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LETTER

Infectious diseases

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# COVID-19 and rationally layered social distancing

I would like to thank Dr Thomson for the very pertinent and relevant points that he raised in his thoughtful letter *Where are we now with COVID-19?*[1] As my response will illustrate, and in what probably will become a defining feature of conversations surrounding COVID-19 for quite some time, attempts to answer will only make room for more questions.

As COVID-19 is unfolding, every day is marked by novel developments. Since the editorial went to press,[2] the outbreak has expanded considerably. Over 128 000 individuals were infected worldwide as of 13 March 2020, leading to 4720 deaths.[3] In early March, while the outbreak in China appeared to start to subside,[4] it started to amplify in Europe and the United States. The first fatality in the United States occurred on 29 February 2020 in a suburb of Seattle. On 4 March, the first death was reported outside WA state, in CA, and was the 11th death in the United States. On 6 March, the first two fatalities were reported in Florida. On 11 March 2020, the World Health Organization declared the outbreak a pandemic.[5]

Some aspects about the outbreak were anticipated. Its rapid worldwide spread within and across countries was predictable, and so was the increased mortality among certain population groups. The magnitude of the outbreak in various countries, however, came somewhat as a surprise. The first two cases in Italy were detected on 29 January 2020.[6] As of 13 March 2020, the country experienced 12 462 infections and 827 deaths,[3] becoming to date the largest one and the one that claimed most fatalities outside of Asia.

Several scenarios may explain the large outbreak and the high COVID-19 mortality rate in Italy. Prior to the first COVID-19 diagnoses in Italy, it was reported that an unusually high number of people with pneumonia were diagnosed at a hospital in the Northern part of the country, opening the possibility that they were the first cases but they had been treated as if they had the flu.[7] It is also conceivable that by the time the outbreak in Italy was noticed, several transmission chains were already becoming established in the country.[8] Additionally, Italy has one of the world's oldest populations. In 2015 and 2016, 21%-22% of its residents were aged 65 and over, and the average life expectancy at birth, 82.7 years, is one of the highest in the world.[8,9] The high COVID-19 mortality in Italy may at least in part reflect the disproportionately high mortality that it causes in elderly individuals.

A critical facet of COVID-19, which was not always adequately underscored in the media, yet probably holds the most critical insight towards helping design and implement preventive and supportive interventions, is the breakdown of case-fatality rates by age groups. An analysis of 44 672 patients with confirmed infection in China, before 11 February 2020, helped understand the distribution of case-fatality rates across age groups. Even though the overall case fatality rate was 2.3%, higher in males (2.8%) than in females (1.7%), no fatalities were recorded for those under age 9, and the case fatality rates were 0.2% for the 10-19, 20-29 and 30-39 age groups, and increased to 0.4%, 1.3%, 3.6%, 8% and 14.8% in those 40-49, 50-59, 60-69, 70-79 ≥ 80 years old, respectively (Figure 1).[10] Notably, based on these data, COVID-19 causes disproportionately higher mortality among individuals over 60 years old, and particularly over 80 years old, than among infants and children. This is markedly distinct from influenza, which causes more severe illness and higher mortality in young children, especially infants under 6 months,[11-13] and in those 65 years and older.[14,15] The same study revealed that while case-fatality rates were 0.9% in patients without comorbidities, they were much higher in patients with comorbidities: 10.5% in those with cardiovascular disease, 7.3% in those with diabetes, 6.3% in those with chronic respiratory diseases, 6% for those with hypertension and 5.6% for those with cancer.[10,16] These findings stem from a single analysis conducted in China on patients affected during the early stages of the outbreak. It is important to consider that mortality rates, the age group distribution of mortality and the comorbidities that may shape the clinical course may be very different in other countries and during later stages of the outbreak. That is something that only time will tell.

Population genetic analyses of 103 sequenced genomes of SARS-CoV-2 indicate that there are two strains: L, more prevalent (70%) in the early stages of the outbreak and more aggressive, and S, less prevalent (30%) and less aggressive.[17] It will be important to examine whether the two strains differ with respect to incubation periods, clinical manifestations and mortality rates.

