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EDITORIAL COMMENTARY

Death and the Virus

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The results are in. With near certainty, we do not know the case fatality rate (CFR) for coronavirus disease 2019 (COVID-19). First, it is not a rate (neither the number of deaths/cases/time nor a survival probability based on time) [1]. Nor is it a ratio, which would be the odds of death. Rather, it is a proportion or a risk (the term used by Deng et al [2] in this issue), or more generically, a percentage. Second, this seemingly simple metric poses many problems, especially in the fog of COVID-19.

The worldwide risk on 11 May 2020 was 0.068 [3]. The risk in China was 0.056. The risk in the United States was 0.059. The range of risks in the United States was from 0.010 (South Dakota) to 0.097 (Michigan), an order of magnitude difference. The personal factors that affect risk are age, sex, ethnicity, location, and comorbidity. The structural factors that affect risk are medical care, diagnostic acumen, testing intensity, the vagaries of reporting, and contact-tracing persistence. The wild card is the virulence of the organism. Nominally, the CFR seems to be the same in the United States and China, but the differences in those factors make the similarity suspect.

Perhaps the problem is that we should not be seeking a single CFR. Risk specificity is far more important. From the individual perspective, what we want to know is a person's probability of dying if infected. From a population perspective, we need to know the groups with the highest risk of death. Some of this is readily apparent: residents of long-term-care facilities [4], minority persons [5, 6], obese persons [7], and people with comorbidities [8]. But a finer-grain understanding of specific CFRs would be a critical tool in targeting interventive approaches.

The article by Deng et al [2] is an object lesson in the importance of specific CFRs and of proper attention to the intimate details of the calculation. Their intimate details start with a meticulous assessment of the validity and accuracy of their 2 datasets, one individual-based and one population-aggregated. They use the raw data, simple description, and a number of manipulative methods (correction factors, curve fitting, regression analysis) to estimate CFR by clinical severity, time-to-event, risk factors, and region. A few simple results illustrate how the CFRs can be used. Half of the cases were aged 45 years and over; half of the deaths were in those aged 75 years and over. The male to female ratio was 60:40. The crude risk ratio between Wuhan, Hubei (the epicenter of the epidemic), and provinces outside Hubei was approximately 10. The CFR among critically ill patients in Wuhan was 86.4%, more than 40 times higher than the CFR in patients with mild disease.

Unfortunately, as interesting and important as these results are, they are not likely to be generalizable. As noted, China and the United States currently have similar CFRs but the relevant factors are substantially different. The therapeutic armamentarium has evolved, and some clinical concerns—coagulopathy [9], cytokine storm [10], ventilatory requirements [11]—were not apparent early on. The learning curve has had a palpable effect on the CFR, which underlines the point that a population-averaged CFR has little meaning.

We should laud Deng et al for their efforts to get inside the CFR, and not focus on comparability. The components of composite statistics are often of more value than the overall mean, and only knowledge of those components permits comparison. As with so many epidemiologic parameters, the CFR is a weighted average of subgroups, and knowing the CFRs and proportions of the subgroups permits interventive targeting. In a simple thought experiment, if we hold the age-, sex-, race-specific CFRs constant and simply vary the proportions of each age/sex/race category affected, the overall CFR will obviously change. Targeting older persons and persons of color would lower the prevalence, lower the R_0, and thereby lower the CFR, and we would be able to say why.

In the months to come, we can expect changes in the critical factors that may work on the CFR in different directions. As our knowledge of the clinical virology improves, and with it better antigen, antibody, and genetic tests, we can expect a much broader understanding of the clinical epidemiology: incubation period and the infectious stages, asymptomatic infectious carriage, and necessary and sufficient contact with humans and surfaces. Prevention measures will evolve that fit a better understanding of the transmission

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dynamics. In contrast, viral mutation may foster greater virulence [12]. Our great hope—drugs and a vaccine—will be the ultimate determinant of the CFR.

The proportion of people who die plays a primary role in the trajectory of the epidemic and is perhaps foremost in people's minds. Systematic reporting of the components of the CFR can be a powerful tool for shaping policy and evaluating impact. For example, the current interventions at our disposal—testing, quarantine and isolation, lockdown, contact tracing—have added an economic cataclysm to the pandemic's destruction. For reasons that go beyond population health and economics, Death and The Economy have been turned into bizarre adversaries. But they are intimately intertwined, and success in either depends on their mutual management. As we attempt to optimize policy for both, the components of the CFR are a vital statistic.

Note

Potential conflicts of interest. The author: No reported conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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