Change in country-level COVID-19 case fatality rate is associated with improved testing; no apparent role of medical care or disease-specific knowledge

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Abstract

Observed case fatality rate (CFR) of COVID-19 has decreased since the beginning of the pandemic. Reasons for this decline include improved knowledge of COVID-19 pathogenesis, leading to improved medical care of confirmed cases. However, ascertainment also plays a role: as more low-risk individuals are tested and more mild cases identified, observed CFR will decline. Previously I showed that geography-level CFR was cross-sectionally negatively associated with test density; here I test for similar trends within geography over six months, and check plausibility of various posited causes. Although CFR varied between geographies, its association with testing did not: in 141 geographies, CFR dropped by an average of 18% for each doubling of test density. Change in CFR within a given geography was not associated either with that geography's medical spending or with whether the bulk of cases occurred early or late in the pandemic. This shows that medical interventions, including those specific to COVID-19, have only a minimal effect on total CFR. Two major conclusions follow. First, interventions to reduce CFR should be evaluated by comparing groups that received the intervention to those who did not: decline in CFR after an intervention is not evidence of effectiveness. Second, improving clinical care of confirmed COVID-19 cases has only a minimal effect on death rates. To minimize the total death toll of COVID-19, policymakers should prioritize reducing infections.

Introduction

Observed case fatality rate (CFR) of COVID-19 has dropped since the beginning of the pandemic, from 10% to 3% in the US¹ and similarly elsewhere.² Cited reasons for this decline include improved understanding of disease pathogenesis leading to better treatment, as well as the abandonment of ineffective therapies.² However, ascertainment bias almost certainly also plays a role: early in the pandemic, tests were reserved for individuals at high risk of complications and many low-risk cases were missed. Seroprevalence data from early in the pandemic,³ when CFR in the US based on testing approached 10%,¹ suggested that when all cases were included true CFR was usually below 1% and often below 0.50%; it has already dropped below 2%.¹

It has already been shown⁴ that CFR of COVID-19 is lower in geographic regions where test density is higher. This association is similar on all continents, even though baseline CFR is higher on some continents than others. However, these cross-sectional data are confounded by geography-level factors such as population age structure, presence of comorbidities, and access to critical care. Thus while it is likely that ascertainment bias plays a role in the observed drop in CFR as test density increases, the size and consistency of this effect is not known.

The current paper investigates the role of test density in driving changes in observed geography-level CFR over a six-month period. As alternative explanations for observed changes in CFR I consider per capita medical spending as an indicator of critical-care access; and timing of the pandemic as an indicator of each geography's ability to benefit from rapidly-evolving knowledge. This technique eliminates variation

in CFR driven by geography-level factors, and thus allows an unbiased estimate of the role of ascertainment in driving observed decreases in COVID-19 lethality.

Methods

Study Design and Data Collection

I estimate the slope of the association between change in test density, and change in observed CFR, in resolved cases of COVID-19 between July 3, 2020 and January 5, 2021. I then investigate the role of two factors (timing of the epidemic and medical spending) in driving this change.

COVID-19 data are from every geography for which they were available from a publicly-available real-time counter¹ and in which at least one death had occurred by the earlier timepoint. Timing of the epidemic was expressed as the percent of total cumulative cases at the later timepoint that occurred after the earlier timepoint. Medical spending (USD per capita, 2015) was downloaded from the World Health Organization.⁵

Statistical Analysis

For each geography I calculate changes in CFR (ratio between total deaths and total resolved cases) and test density per thousand residents, between the two timepoints. These data are presented as summary statistics and in corrected linear models. These models used log-log linear regression weighted by log average number of cases (mean of case count at the two timepoints.) Outputs were then reverse-transformed and expressed as percent change in CFR per unit change in predictor (e.g. per doubling of test density.) I also estimate the effect of other predictors (timing of the pandemic or medical spending) on CFR change.

Change in CFR, change in test density, and total cases were all approximately log-normally distributed and thus were log-transformed for normality in all analyses. Timing of the epidemic (percent of total cases that occurred after July 3) was skewed and thus it was categorized into *early*, *middle*, and *late* based on 10th and 50th percentiles.

Results

In countries with complete COVID-19 data (n=162) median CFR was 4.08% (IQR 2.2 – 6.9) on July 3 and 2.04% (1.3 – 3.1) on January 5. Median test density was 23 tests per thousand population (IQR 6.6 – 60) at the earlier timepoint, and 1200 (274 - 5000) at the later timepoint. A median of 88% of total cases occurred after July 3 (IQR 83 - 94%; 10th percentile, 48%.)

Data on medical spending was available for 141 geographies, which included 99.8% of COVID-19 cases. Median medical spending was \$1010 per person per year (IQR 350 – 2200.)

Of those 141 geographies, CFR decreased in 120 (85%) which contained 95% of cases; and because test density was cumulative, it increased in every geography. For each doubling in test density, mean CFR decreased by 18% (Figure 1 ($p < 0.0001$, R^2 0.08.))

Neither medical spending nor timing of the pandemic was associated with change in CFR (Figure 2.) This null association was supported by linear regression models (both $p > 0.10$).

Discussion

Country-level case fatality rate of COVID-19 decreased as test density increased, and on average this decline was almost the same as was previously observed between geographies at a single timepoint.⁴ This further supports the role of improved ascertainment in driving it. In contrast, rate of CFR decline did not vary with either access to medical care or existence of COVID-19-specific knowledge.

These results are unexpected because COVID-19 treatment undoubtedly improved during the study period. Treatments previously approved for emergency use, such as hydroxychloroquine,⁶ were shown to be ineffective and consequently abandoned; while therapies such as pronation and continuous positive airway pressure (CPAP) have been shown to be effective and implemented widely.⁷ This contrast suggests one possible explanation for the lack of observed effect of country-level medical-care access: if some treatments increase survival and some decrease it, the net effect of care access may be neutral.

This also may explain the lack of effect of timing of the pandemic. If treatment quality and consequent survivorship have improved over time, CFR should decrease more sharply in countries where most cases occurred after those improvements became public. This did not occur. In addition to low statistical power, this may be due to the relatively small number of COVID-19 cases who can benefit from improvements in care. These improvements benefit only those patients whose symptoms are severe enough to warrant COVID-specific medical care, but not so severe as to be beyond help. Since most cases are asymptomatic⁸ and able to recover without COVID-specific care, this group is a minority. Thus while treatment improvements certainly benefit the patients who receive them⁷ they may not have a detectable effect at the population level.

Conclusions

These findings have two major implications. First, research should explicitly consider the role of ascertainment bias. Evaluation of interventions should compare groups that received it to those who did not, rather than interpreting a decline in CFR after an intervention⁹ as evidence of effectiveness. Second, improvements in clinical care appear to have only a minor effect on case fatality rate. To minimize the death toll of COVID-19, the priority should be to reduce infection.

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Figures

Case fatality rate of COVID-19 declines with improved testing July 3, 2020 – January 5, 2021

Figure 1

Case fatality rate of COVID-19 declines with improved testing Color coding for continent. Bubble size for number of cases. Regression line of best fit for 18% decrease in CFR per doubling of test density.

Neither timing of the pandemic, nor medical care, predicts changes in COVID-19 case fatality rate

Figure 2

Changes in case fatality rate of COVID-19 are not associated with either medical spending or timing of the pandemic Color coding for timing of the pandemic. Bubble size for number of cases.