Towards a better case fatality estimate for SARS-CoV-2 during the early phase of the United States outbreak.

Jeremy Samuel Faust, MD MS
Brigham and Women's Hospital Department of Emergency Medicine,
Division of Health Policy and Public Health,
10 Vining St
Boston MA 02115
Harvard Medical School, Boston MA.
jsfaust@gmail.com
530-867-2263

The determination of a valid case fatality rate during any initial outbreak must overcome difficulties in the ascertainment of reliable numerator and denominator statements. In the absence of either universal testing or adequate random surveillance testing data from which reasonably dependable estimates can be made, determining the accurate number of circulating cases (denominator statements) can thwarted by insurmountable challenges. Many of the expected obstacles appear to have hindered accurate estimates of the prevalence of SARS-CoV-2 in many nations during the initial phase of this pandemic.[1] An insight provided in the work by Kou *et al* in this issue represents a potentially important step towards unveiling a better denominator for the early phase of the covid-19 outbreak in the United States. Using the gap between influenza-like-illness levels reported to the Centers for Disease Control and Prevention and the estimated number of influenza cases based on oseltamivir prescriptions in order to triangulate the number of active COVID-19 cases in the US is a clever concept. However, it appears to have carried the most validity during the three weeks of the initial outbreak (the weeks ending March 7 through March 21st) here in the US. After that period, the model appears to lose accuracy and any proposed figures derived from the subsequent weeks can at best be understood as low-end estimates of a lower boundary for the true number of circulating symptomatic cases. There several reasons for this. First, after March 21, we observe that a rapid decline in ILI reported to the CDC occurred, even though COVID-19 cases continued to grow rapidly during that time. The drop-off in ILI reporting to the CDC after March 21st renders the exercise of estimating case counts based upon the proposed model far less accurate. That this drop occurred during the fourth week of March should not be surprising given contemporaneous events. First, telemedicine in the United States began a rapid and unprecedented expansion around that time. This was propelled by the Centers for Medicare and Medicaid Services announcement of a rule change on March 18th that vigorously supported the adoption of these practices during the pandemic.[2] Second, shelter-in-place orders were initiated around the country beginning March 23rd and steadily expanding over the next two weeks. Third, arising out of the first two reasons, visits to clinics and emergency departments plummeted shortly thereafter.

Given the above considerations, data from the model as proposed by Kou *et al* can be harnessed for calculating a denominator statement with acceptable face validity for symptomatic disease at three time points, ranging from March 7 to March 21. We can further posit an alternative denominator that takes asymptomatic infection into account—which their model does not. While some estimates state that only 11 percent of cases are ultimately asymptomatic, other estimates are closer to 18 percent. But presymptomatic disease comprises a substantial fraction of infections at any given time and should therefore also be considered. Universal screening among one healthy population detected that the rate of asymptomatic or presymptomatic disease was as high as 88 percent.[3] Another study of older patients who were sicker at baseline found that 56 percent of patients with a positive SARS-CoV-2 swab were asymptomatic at the time of testing, and only developed symptoms later (median time from test to symptoms = 4 days). Such patients would not be picked up in the final data point in use. Taken together, a reasonably conservative attempt to add symptom-free cases to numbers proposed by Kou *et al* could include a 50 percent addition to their estimates.[4 5]

Numerator statements, meanwhile, can reasonably be assumed to be sufficiently close to the running cumulative total number of counted covid-19 deaths as recorded at least two weeks after the day used to estimate the denominator. These counts are relatively reliable because covid-19 is currently a reportable cause of death in all US states and territories. While excess deaths may ultimately offer an attractive alternative for use as the numerator, expected lags in all-cause mortality reporting renders these numbers incomplete for several weeks.[6] Once those numbers are available, they may serve as a partial measure of quality for numerator statements based on counted covid-19 deaths, which are prone to some degree of error. Thus, the use of excess mortality may at some point provide another lens through which to verify the accuracy of these counts, as excess all-cause mortality figures does not rely on the subjective judgement of those filling out death certificates.

March 21st appears to be the best available date upon which to estimate a denominator for the CFR of SARS-SoV-2 using the model provided by Kou *et al*. This date has the advantage both of being the peak of ILI reporting to the CDC while being directly prior to the time when the effects of many of the mitigation strategies and changes in public behavior mentioned above began to become noticeable on a systemic level. As of April 5th, public COVID-19 trackers reported a crude CFR of 3.5 percent worldwide. Using the Kou model as a source for the denominator (cases as of March 21st) and all deaths through April 4th as the numerator (including all deaths that occurred on US soil prior to March 21), the calculated CFR appears to have been approximately 22 percent of estimates on public-facing COVID19 trackers—and this only accounts for symptomatic cases (Table 1, column 1). Further, allowing for the addition of pre- or asymptomatic cases into the denominator reveals a CFR of just 12 percent of the figures published on COVID-19 trackers (Table 1, column 2).

