A two-step strategy to reopen America

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Abstract

New antibody tests for SARS-CoV-2 are providing better estimates of the mortality rate of COVID-19. Prior to serology testing, the prevalence of novel-coronavirus infection was calculated to be only 0.26% in the US with a mortality rate of 5.60%. Serology tests, however, now show the infection prevalence to be far higher with a calculated mortality rate of about 0.18%. With age-selective quarantining in combination with widespread testing, telemedicine consultations and early treatment with hydroxychloroquine, azithromycin and zinc, the mortality rate could be reduced to 0.03%. By instituting these measures, the projected number of deaths moving forward could be fewer than the number of deaths in the flu season of 2017-2018.

Background

Without reliable estimates on the mortality rate of COVID-19, many countries including the US took drastic measures to stop the spread of infection and "flatten the curve". These measures included strict quarantines, travel restrictions and suspension of commercial activity. The result has been havoc on the American economy. A record 26 million Americans sought unemployment benefits this past month.[1] An estimated 7.5 million small businesses may permanently close if the pandemic persists for the next few months.[2] Americans want to visit family and friends, which is prohibited in select states. These were measures taken in a time of uncertainty, which may be coming to an end.

Recently developed rapid serology tests for COVID-19 IgG and IgM antibodies are now available that enable us to more accurately estimate the number of people infected with SARS-CoV-2. Antibody testing allows us to both approximate immunity in populations as well as better estimate the COVID-19 mortality rate.

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It has long been suspected that the true infection rate of SARS-CoV-2 is far higher than the prevalence determined by positive tests as reported by Johns Hopkins, The COVID Project and Worldometer.[3][4][5] This is not surprising given delayed availability of testing and new evidence from autopsies that show the first positive COVID-19 cases in the US were in mid-January and not late-February as previously reported.[6] It is now known that the first identified death was a result of community transmission, making it entirely possible that undetected cases were present in the United States as early as December 2019—long before widespread testing was deployed in mid-March.

There are two notable studies released this month on SARS-CoV-2 antibody prevalence in Santa Clara and LA County. The first published on April 11 is a Stanford study of antibody testing in 3,330 subjects in Santa Clara that reports a prevalence of SARS-CoV-2 infection between 2.49% and 4.16% in the local population.[7]

A second study by the University of Southern California (USC) published results on April 20 with similar findings in Southern California, estimating antibody prevalence between 2.8% and 5.6% in LA County.[8]

The methodology of these studies—particularly the accuracy of the antibody test—has been challenged despite both studies statistically adjusting prevalence to account for false positives. The infection prevalence results are further validated though upon comparison with Global Epidemic and Mobility Model (GLEAM), an individual-based, stochastic, and spatial epidemic model that inputs real-world data to perform in-silico simulations of the spatial spread of infectious diseases. GLEAM currently estimates a cumulative infection prevalence of 3.4% [2.1% - 5.9%].[9]

Empowered with a more reliable infection rate, as well as population size and known deaths due to COVID-19, we can better approximate the mortality rate of COVID-19.

COVID-19 mortality rate

The current mortality rate for all ages based on positive COVID-19 testing (not antibody testing) is 5.60%,[5] with age distributed mortality rates shown below.

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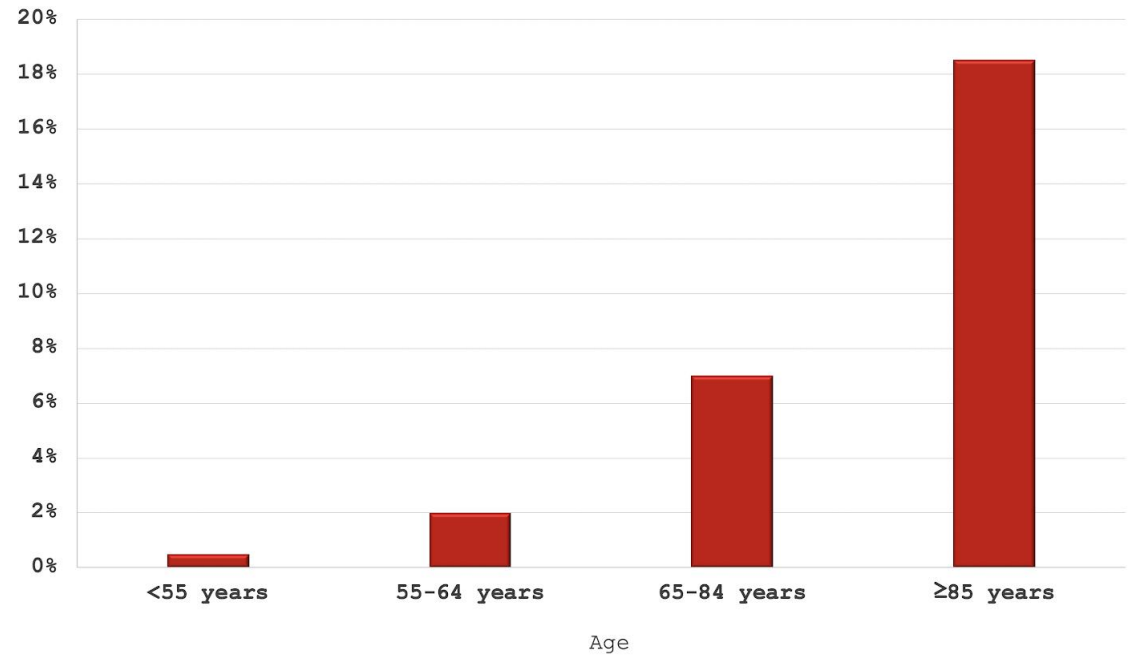
Figure 1. COVID-19 mortality rate by age



