV-2 and the risk of acquisition per contact is identical for each age class. We assumed that transmission is possible during pre-symptomatic and asymptomatic infections. We used age-specific contact matrices to model contact patterns according to age class (contact matrix derived by Zhang et al. for Hubei , and the POLYMOD contact matrix for the six European areas ). In addition, we modelled the decrease in the transmission of SARS-CoV-2 due to the progressive implementation of control measures by using a logistic function for the transmission rate.

In the model, after an average incubation period of 5.0 days , 81% (95%CrI: 71-89) of infected people develop symptoms of any severity and become infectious, while the remainder are asymptomatic . The estimated proportion of symptomatic infections has been collected from a meta-analysis and is implemented as a beta distribution to propagate uncertainty . Studies that estimated the proportion of asymptomatics by age did not provide conclusive evidence of an age trend, so we assumed it to be constant across age groups . We assumed reduced infectiousness during the period of 2.3 days that precedes symptoms (pre-symptomatic compartment) and also among asymptomatic individuals .

The model was used to compute the number of symptomatic SARS-CoV-2 infections by day of disease onset in each age class. We applied an age-specific ascertainment proportion to the number of symptomatic infections to estimate the number of reported cases of SARS-CoV-2 infections by date of disease onset. To identify the parameters, we assumed that 100% of infected patients aged 80 years and older were reported. We assumed that mortality only occurred in symptomatic people, and that the time from disease onset to death followed a log-normal distribution with mean 20.2 days and standard deviation 11.6 . This allowed us to account for the deaths occurring after the date of data collection.

For each of the seven areas - Hubei and the six European areas - we simultaneously fitted our model to the data sets described above (Figure [fig:desc]): (1) the number of confirmed cases by day of disease onset, (2) the number of deaths by day of occurrence, (3) the age distribution of all confirmed cases and (4) the age distribution of all reported deaths. We assumed a negative binomial distribution for data (1) and (2), and a multinomial distribution for data (3) and (4). All parameters were estimated from data except for the incubation period, the generation time, the contribution of presymptomatics to SARS-CoV-2 infection, the presymptomatic duration and the time from disease onset to death.

The fitted model was used to produce estimates (median posterior distributions with 95% credible intervals, CrI) of the total number of symptomatic and pre-/a-symptomatic infections (corrected for preferential ascertainment) and of the total number of deaths (corrected for right-censoring), which were then transformed into adjusted estimates of SFR and IFR. Besides parameter values and model structure, these estimates rely on the following additional assumptions:

1. The severity of symptoms differs by age group and influences the probability of reporting;
2. All deaths due to SARS-CoV-2 infection have been identified and reported;
3. The susceptibility to SARS-CoV-2 infection is identical across age;
4. The average standard of care is stable between the period of interest and the following period of two months during which a proportion of the infected people will eventually die;
5. The ascertainment probability by age is constant over the periods considered.

## Sensitivity analysis

From 12 February, China authorities changed their criteria for counting diagnoses of the virus, leading to an artificial jump of more 25,000 new cases. Such a jump was also observed in reported deaths on 16 April, when Wuhan city revised its death toll by adding 1290 deaths. To investigate the impact of this later correction of both cases and deaths in Hubei province, we ran a sensitivity analysis with corrected numbers of cases and deaths. Additionally, we also examined the impact of a 50% lower susceptibility in children (0-19 years old) and a lower ascertainment proportion among 80+ year olds going from 10% to 90% (compared to a fixed proportion of 100% in the main analysis). We also ran the analysis with different dates of data collection (from 12 January to 11 February) to see how increasing data/evidence with time might impact the outputs. Additional sensitivity analyses are presented in S1 Text, section 5.

We implemented the model in a Bayesian framework using Stan . All code and data are available from . Further details about the method are available in S1 Text, section 2.

# Results

Our model accurately describes the dynamics of transmission and mortality by age group during the SARS-CoV-2 epidemic in Hubei from 1 January to 11 February 2020 (Figure [fig:fit]). The model predicts that control measures implemented from 20 January reduced SARS-CoV-2 transmissibility by 92% (95% credible interval [CrI]: 87-100), with a steep diminution in case incidence after 4.3 (95%CrI: 3.2-5.4) days. Assuming 100% of cases aged 80 and older were initially reported, we estimate that a total of 83,300 individuals (95%CrI: 73,000-98,600) were infected in Hubei between 1 January and 11 February 2020. Of these, the number of symptomatic cases is estimated at 67,000 (95%CrI: 60,500-73,600), 1.6 times (95%CrI: 1.5-1.8) more than the 41,092 reported cases during that period. Accounting for the later correction in the number of reported cases, the total number of infected increases to 138,000 (95%CrI: 120,000-162,000). The proportion of ascertained cases showed a clear age trend, from less than 9% (95%CrI: 8-10) under 20 years old to 93% (95%CrI: 88-98) in the age group 70-79 (it was assumed that the ascertainment proportion was 100% in the age group 80+, Figure [fig:sst]A).