Predicting patients who may have a more severe clinical course, or face higher mortality, remains one of the million-dollar questions in COVID-19. Several studies found that certain plasma biomarkers could predict the course of the illness and guide therapeutic interventions. A retrospective multicenter study that used the databases of two hospitals from China revealed that among patients infected with SARS-CoV-2, the risk of death was significantly increased among those with cardiovascular diseases. As compared to patients who were discharged, in this analysis, patients who died had significantly higher levels of cardiac troponin, myoglobin, C-reactive protein and IL-6. Secondary infections, underlying disease and elevated blood inflammatory markers emerged in this study, in addition to

  

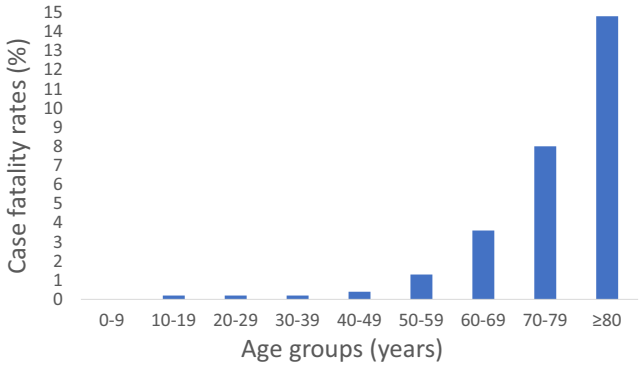


**FIGURE 1** COVID-19 case fatality rates by age group

age, as predictors of fatal outcome after COVID-19.[18] The higher risk of mortality among COVID-19 patients with cardiovascular disease was also reported in a retrospective analysis of patients admitted to the western district of Union Hospital in Wuhan between 20 January 2020 and 15 February 2020; in this study, lymphocyte counts were significantly lower in critical patients.[19]

It appears that SARS-CoV-2 is less pathogenic than SARS, which was fatal in ~10% of the patients and ~50% of patients over age 60, and less pathogenic than MERS, which was fatal in 40%-50% of the patients.[20-23] However, COVID-19 mortality rates are preliminary, and the values may change as more individuals will be confirmed retrospectively with mild respiratory illnesses that were attributed at the time to the common cold, or to have died from COVID-19 that was believed to be another respiratory illness.

One of the major differences between SARS-CoV and SARS-CoV-2, which may shape to a great extent the epidemiological distinctions between the two outbreaks, is the time when viral shedding is most extensive. For SARS-CoV, viral shedding in the saliva and transmission risk appeared to be low during the prodromal phase.[24] Respiratory shedding increased over the first week after the onset of clinical illness and remained high during the second week, when most patients were already hospitalised.[25] This partly explains why hospital workers were predominantly affected.[26] In contrast, individuals infected with SARS-CoV-2 appear to shed the virus from their respiratory tract during the prodromal period,[27] and viral shedding appears to occur in individuals who have minor clinical manifestations,[28] contributing to the extensive community transmission that we are currently witnessing.

Despite a wealth of information that emerged over the past few weeks about SARS-CoV-2, we know woefully little about the virus and about COVID-19. The learning curve will be fraught with uncertainties, unchartered territories, surprises and frustrations. While we will certainly gain more insight into COVID-19 susceptible groups, at this point it appears critical to implement social distancing in a *rationally layered* manner. Young, healthy adults have a relatively lower risk of mortality, while individuals over their 60s, and particularly those in their 80s, have a disproportionately higher mortality risk. Additionally, individuals with hypertension, cardiovascular disease, diabetes, chronic respiratory diseases and cancer are at a higher risk of mortality. It is imperative to take into consideration the increased mortality in these groups and to support social distancing interventions that are ideally positioned to protect everyone in a population and, at the same time, to more powerfully protect individuals from these highly susceptible groups. Such rationally layered social distancing interventions will constitute the most decisive determinant and predictor of successful epidemic and pandemic preparedness.

Richard A. Stein[1,2]

[1]*Chemical and Biomolecular Engineering, New York University, Tandon School of Engineering, Brooklyn, NY, USA*
[2]*Department of Natural Sciences, LaGuardia Community College, Long Island City, NY, USA*
*Email: steinr01@nyu.edu richardastein@gmail.com*

## ORCID

*Richard A. Stein* https://orcid.org/0000-0002-5944-8008

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