Magnitude of COVID-19 deaths relative to other leading causes of death: a global analysis

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ABSTRACT

Objectives To quantify the burden of death that COVID-19 contributes relative to the top three causes of death for all countries.

Design We performed uncertainty analyses and created contour plots for COVID-19 mortality to place the number of COVID-19 deaths in context relative to the top three causes of death in each country, across a plausible range of values for two key parameters: case fatality rate and magnitude of under-reporting.

Setting All countries that have reported COVID-19 cases to the WHO and are included in the Global Burden of Disease Study by the Institute of Health Metrics and Evaluation.

Main outcomes and measures Monthly number of deaths caused by COVID-19 and monthly number of deaths caused by the top three causes of death for every country.

Results For countries that were particularly hard hit during the outbreak in 2020, most combinations of model parameters resulted in COVID-19 ranking within the top three causes of death. For countries not as hard hit on a per-capita basis, such as China and India, COVID-19 did not rank higher than the third leading cause of death at any combination of the model parameters within the given ranges. Up-to-date ranking of COVID-19 deaths relative to the top three causes of death for all countries globally is provided in an interactive online application.

Conclusions Estimating the country-level burden of death that COVID-19 contributes relative to the top three causes of death is feasible through contour graphs, even when the actual number of deaths or cases is unknown. This method can help convey importance by placing the magnitude of COVID-related deaths in context relative to more familiar causes of death by communicating when COVID-related deaths rank among the top three causes of death.

INTRODUCTION

Since January 2020, SARS-CoV-2 has progressively moved across the world, leaving almost no country untouched. As resources are finite, reallocating resources to reduce COVID-19 deaths may divert resources from interventions effective for preventing deaths from other causes. Concerns have been raised about whether privileging resources for COVID-19 represents a worthy trade-off, or whether more common diseases are being neglected, resulting in overall net increased all-cause mortality.

In this manuscript, we aim to address the country-level impact of COVID-19 by estimating the magnitude of the disease relative to leading non-COVID-19 causes of death in each country around the world using an uncertainty analysis model. Since the number of cases and deaths due to COVID-19 is under-reported, especially in low-resource settings without testing and data reporting infrastructures, it is difficult to determine the true effects of COVID-19 relative to other non-COVID-19 causes of death, which makes it difficult for citizens to understand the relative importance of the pandemic compared with other more familiar causes of death, and for policymakers and healthcare providers to decide whether to privilege COVID-related care over routine care during a pandemic. Uncertainty analyses can be used to map the likely impact of COVID-19 relative to other causes of death.

Although we have performed the analysis for all countries that have reported COVID-19 cases (available in an up-to-date online app), we will focus the discussion in the main manuscript on eight countries: the USA, Brazil, South Africa, Iran, the UK, Russia, China and India. We chose these countries to provide a
broad representation across continents and across high-income and middle-income countries.

METHODS

Inspired by Helleringer and Noymer’s uncertainty analysis for Ebola,\textsuperscript{1} we performed uncertainty analyses for COVID-19 mortality to place the number of COVID-19 deaths in context relative to the top three causes of death in each country, across a plausible range of values for two key parameters: case fatality rate (CFR) and magnitude of under-reporting. Together, these two parameters provide plausible ranges of infection fatality rates (IFR). Online supplemental file 1 provides the extended explanation of the methodology. While we display the results for a subset of countries in this commentary, analyses for all countries are available in an online interactive application, which is updated: https://medicimagic.shinyapps.io/COVID-19_uncertainty_analysis/.

To calculate the estimated number of deaths due to COVID-19 based on the number of reported COVID-19 cases and accounting for the correction factor ($\beta$) and the CFR ($\%$), we use the following formula:

$$\text{Estimated \# of deaths} = \frac{\beta \times \text{CFR} \times \text{# of reported cases}}{100\%} \times \text{#} \ (1).$$