The model predicts a total of 2,450 deaths (95%CrI: 2,230-2,700) among all people infected until 11 February in Hubei (compared with 979 deaths at this point without correcting for right-censoring). This results in an estimated IFR of 2.9% (95%CrI: 2.4-3.5, Table [table:country]). Assuming the later correction of deaths was evenly distributed, the total number of deaths increases to 3,430 (95%CrI: 3,120-3,760). When using the corrected numbers of cases and deaths, we derived an IFR of 2.5% (95%CrI: 2.1-2.9).

The SFR, more relevant to the clinical situation, is estimated to 3.7% (95%CrI: 3.2-4.2) and 3.1% (95%CrI: 2.7-3.6) after the later correction of reported cases and deaths by the local authorities of Hubei. Under 20 years of age, the SFR is estimated below 1 in 1,000 and rises to between 3 and 9 per 1,000 symptomatic infections for individuals aged 20 to 49 years. We estimate the SFR to 2.5% (95%CrI: 2.0-3.1) among individuals aged 50-59, 8.0% (95%CrI: 6.7-9.6) among individuals aged 60-69, 19.2% (95%CrI: 16.1-22.7) among individuals aged 70-79 and reaches 39.0% (95%CrI: 31.6-48.0) among individuals aged 80 and more.

We conducted several sensitivities analyses to assess the robustness of the results obtained for Hubei. First, the later correction of the number of reported cases (+65%) and deaths (+40%) in Hubei by the local authorities did not influence the ascertainment proportion (Figure [fig:sst]A) but led to a proportional decrease of the SFR and IFR estimates by 15% as expected from the correction applied (, Figure [fig:sst]B and Table [table:country]). Second, lowering the susceptibility of individuals aged 0-19 by 50% did not impact the estimates of the ascertainment proportion nor the SFR in other age groups (Figure [fig:sst]A and B). The decrease in the denominator led to a proportional increase of total SFR and IFR. Third, we relaxed the assumption that 100% of cases among individuals aged 80 and older (Figure [fig:sst]C). Lowering this assumption to 90% and down to 10% led to a proportional decrease of the SFR and IFR. Finally, the model was also refitted at different stages of the epidemic in Hubei between 12 January and 6 February (Figure [fig:sst]D). This analysis highlights the changing patterns in the observed mortality as the epidemic progresses, with an increase in the crude CFR estimate as delayed deaths are reported. It also suggests that our proposed approach for estimating the SFR and IFR is biased upwards before the peak of incidence is reached (around 27 January), and stabilizes afterwards. We conducted additional sensitivity analyses with various assumptions regarding the contribution of presymptomatic transmission, the susceptibility of children and the value of different delays that did not impact the results (S1 Text, section 5).

![Model fit for Hubei, China of (A) incident cases of SARS-CoV-2 infection by date of disease onset, (B) total cases, (C) age distribution of cases, (D) incidence of deaths, (E) total number of deaths among individuals infected until 11 February 2020 and (F) age distribution of deaths. White circles and bars represent data. Lines and shaded areas or points and ranges show the posterior median and 95% credible intervals for six types of model output: reported cases, symptomatic cases, overall cases (i.e. symptomatic and asymptomatic cases), reported deaths until 11 February 2020, projected deaths after 11 February 2020 and overall deaths.](data:application/pdf;base64,)

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![(A) Estimated proportion of cases ascertained by age group in Hubei, China (baseline, after the later correction of the number of reported cases and deaths, and assuming 50% lower susceptibility of children aged 0-19). (B) Estimated symptomatic fatality rate by age group in Hubei, China. (C) Impact of varying the fixed proportion of cases ascertained among individuals aged 80 and older from 10% to 100% on the mortality estimates. (D) Mortality estimates estimated at different points of the epidemic (every 7 days from January 12 to February 11).](data:application/pdf;base64,)

