The 5% of the Population at High Risk for Severe COVID-19 Infection Is Identifiable and Needs to Be Taken Into Account When Reopening the Economy

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The goal of this column is to help mental health care professionals understand coronavirus disease 2019 (COVID-19) so that they can better explain the complexities of the current crisis to their patients. The bottom-line of this column is that, while COVID-19 can infect virtually everyone in the human population, only about 5% are susceptible to severe infection requiring admission to an intensive care unit and/or causing a fatal outcome and this population can be identified on the basis of comorbid medical illness and/or age. These numbers are based on experience in China, the United States, and Europe. Table 1 presents an analysis conducted by the US Centers for Disease Control and Prevention (CDC), which is further supported by several other sources reviewed in the article. The population at risk for severe infection are individuals with comorbid medical illness and those 85 years of age and older. The comorbid medical illnesses identified as risk factors are preexisting respiratory and cardiovascular disease, immunocompromised status, morbid obesity (ie, body mass index ≥ 40), diabetes mellitus, and possibly significant kidney or liver impairment. Parenthetically, news reports and the literature sometimes cite age 60 years and older as a risk factor but age between 60 and 85 years is likely a surrogate for having 1 or more of these comorbid medical conditions. While 5% may initially seem like a small number, it nevertheless potentially represents 16.5 million people, given the United States population of 330 million. That is a tremendous number of people requiring intensive care unit admission and/or potentially dying, and individuals in this population have overwhelmed the US health care system in some hotspots. For this reason, this column suggests taking this at-risk population into account in mitigation strategies when attempting to open the US economy. The column addresses the following questions: (1) What are the 3 aspects of the race to minimize the damage caused by COVID-19? (2) What data are currently available to help guide decisions to be

made? (3) What strategies have been employed to date and how successful have they been? and (4) Might risk stratification of exposure be a viable strategy to minimize the damage caused by the virus? The race to minimize the damage caused by COVID-19 requires that we obtain knowledge about the disease and its treatment or prevention, how to best safeguard public health and avoid overwhelming the health care system, and how to minimize the societal damage caused by substantial disruption of the economy. Data gathered over the past 4 months since the COVID-19 virus emerged as a human pathogen have provided guidance for our decisions going forward. The most widely adopted strategies for dealing with the COVID-19 pandemic to date have involved the epidemiological approach of encouraging good hygiene practices and social distancing, including orders to “shelter in place,” quarantine of high-risk individuals, and isolation of infected individuals. The goal of this epidemiological approach has been to “flatten the

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curve” by reducing the height of the peak of the infection to avoid overwhelming the health care system and society in general, while buying time to learn more about the disease and find more effective ways to deal with it. However, now that more is known about COVID-19 and the portion of the population that is most at risk for serious adverse outcomes including death, it may be possible to move from a shelter-in-place approach for the entire population to focus on those at most risk and thus facilitate a gradual and rational phased reduction of social restrictions to reopen the economy. Such a graduated opening would be based on regions of countries meeting specific criteria in terms of being able to contain the virus, coupled with vigorous monitoring to look for outbreaks, followed by case monitoring, isolation of infected individuals and quarantine of exposed individuals, and increased use of testing for active disease as well as for immunity. Taking the data on high-risk individuals into account would allow for a gradual lifting of restrictions on the majority of the population while maintaining more stringent safeguards to protect the vulnerable portion of the population. Nevertheless, the entire population would need to continue to practice good hygiene and social distancing while simultaneously—and perhaps even more vigorously—focusing on sheltering the vulnerable population until adequate community immunity has been achieved to prevent the spread of the virus, whether that is accomplished through natural exposure alone or with the addition of safe and effective vaccine(s) which may not be available for a year. Continued widespread testing for antibodies will help determine how far or close this country is—and other countries are—from developing effective community immunity.

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KEY WORDS: coronavirus disease 2019 (COVID-19), mental health professionals, tests, immunity, treatments, medications, vaccines, antibodies, risk stratification

This is the second column on this topic, which, like the first column on coronavirus disease 2019 (COVID-19),¹ was written with the hope of helping

mental health care practitioners understand the issues so that they can better explain the complexities of the current crisis to their patients. The same caveats outlined in the first column also apply to this one, which is a personal synthesis of the implications of the extant literature in the public domain.