These figures mirror estimates obtained in closed systems where universal testing was achieved, such as the Diamond Princess cruise. While the crude CFR on the Diamond Princess appears to have settled at around 1.8 percent, passengers aged 70 or older were over-represented as compared to other cohorts by a factor of approximately four.[7 8] This implies an age-adjusted CFR for the Diamond Princess of 0.45, which is remarkably similar to implied rates we calculate here using the denominator based on Kou *et al* with adjustment for symptom-free infection (Table 1, column 2). These numbers are higher, though not astronomically, than estimates given in the increasingly controversial Santa Clara County serology study.[9] If we instead use some of the higher reported numbers of pre- or asymptomatic cases found in the emerging literature, the estimated CFR we might calculate would indeed approach the 0.17 percent figure proposed by the authors of the Santa Clara study.

Together, these data imply that a more accurate CFR for SARS-CoV-2 may rest between 0.5 and 0.8 percent for symptomatic cases, and 0.2 and 0.4 percent for all cases including pre- and asymptomatic infections. However, this would also appear to imply that SARS-CoV-2 has a CFR that is between one and eight times greater than reported figures for seasonal flu. Based upon recent ground conditions during the COVID-19 outbreak compared to the peak of the worst flu seasons from recent years (as well as the 2009 H1N1 pandemic), no credible case can be made for ratios this small, unless influenza is considered to have been merely a “contributing cause” of these deaths. In that case, the CFR of 0.1 for seasonal influenza that is commonly cited essentially becomes meaningless as other competing diseases would also need to be included more liberally. Meanwhile, it is clear that SARS-CoV-2 is in fact likely to be at least 20 times more deadly than seasonal influenza.[10] In the future, the methodology for how influenza deaths are estimated, and thus the CFR these data apparently imply, should be revisited.

The author has no potential conflicts to disclose.

Table1 Case fatality rates derived from denominators suggested by the model of Kou *et al*; numerators are derrived from death count from an online COVID-19 tracker.[7]

	CFR-symptomatic (cumulative, 14 days after case count).	CFR including adjustment for pre- and/or asymptomatic cases (all deaths since outbreak as of, 14 days after case count)
7-Mar	0.52	0.29
14-Mar	0.54	0.30
21-Mar	0.76	0.43
28-Mar	1.15	0.65

References:

[1] Niforatos JD, Melnick ER, Faust JS. Covid-19 fatality is likely overestimated. U.S. National Library of Medicine, 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32198267. Accessed 17 May 2020.

[2] Fact sheet MEDICARE TELEMEDICINE HEALTH CARE PROVIDER FACT SHEET. Available at: https://www.cms.gov/newsroom/fact-sheets/medicare-telemedicine-health-care-provider-fact-sheet. Accessed 17 May 2020.

[3] Geleris J, Halfmann PJ, Doremalen Nvan. Universal Screening for SARS-CoV-2 in Women Admitted for Delivery: NEJM. 2020. Available at: https://www.nejm.org/doi/full/10.1056/NEJMc2009316. Accessed 17 May 2020.

[4] Gandhi M, Arons MM, Geleris J, Doremalen Nvan, Halfmann PJ, Department of Medicine. Asymptomatic Transmission, the Achilles' Heel of Current Strategies to Control Covid-19: NEJM. 2020. Available at: https://www.nejm.org/doi/full/10.1056/NEJMe2009758. Accessed 17 May 2020.

[5] Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. European Centre for Disease Prevention and Control, 2020. Available at: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.10.2000180. Accessed 17 May 2020.

[6] Excess Deaths Associated with COVID-19. Centers for Disease Control and Prevention, 2020. Available at: https://www.cdc.gov/nchs/nvss/vsrr/covid19/excess_deaths.htm. Accessed 17 May 2020.

[7] COVID-19 Map. Available at: https://coronavirus.jhu.edu/map.html. Accessed 17 May 2020.

[8] Field Briefing: Diamond Princess COVID-19 Cases. Available at: https://www.niid.go.jp/niid/en/2019-ncov-e/9417-covid-dp-fe-02.html. Accessed 17 May 2020.

[9] Bendavid E, Mulaney B, Sood N, et al. COVID-19 Antibody Seroprevalence in Santa Clara County, California. Cold Spring Harbor Laboratory Press, 2020. Available at: https://www.medrxiv.org/content/10.1101/2020.04.14.20062463v2. Accessed 17 May 2020.

[10] Faust JS. Assessment of Deaths From COVID-19 and From Seasonal Influenza. 2020. Available at: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2766121. Accessed 17 May 2020.