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We applied the same model to data from six areas where all required data was available: Austria, two regions of Germany (Baden-Württemberg and Bavaria), one region of Italy (Lombardy), Spain and Switzerland. The model fit was satisfactory in all cases (S1 Text, section 3). Heterogeneity in the surveillance system, as well as the fact that data was available at different stages of the epidemic, led to a large variation in the crude CFR estimates. Conversely the SFR and IFR estimates were much closer from each other (Figure [fig:country]A). Model estimates of IFR still showed marked heterogeneity, from 0.5% (95% CrI: 0.4-0.6) in Switzerland to 1.4% (95%CrI: 1.1-1.6) in Lombardy (Table [table:country]). The patterns of age-specific IFR estimates were similar across areas (Figure [fig:country]B), although there were important differences in the surveillance systems across areas, as shown by the heterogeneity in the age distribution of cases (Figure [fig:country]C). Some degree of variability remained between age-specific IFR estimates, especially in older age groups, indicating that the outcome of SARS-CoV-2 infection also depends on local characteristics. Compared to Hubei province, the age distribution of cases in European areas suggests a more pronounced focus on older individuals, and thus a higher impact of preferential ascertainment of severe cases. This appears in the estimated patterns of the age-specific ascertainment proportion, with a generally lower ascertainment of age groups 20-79 in Europe compared to Hubei (Figure [fig:country]D).

![(A) Case fatality rate, symptomatic fatality rate and infection fatality rate estimates by area. (B) Infection fatality rate estimates by age group and area (the estimates are adapted to the different age groups available in Austria, from 0-4 to 75+). (C) Proportion of cases ascertained by age group and area (the same color code as panel B applies). (D) Distribution of reported cases by age group by area (the same color code as panel B applies).](data:application/pdf;base64,)

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# Discussion

In this modelling study, we estimate mortality from SARS-CoV-2 infection in the Hubei province of China and six areas of Europe. After correcting for right-censoring and preferential ascertainment, we estimate the IFR in Hubei to 2.9% (2.4-3.5), higher than the crude CFR of 2.4%. In Europe, we estimate the IFR between 0.5% (95%CrI: 0.4-0.6) in Switzerland and 1.4% (95%CrI: 1.1-1.6) in Lombardy, while the crude CFR varied between 3.0% (95%CrI: 2.4-3.7) in Austria and 18.2% (95%CrI: 15.7-21.0) in Lombardy. The model estimates show a strong age trend in mortality, with a sharp increase in mortality after 50 years old, reaching very high values in people aged 80 and older: between 20% (95%CrI: 16-26) in Switzerland and 34% (95%CrI: 28-40) in Lombardy. While some between-country variability remains, the remarkable convergence between results obtained in different settings with different surveillance strategies provides internal validation to our approach. Nonetheless, adjusted IFR estimates still vary across settings, indicating that mortality depends on local conditions.

## Strengths and limitations

Our work has three important strengths. First, we use a mechanistic model for the transmission of, and the mortality associated with SARS-CoV-2 infection which directly translates the data-generating mechanisms leading to biased observations of the number of deaths (because of right-censoring) and of cases (because of preferential ascertainment). Our model also accounts for the effect of control measures on disease transmission. We implemented the model in a Bayesian framework in order to propagate most sources of uncertainty from data and parameter values into the estimates. In Hubei, as the model captured most of the epidemic wave, the predicted number and timing of deaths could be compared with later reports of SARS-CoV-2 deaths, providing some degree of external validation (S1 Text, section 3). Second, our model is stratified by age group, which has been shown as a crucial feature for modelling emerging respiratory infections . Third, the model relies on routinely collected surveillance data, and does not require individual-level data or studies in the general population.

Our results also come with several limitations. First, we assume that the deficit of reported cases among younger age groups is a result of preferential ascertainment, whereby younger individuals have milder symptoms and are less likely to seek care, and does not reflect a lower risk of infection in younger individuals. The reason for the shifted age distribution of reported cases is unclear. When SARS-CoV-2 infection is detected independently from symptoms, as was done in a contact tracing survey in Shenzhen, China, the incidence does not appear to have an age trend . During the pandemic of H1N1 influenza, lower circulation in older individuals was attributed to residual immunity . Lower susceptibility of younger individuals for immunological reasons seems unlikely. There is no indication of pre-existing immunity to SARS-CoV-2 in humans . Different contact patterns could contribute to different attack rates by age group, but we include age-specific contact patterns in the model. As a result, our results are dependent on the contact matrix used. We also conducted a sensitivity analyses with a reduction of 50% of the susceptibility of children, which did not impact the estimates of IFR in other age groups, and only led to a lower total number of total infections and thus to a higher IFR.