The goal is to minimize the damage caused by COVID-19. Although this column will focus on the United States, the principles are generalizable to many, if not all, countries in the world, with the recognition that there are important differences among these countries which need to be taken into account in the details of their specific plans. This column, which will also use data from different countries, addresses the following questions:

- (1) What are the 3 aspects of the race to minimize the damage caused by COVID-19?
- (2) What data are currently available and how does the understanding derived from those data bear on decisions to be made?
- (3) What strategies have been employed to date and how successful have they been?
- (4) Might risk stratification of exposure be a viable strategy to minimize the damage caused by the virus in all domains: severity of the illness and economic damage which also can devastate and cost lives?

BACKGROUND

COVID-19 is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).^{2–5} This virus “jumped” from an animal species (possibly a bat or an anteater) to humans in China in December 2019. This virus causes a respiratory illness in humans that ranges in severity from no symptoms to cold-like symptoms to a severe, even fatal, respiratory illness.^{2–5}

COVID-19 is commonly referred to as a “novel” coronavirus because of its recent emergence in late 2019 as a human pathogen. Due to its novel nature, humans had little to no immunity to this virus when it emerged as a human pathogen, and data were not available about the severity of the illness it could cause, the percentage of the population that could be affected, and whether risk factors could be identified for its severest forms. Concern about SARS-CoV-2 was heightened by the fact that, since 2002, 2 other

novel coronaviruses [the SARS-CoV-1 and the Middle East respiratory syndrome (MERS) viruses] had “jumped” from animals to man and caused serious, even fatal, illnesses. As it turned out, these earlier viruses had much higher fatality rates than COVID-19 infections: 10% for SARS-CoV-1 and 34% for MERS, compared with an estimated fatality rate of 2% for SARS-CoV-2 which causes COVID-19 and <0.1% for seasonal flu.⁶

However, it is important to keep a caveat in mind concerning the death rate for SARS-CoV-2. It is a general number for the whole population, but it varies widely based on subpopulations, as it is <1% in adults who are not of advanced age (ie, 85 y and older) and who do not have certain specific serious comorbid medical conditions. When these 2 groups are excluded, most people who become infected with the SARS-CoV-2 virus have minimal to mild-moderate symptoms that do not require hospitalization, and even those who require non-intensive care unit (ICU) hospitalization are generally admitted only for a short time. Thus, readers should keep in mind that estimates concerning fatality rates from COVID-19 are influenced by at least 2 factors: (a) estimated rates will be higher based on the percentage of the population that has the risk factors of comorbid medical illness and/or is 85 years of age and older (eg, a nursing home population versus the general population), and (b) estimated rates may be substantially lower once sufficient results of antibody testing are available to determine the percentage of the population who have been asymptomatic or mildly symptomatic and have developed an antibody response to the virus.

Data concerning these issues will be discussed in more detail below but, at this point, suffice it to say that COVID-19 did overwhelm the health care system in many countries and in some areas of the United States. Since there were no scientifically proven effective and safe treatments nor a vaccine in the earlier phases of this pandemic—and that those limitations continue as of the writing of this article (April 20, 2020), the response has been to try to limit the spread of the virus by good hygiene practices and social distancing. This has included orders to “shelter in place,” quarantining exposed individuals and isolating those who are infected. This approach has resulted in shutdowns of major parts of the economy and thus sudden high unemployment which has its own negative consequences.

THE 3 COMPONENTS OF THE RACE TO MINIMIZE DAMAGE FROM COVID-19?

The 3 components of the race to minimize the damage caused by COVID-19 are the result of the background outlined above. We have needed and continue to need more knowledge about (1) the nature of the disease and its treatment or prevention, (2) how to best safeguard public health and avoid overwhelming the health care system, and (3) how to minimize the societal damage caused by the substantial disruption of the economy currently being experienced. These are 3 quite different dilemmas, which require different expertise and the ability to balance risk in these different domains.