While several CFR estimates are available, precise CFR estimation remains infeasible (incomplete ascertainment of cases and deaths), and is context dependent (dependent on age, comorbidities and access to healthcare). At the beginning of the pandemic, WHO\textsuperscript{2} reported that the crude CFR of COVID-19 ranged from less than 0.1% to over 25%. As the pandemic progressed, the uncertainty of CFR estimates has decreased. For example, Oke and Heneghan\textsuperscript{3} give 95% prediction intervals of the CFR for every country (with 1000 cases or greater) along with the CFR for each continent, with country-level estimates ranging from 0.06% to 19.64%. Since we focus on eight countries in this manuscript, we chose a range of 0.1%–5% as the plausible estimates of CFR as it encompasses the current CFR estimates for this subset of countries according to Oke and Heneghan.\textsuperscript{3} See table 1 for the CFR estimates as of 21 June 2021. Similarly, to estimate the extent of under-reporting due to the different testing strategies across countries and the lack of seroprevalence studies, it is also difficult to precisely determine the appropriate range for the under-reporting correction factor (defined as the ratio of true to confirmed cases). Therefore, we explored the proportion of people infected by the coronavirus who show few or no symptoms, which ranged from 17.9% to 80%,\textsuperscript{4–7} to provide an appropriate range for our model. Given this range in asymptomatic or paucisymptomatic infection, we assumed an under-reporting correction factor varying between 1 and 8. Using equation 1 for every combination of the ranges of values for CFR and $\beta$ gives us a matrix of values that represents the range of estimates for COVID-19 deaths. In our analysis in this manuscript, we use the number of COVID-19 cases reported by WHO\textsuperscript{8} throughout the year 2020.

For our uncertainty analysis, our contour plots are coloured according to the rank of leading causes of deaths: the red regions indicate that COVID-19 would be the leading cause of death; the yellow regions indicate that COVID-19 would be the second leading cause of death; the cyan regions indicate that COVID-19 would be the third leading cause of death; and lastly, the dark blue regions indicate that COVID-19 would not rank in the top three causes of death. To determine where the contours are located on the plot, we compare the range of COVID-19 death estimates to the national estimates of the top three causes of death for each country. Using the data on level 3 causes of death from the Institute of Health Metrics and Evaluation’s (IHME) Global Burden of Disease (GBD) Study 2019,\textsuperscript{9} we estimated the latest available estimates for each cause of death using a cubic regression, and determined the top three causes of death and the estimation on the number of deaths due to each respective cause based on the extrapolated results. These estimates on the number of deaths due to the top three causes of death determine the location of the contours in our figures.

We also plotted the number of deaths due to COVID-19 reported by WHO on the contour plots, indicated in black. These contour lines allow users to see the ranking of COVID-19 (solely based on the reported value) relative to other more familiar causes of death by observing which coloured region the line is in, and allow users to determine possible combinations of the CFR and the correction factor that make up the reported number of deaths. This further allows us to determine the IFR of the disease.

Patient and public involvement

Patients and the public were not involved in the development of the research question, outcome measures, design study, recruitment or conduct of study.

RESULTS

Similar to Helleringer and Noymer,\textsuperscript{1} for all combinations of the model parameters, we mapped where COVID-19

<table>
<thead>
<tr>
<th>Country</th>
<th>CFR (%) (95% prediction interval)</th>
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</thead>
<tbody>
<tr>
<td>USA</td>
<td>1.79 (1.79–1.80)</td>
</tr>
<tr>
<td>Brazil</td>
<td>2.80 (2.79–2.81)</td>
</tr>
<tr>
<td>South Africa</td>
<td>3.22 (3.19–3.25)</td>
</tr>
<tr>
<td>Iran</td>
<td>2.68 (2.66–2.69)</td>
</tr>
<tr>
<td>UK</td>
<td>2.76 (2.75–2.78)</td>
</tr>
<tr>
<td>Russia</td>
<td>2.43 (2.42–2.45)</td>
</tr>
<tr>
<td>China</td>
<td>5.06 (4.92–5.20)</td>
</tr>
<tr>
<td>India</td>
<td>1.30 (1.29–1.30)</td>
</tr>
</tbody>
</table>

CFR, case fatality rate.
deaths ranked relative to the top three causes of death in each respective country in 2020 (figure 1). To aid in figure interpretation, we use the USA as an example to demonstrate how one would determine the ranking of COVID-19 as one of the leading causes of death in the country. Despite knowing the number of reported deaths due to COVID-19 in the USA, these values are potentially under-reported for various reasons such as not testing the deceased for COVID-19 due to lack of resources (especially during the height of the pandemic), or differing
definitions as to what constitutes as death due to COVID-19. As shown in table 1, Oke and Heneghan predicted that the CFR for the USA is approximately 1.79%. If we also assumed that the number of reported cases is indeed the true number of COVID-19 infections that occurred in the USA in 2020 (ie, β=1), then we can see that the region corresponding to these parameters is yellow, indicating that COVID-19 would be at least the second leading cause of death in the country. However, as we recognise that the number of cases is under-reported, if the correction factor is greater than approximately 1.9 (and if we assume that the CFR is equal to the IFR), this will mean that COVID-19 would have been the leading cause of death in the USA in 2020.