Source: Centers for Disease Control and Prevention (https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e2.htm)

The Stanford study estimates between 48,000 and 81,000 infections in Santa Clara based on antibody testing on April 3-4, 2020 (compared to the 956 documented positive cases at the time). With 50 reported deaths from COVID-19 in Santa Clara and accounting for likely unconfirmed COVID-19 deaths, experts project an upper limit of 100 deaths at the time of study.[7] Based on a 100-death count, the mortality rate of COVID-19 is 0.12% to 0.2%.

The USC study appears to include a more randomized selection of nearly 1,000 subjects, but reports similar results.[8] They estimate an infection prevalence of 221,000 to 442,000 adults in LA County in early April (compared to the 7,994 confirmed cases at the time). This is a multiple of 28 to 55 times higher than the number of reported cases, and implies a mortality rate of 0.14% to 0.27% based on documented deaths from COVID-19 in LA County.

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Averaging the mortality rates from these antibody studies result in a **calculated mortality rate of 0.18%** instead of the widely reported 5%.[10]

Two-step strategy to reduce mortality

1. Early treatment with hydroxychloroquine, azithromycin and zinc

The above mortality rates are without widespread early treatment with hydroxychloroquine (HCQ) and azithromycin (AZ), which may reduce the mortality rate by up to 80% according to treatment studies by Didier Raoult MD/PhD in Marseilles.[11][12][13][14] Wide spread testing combined with telemedicine consultations and remote EKG monitoring could allow rapid diagnosis and treatment of COVID-19 with HCQ and AZ within 48-72 hours of symptom onset.[15][16] Nearly all antiviral agents effective against acute infections (e.g. Tamiflu, zanamivir, peramivir, zinc, rimantadine and amantadine) are most effective if administered within the first 48 hours of symptom onset.[17] Similarly, HCQ is likely most effective at preventing progression to invasive ventilation and death if administered in this timeframe.

Of note, there is tremendous controversy surrounding the therapeutic effects of HCQ and AZ in treatment of COVID-19. This report is not meant to be a detailed discussion of the efficacy of this treatment option. In brief, however, nearly all studies evaluating the efficacy of HCQ and AZ in *early treatment* of COVID-19 have found significantly reduced mortality rates and/or decreases in viral shedding durations. Furthermore, in the largest survey of physicians treating COVID-19 by Sermo, HCQ was elected the most effective treatment presently available. Recent negative studies showing minimal or no significant benefit of HCQ have all evaluated *late treatment* with HCQ. The average time to treatment in the majority of these negative studies was over 2 weeks from symptom onset to treatment—far too late for the antiviral effects of HCQ to show benefit.[18][19][20][21]

2. Age selective self-quarantining

If persons over age 65 were encouraged to stay home, the mortality rate could be further reduced by limiting the majority of infections to an age range with a very low mortality rate (see Figure 1 above). This could reduce the mortality rate by another 80% to 90%.[22]