NEED FOR MORE KNOWLEDGE ABOUT THE DISEASE AND ITS TREATMENT AND PREVENTION

The good news is that we have learned a lot about the virus and the illness it can cause over the past 4 to 5 months since it was first recognized in December 2019. Within 2 weeks of the discovery of COVID-19, researchers at the United States National Institute of Allergy and Infectious Diseases had determined how the virus enters human cells and, within 2 months, sites began Phase 1 trials of a potential mechanism-based treatment (remdesivir) and a vaccine (mRNA-1273).³ The problem is that treatment and vaccine trials historically take more than a year at the earliest to be successful. So, while these approaches are the most likely game changers, they are not likely to be ready in time to prevent loss of lives from the illness and negative economic fall-out. For this reason, there are 692 trials listed on clinicaltrials.gov examining the potential efficacy and safety of different treatments on COVID-19 as of April 20, 2020.⁷ Most—if not all—of these studies are examining the effect of already marketed drugs because historically it takes many years to develop a completely new molecular entity specifically targeted for a given illness.

WHAT CURRENT DATA AND PRINCIPLES BEAR ON DECISIONS TO BE MADE?

Since December 2019, much has also been learned about the natural history of the COVID-19 illness. The virus has a high enough basic reproduction number (R_0) to be significantly contagious. The R_0 value refers to the expected number of cases directly

generated by 1 case in a population where all individuals are susceptible to infection, as was the case for the world human population when this virus became a human pathogen. The R_0 values for COVID-19 range from 1.4 to 5.7. For comparison, the R_0 values for COVID-19 are higher than reported for the 2 earlier coronaviruses mentioned above (SARS-CoV-1 and MERS) and higher than for seasonal strains of influenza, which have R_0 values ranging from 0.9 to 2.1, but they are substantially lower than the R_0 values for measles, one of the most infectious of all human viruses, which range from 12 to 18.⁸

The R_0 value can be used to estimate the fraction of the population that needs to be immune to the virus—whether by natural exposure or vaccination—to slow or stop the spread of the virus among nonimmune individuals. This fraction is referred to as *community* (or “herd”) *immunity*. Due to its very high R_0 values, the threshold for effective community immunity for measles is 93% to 95% of the population being immune to the measles virus. For COVID-19, the threshold to achieve community immunity is estimated to be between 50% and 66%, according to Justin Lessler, PhD, Associate Professor of Epidemiology at Johns Hopkins University.⁹ Those figures are consistent with estimates that 50% to 70% of American and European populations will likely become infected with the SARS-CoV-2 virus.¹⁰ Complicating this problem is the fact that somewhere

between 25% and 50% of people infected with the virus are at least initially asymptomatic but nevertheless infectious to others based on data from the United States Centers for Disease Control and Prevention (CDC) and epidemiology studies in Iceland.¹⁰

Since December 2019, much has also been learned about risk factors for the seriousness of the illness as reflected in the data in Table 1, which were published by the CDC on March 27, 2020.¹¹ Clearly, age is an important risk factor but so also are comorbid medical illnesses, particularly preexisting respiratory and cardiovascular disease, immunocompromised status, morbid obesity (ie, body mass index ≥ 40), diabetes mellitus, and possibly significant kidney or liver impairment. Age and these comorbid medical illnesses are correlated—that is, the older a person is, the more likely that he or she has 1 or more of these comorbid illnesses. However, what is not known is whether age is simply a surrogate for having comorbid illnesses or is an independent risk factor. When younger people (ie, those younger than 55 y of age) have serious and even fatal outcomes to COVID-19, they most often have 1 or more of the medical illnesses listed above, including severe asthma. In fact, almost 90% of all patients hospitalized for COVID-19 independent of age had 1 or more of the listed comorbid conditions.¹² That means that 90% of the individuals who were hospitalized, admitted to the ICU, or died (ie, those listed in the 3 columns in Table 1)

TABLE 1. Hospitalization, Intensive Care Unit (ICU) Admission, and Case-fatality Percentages for Reported COVID-19 Cases, by Age Group—United States, February 12 to March 16, 2020

Age Group (y)	No. Cases	%*		
		Hospitalization	ICU Admission	Case-fatality
0-19	123	1.6-2.5	0	0
20-44	705	14.3-20.8	2.0-4.2	0.1-0.2
45-54	429	21.2-28.3	5.4-10.4	0.5-0.8
55-64	429	20.5-30.1	4.7-11.2	1.4-2.6
65-74	409	28.6-43.5	8.1-18.8	2.7-4.9
75-84	210	30.5-58.7	10.5-31.0	4.3-10.5
≥ 85	144	31.3-70.3	6.3-29.0	10.4-27.3
Total	2449	20.7-31.4	4.9-11.5	1.8-3.4

*Lower bound of range = number of persons hospitalized, admitted to ICU, or who died among total in age group; upper bound of range = number of persons hospitalized, admitted to ICU, or who died among total in the age group with known hospitalization status, ICU admission status, or death.