Second, we assume that, as a result of more severe symptoms at older ages, all cases in symptomatic individuals aged 80 years were reported. We cannot confirm this, but the high risk of death from SARS-CoV-2 infection amongst the elderly was reported very early on , so we believe that most old people with symptoms sought care. If this assumption is wrong, the SFR and IFR in our study would be overestimated. Sensitivity analyses show a linear relation between the ascertainment proportion for the people aged 80 years and older and mortality.

Third, the proportion of asymptomatic infections is still uncertain at this stage. Detection of asymptomatic SARS-CoV-2 infection is limited by the focus of testing on symptomatic patients seeking care. To propagate this uncertainty, we implemented this information with prior distribution that is informed from a living systematic review and meta-analysis . On its last available update, this work reported a pooled estimate of 81% (95% confidence interval: 71-91) from four studies reporting results from four outbreak investigations . This estimate is in agreement with two additional independent studies, with slightly more uncertainty. During the outbreak on the cruise ship “Diamond Princess”, nearly all individuals were tested regardless of symptoms, leading to an average proportion of symptomatic infections of 82.1% (95%CrI: 79.8-84.5) of infected people develop symptoms and become infectious . Another study of 87 contacts of infected cases in Shenzhen, China, estimated that 80.4% (95%CrI: 70.9-87.4) were symptomatic . Additionally, dichotomization into asymptomatic and symptomatic is a simplification; SARS-CoV-2 causes a spectrum of symptoms, likely depending on age, sex and comorbidities. Serological surveys in the general population will be needed to better characterize asymptomatic infections .

Fourth, our model relies on surveillance data about the incidence of cases of reported SARS-CoV-2 by date of disease onset, which is not released systematically. When information on disease onset is only available for a subset of cases, we have to assume that data is missing at random. Additionally, within a given area, the model assumes a constant ascertainment proportion and a constant mortality for each age group during the period. When repeating the analysis at different stages of the epidemic in Hubei, we find that estimates obtained before the epidemic peak is reached lead to overestimation of the SFR and IFR (Figure [fig:sst]D). This may be linked to a decrease in mortality as the epidemic progresses, but also to a lower ability of the model to estimate the epidemic size before epidemic peak is reached, a common problem in epidemic modelling . We also consider each area separately, where a hierarchical structure may allow for improved estimates using partial pooling. All these limitations constitutes directions for future improvements.

## Comparison with other studies

Estimates of mortality from SARS-CoV-2 in China adjusting for bias vary. Our estimate for Hubei province is higher than the SFR of 1.4% estimated in two studies . Differences in modelling approaches and assumptions explain this difference. Verity et al. used a similar approach as us but applied to all of mainland China, where mortality appears to be lower outside the Hubei province . This paper also assumed a homogeneous attack rate across age groups rather than simulating epidemics using an age-specific contact matrix. Wu et al. used another approach, whereby susceptibility to infection varies by age. Both Verity et al. and Wu et al. used individuals travelling away from Wuhan before lockdown was implemented to infer ascertainment, where we fixed it to 100% for the older age group. This resulted in comparatively lower ascertainment proportions (up to 70% for the oldest age groups in Verity et al. , 2% for Wu et al.), and consequently to higher estimates of epidemic size. While both approaches are sensible, relying on travelling individuals carries possible bias as travellers cannot be considered as a random sample of the general population.

Other studies that attempt to correct for right-censoring of deaths give higher estimates of mortality than in our study. A study using a competing risk model estimated mortality at 7.2% (95% confidence interval: 6.6%-8.0%) for Hubei province . Using data on exported cases, another team estimated mortality of 5.3% (95% confidence interval: 3.5%, 7.5%) among confirmed cases in China . Another team reported a CFR of 18% (95% credible interval: 11-81%) among cases detected in Hubei, accounting for the delay in mortality and estimated the IFR at 1.0% (95% CI: 0.5%-4%), based on data from the early epidemic in Hubei and from cases reported outside China . Our estimate of mortality among all infected cases in Hubei is also higher than in an earlier version of this work (2.9% against 1.6%) . We believe the newer estimate to be more reliable for two reasons. First, we implemented age-specific risks of transmission through a contact matrix, which partially explains the age patterns in reported SARS-CoV-2 infections and leads to lower estimates of the total number of infections, thus increasing mortality. Second, a higher estimated proportion of symptomatic people based on new data also led to higher estimates of mortality among all infected.