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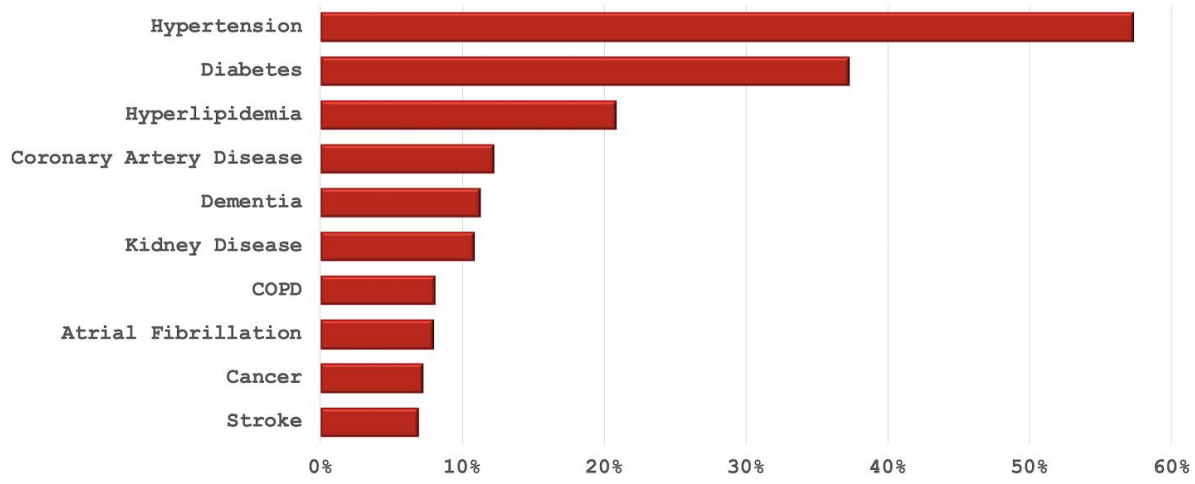
In addition to those over age 65, persons with high risk comorbidities should also consider self-quarantine as studies have shown COPD, diabetes and coronary artery disease result in significantly higher rates of admission to ICU, invasive ventilation or death.[23] Shown in Figure 2 below are the leading comorbidities among COVID-19 deaths in New York as of April 22, 2020.

Figure 2. Leading comorbidities among COVID-19 deaths in New York



Source: New York State Department of Health. Data reported daily by hospitals, nursing homes and other healthcare facilities.

Deploying the above two-step strategy, it may be possible to decrease the mortality rate from 0.18% to 0.03% based on the following assumptions. **(1)** Early treatment with HCQ and AZ reduces mortality by at least half (recall the French study estimates a reduction by 80%) resulting in an adjusted mortality rate of 0.09%. **(2)** By encouraging the majority of the elderly and those with high-risk comorbidities to self-quarantine, the mortality rate could be conservatively reduced by another two-thirds resulting in a final COVID-19 adjusted mortality rate of 0.03%.

Comparison to the seasonal flu

To compare COVID-19 to the seasonal flu (influenza), the most important number is how many people have lost and will lose their lives in this pandemic.

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With little immunity, novel-coronavirus is far more contagious than the seasonal flu. Extrapolating the Stanford and USC reported prevalence of 28 to 85 times more cases than the current 822,976 documented positive cases results in a projected 23-70 million US cases as of April 22, 2020.[5] It is possible that more people have been infected with novel-coronavirus in the past 2 months than infected with the flu in an entire flu season. We must account for this as it will increase the total deaths from COVID-19.

Experts and simulation models project that 60-70% of persons (approximately 200 million persons in the US) will be infected with novel-coronavirus before herd immunity is in effect.[24] If we multiply our adjusted mortality rate of 0.03% and 200 million, **we project 60,000 additional deaths over the next few months** (there are currently 46,122 US deaths as of April 22, 2020) from COVID-19 in the United States with quarantining of the elderly and early treatment with HCQ and AZ in effect.[25]

How does this compare to the seasonal flu? There were 45 million flu infections in the 2017-2018 flu season with a mortality rate of almost 0.14%, **resulting in a total of 61,000 US deaths.**[26]

Conclusion

Empowered with a plan to rapidly test and manage COVID-19 patients with telemedicine and treatment with HCQ and AZ, as well as age-selective quarantining, it may be possible to reopen the United States with a projected death count similar to that of a typical flu season.

This strategy could be deployed immediately in states resistant to quarantining, such as Georgia, that are likely to reopen soon regardless. In less than a month, it will be apparent if the strategy is effective and to be replicated in other states. This appears to be the best plan to get the US back to work and our economy back on track.

Community Steps

1. Disseminate this publication to the medical community. Get their input including risks to this strategy. It will be important for physicians, nurses and healthcare administrators to scale telemedicine operations and stay protected from COVID-19 when possible.

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2. Send this publication to local and state policy makers which may include your state governor. They are the ones primarily responsible for altering your state quarantine.
3. Translate this paper into all languages to determine if this strategy could be used in other countries.

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