For countries that struggled to manage the virus in 2020, such as the USA, Brazil, South Africa, Iran, the UK and Russia, most combinations of model parameters (CFR=0.1%–5% and β=1–8) resulted in COVID-19 ranking within the top three causes of death. Even though the contour plot may look similar for these countries, this does not necessarily mean similar severity of COVID-19, since different countries have different degrees of under-reporting—high-income countries are likely to have a lower correction factor as they have resources to test large number of people, whereas low-income countries are most likely to have a higher correction factor due to lack of testing kits. This suggests that despite what appears to be similar outcomes between countries, low-income countries are more likely to have more severe impact by COVID-19 (due to having high β) in comparison to high-income countries (which could have a similar CFR but low β). On the other hand, for countries not as hard hit on a per-capita basis in 2020, such as China and India, COVID-19 would only rank in the top three causes of death for combinations of large CFR and β. Lastly, for countries that were able to control the virus early in the pandemic, such as China, COVID-19 would not rank higher than the third leading cause of death at any combination of the model parameters within the given ranges.

Additionally, we can use this uncertainty analysis model to determine the possible combinations of CFR and correction factor based on the reported number of deaths. For example, in figure 1, we observe that COVID-19 was the second leading cause of death (since the black contour line is located in the yellow region of the contour plot) in the USA in 2020 (based on our projections on the number of non-COVID-19 deaths). Additionally, we observe that if we assumed that the reported number of cases is the true number of COVID-19 cases, then the CFR is very close to the estimate that Oke and Heneghan calculated. However, due to the number of COVID-19 cases being under-reported, by increasing the correction factor, we can observe the relationship between β and CFR. For example, according to Kalish et al. in the first 6 months of the COVID-19 pandemic, there were 4.8 undiagnosed SARS-CoV-2 infections for every diagnosed case. If we take β=4.8 and follow the contour line, we find that the corresponding CFR is approximately 0.26%. This could potentially give us an idea what the IFR is in the USA.

Our analysis provided in figure 1 gives a broad snapshot as to how COVID-19 has affected each country in 2020 but does not necessarily provide a true sense of the current circumstance, given continued pandemic growth. For updates, we have provided an interactive application (https://medicimagic.shinyapps.io/COVID-19_uncertainty_analysis/) allowing users to observe how COVID-19 is currently affecting each country and to determine whether the virus is the leading cause of death in their country over adjustable periods of time. This provides more relatable benchmarks for users to understand when the burden of COVID-related deaths has rivalled the most common causes of death in their country, while allowing for users to vary the likely under-reporting and CFR, each of which can never be precisely known. When the COVID-related deaths have surpassed the contour for other most common causes of deaths for all combinations of plausible CFRs and cases (or ratio of unreported:reported cases), it can be assumed that regardless of the uncertainties in number reported, COVID-19 has overtaken all other leading causes of death.

**DISCUSSION**

Estimating the country-level burden of death that COVID-19 contributes relative to the top three causes of death is feasible through uncertainty analyses, even when the exact number of deaths or cases is unknown. This method can help place the importance and magnitude of COVID-related deaths in context relative to more familiar causes of death by communicating when COVID-related deaths rank among the top three causes of death.

This analysis should be interpreted with caveats since collateral increases in non-COVID-19 deaths due to decreased healthcare utilisation are unaccounted for. Additionally, at the time of writing, there was insufficient information about the number of deaths due to non-COVID-19 causes of deaths, and therefore, we estimated both the top three causes of death for each country and the value corresponding to each cause based on the data provided by IHME’s GBD Study. Due to preventative measures that were taken to slow the pandemic, the leading causes of non-COVID-19 deaths and the corresponding values that we estimated may not necessarily be accurate, especially over the longer term due to collateral pandemic-related effects on cardiovascular disease, stroke and cancer (changes in access to healthcare, and changes in lifestyle) which may not become apparent until significant time has passed. Lastly, once the pandemic has matured, plausible ranges for CFR and under-reporting may require adjustment.

Despite the limitations, uncertainty analyses provide opportunity to quantify the burden of disease that COVID-19 contributes to each country relative to other causes of death, across a broad range of possibilities. During the current pandemic, and in future pandemics,
timely application of this tool may better inform reflex assumptions that COVID-related burden of death is not worthy of the actions taken, or that under-reporting negates any credibility of the reported statistics. The online tool may also facilitate decision makers to determine the most appropriate course of action given limited healthcare resources at different stages of the outbreak.

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