Other works have been estimating mortality in areas that are included in our analysis. A study of excess mortality in Italy estimated 17,786 269 deaths in Lombardy, close to our credibility interval for the number of total deaths . This study did not attempt to estimate the size of the epidemic, but only applied the proportion of positive tests to the population to obtain an upper limit of epidemic size, which resulted in a lower limit for the IFR of 0.6% in Lombardy. In Switzerland, a seroprevalence study estimated an attack rate of 9.7% in Geneva, resulting in an IFR of 0.6%, very close to our estimate for Switzerland .

## Interpretation and implications

In this study, we propose a comprehensive solution to the estimation of mortality from surveillance data during outbreaks . Our findings show that crude CFR estimates are a poor predictor of mortality and should not be used for evaluating policy or compare across settings. Our estimates of the IFR associated with SARS-CoV-2 are of interest for assessment of the potential consequences of the pandemic, e.g. using theoretical estimates of final epidemic size . Conversely, estimates of SFR are particularly important for clinicians, who need to assess prognosis and prioritize care when healthcare systems are overwhelmed, as appears to have occurred in several places. Adjusted for right-censoring and preferential ascertainment of severe cases, our estimates of the SFR and IFR in seven areas can be clustered in three groups: Hubei province, Lombardy and the other five areas (Figure [fig:country]A).

The highest estimate was found in Hubei province, where we find an IFR of 2.9% (95%CrI: 2.4-3.5) in our baseline analysis. Our approach for correcting right-censoring shows good predictive ability compared to reported of SARS-CoV-2-associated deaths in Hubei province after 11 February (S1 Text, section 3). We conducted several sensitivity analyses to assess the robustness of this result, and understand what assumptions influence the outcomes. The estimate decreases to 2.5% (95%CrI: 2.1-2.9) when accounting for the later correction of reported cases and deaths by the local authorities, and increases to 3.3% (95%CrI: 2.7-4.0) if we consider a lower susceptibility of individuals under 20. These estimates rely upon the assumption that 100% of infected individuals aged 80 and more have been ascertained. We show that IFR estimates decrease linearly with the ascertainment proportion in this group (Figure [fig:sst]C). An IFR estimate below 0.5% in Hubei province would imply that less than 15% of infected individuals aged 80 and more would have been ascertained by the local authorities. We also show that applying our model at earlier stages of the epidemic would have resulted in higher estimates of SFR and IFR, and more uncertainty (Figure [fig:sst]D). However, our estimates here correspond to an average value over the considered period, and it was demonstrated that mortality rates have changed over time as a result of an improvement of the standard of care . Conversely, because of right-censoring of deaths, early CFR estimates underestimate mortality associated with SARS-CoV-2 infection. Other sensitivity analyses are shown in S1 Text (section 5).

The IFR in Lombardy was estimated to 1.4% (95%CrI: 1.1-1.6), lower than in Hubei province, while the IFR estimates were lower in the other five European areas considered, ranging between 0.5% (95%CrI: 0.4-0.6) in Switzerland and 1.1% (95%CrI: 0.8-1.3) in Austria. These differences highlight the importance of local factors on the outcome of SARS-CoV-2 infection. Consequently, we advise not to directly apply the mortality estimates to all settings in order to estimate the total size of the epidemic . A partial explanation for the remaining heterogeneity is the lower degree of preparation in northern Italy, which in Europe was affected first by the SARS-CoV-2 epidemic. Further research is necessary to better understand the factors associated with SARS-CoV-2 mortality.

# Conclusions

We developed a mechanistic approach to correct the crude CFR for bias due to right-censoring and preferential ascertainment and provide adjusted estimates of mortality due to SARS-CoV-2 infection by age group. We applied this approach to seven different settings, showing that widely different estimates for the crude CFR corresponded in fact to fairly similar estimates of the IFR, around 3% in Hubei province, China, and ranging between 0.5 and 1.4% in six included European areas. Despite these similarities, substantial heterogeneity remains in the IFR estimates across settings, indicating the influence of local conditions on the outcome of SARS-CoV-2 infection. The steep increase in mortality among people aged 60 years and older, reaching very high values in people aged 80 years and older is of concern.

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# Conflict of interest

None.

# Authors’ contributions

AH and JR designed the study. AH, MC, CM and JR implemented the model and performed the statistical analyses. AH, MC, CM, GK, NL, CA and JR interpreted the results and wrote the manuscript.