Source: CDC COVID-19 Response Team.¹¹

TABLE 2. Potential Outcomes of Different Severities of COVID-19 Infections

Severity Level	Description	Definition	Outcome
0	Asymptomatic infection	<ul style="list-style-type: none"> •Individuals who have been found to be shedding the virus but otherwise have no signs of infection at the time of testing •Represents between 25% and 50% of the infected population, with the caveat that some of these individuals may become symptomatic later, although data on that question are not yet available, at least in the public domain 	This group is particularly important in terms of spreading the disease because they are asymptomatic. Asymptomatic individuals should avoid the 5% to 10% of the population who are susceptible to serious, even fatal, infections. Once those in this group are no longer shedding virus based on testing, they should be tested for immunity
1	Mild-moderate infection	<ul style="list-style-type: none"> •Individuals who have either “cold-like” or mild to moderate flu-like symptoms but do not require hospitalization •Likely represents an additional 50% of the infected population who are not ≥ 85 y of age and who do not have comorbid conditions* that place them at greater risk of developing a more severe infection 	This group must also remain vigilant to protect more vulnerable populations. They will also account for increased days of sick leave and loss of productivity, as well as a potential albeit relatively small drain on health care resources
Severity levels 0 and 1 together likely represent 90% to 95% of the infected population			
2	Moderate-severe infection	<ul style="list-style-type: none"> •Individuals with symptoms and functional impairment sufficient to require hospitalization in a regular hospital bed, usually for several days, often to treat fever, dehydration, and concurrent infection (eg, bacterial pneumonia) •The size of this group may be reduced as physicians gain more experience treating this illness. Such a reduction would be enhanced if clinical trials prove that 1 or more of the treatments being studied are capable of preventing or treating the disease •Likely occurs in 1% to 7% of those infected in the nonvulnerable population[†] and in up to 70% among those who are infected and are ≥ 85 y of age or have significant comorbid conditions* 	Increased use of health care resources; increased risk of complications and thus negative outcomes for patients; negative impact on families and economy

TABLE 2. Potential Outcomes of Different Severities of COVID-19 Infections (*continued*)

Severity Level	Description	Definition	Outcome
3	Severe infection	<ul style="list-style-type: none"> •Individuals with sufficient symptoms and functional impairment to require hospital intensive care unit services •Likely occurs in <2% of those infected in the nonvulnerable population (ie, no comorbid medical conditions), but in 6% to 29% of those infected who are ≥ 85 y of age or have significant comorbid conditions* 	Significant impact on health care resources; increased risk of complications and negative outcomes, including fatality; negative impact on family units and economy
4	Death due to COVID-19	<ul style="list-style-type: none"> •Represents 0.1% to 0.5% of those infected in the nonvulnerable population (< 75 y of age and without comorbid medical conditions*) versus 10% to 27% of infected individuals ≥ 85 y of age† 	Significant use of health resources before death; direct and significant negative impact on family units

*On the basis of available data, these conditions include preexisting respiratory and cardiovascular disease, immunocompromised status, morbid obesity (ie, body mass index ≥ 40), diabetes mellitus, and possibly significant kidney or liver impairment.¹¹

†Estimates presented are based on the data shown in Table 1, which include individuals without regard to comorbid medical conditions. Given that ~90% of patients hospitalized for COVID-19 have been found to have comorbid medical illness,¹² these rates would be expected to be 10 times lower in the nonvulnerable population. Estimates concerning fatality rates from COVID-19 may also be substantially lower once the results of sufficient antibody testing are available to estimate the percentage of the population who have been infected but were asymptomatic or so mildly symptomatic that they could not be detected without such testing. COVID-19 indicates coronavirus disease 2019.

had comorbid medical illness. When these individuals are removed, the likelihood of hospitalization, ICU admission, and fatality drops dramatically, in some cases approaching 0. For these reasons, it is probably best to consider both age and medical status when stratifying risk. That was not done in Table 1 but it is likely that it should be done. Age up to 85 years and older is likely mainly a surrogate for comorbid medical illness. At age 85 years and above, the vital capacity of many organs, such as forced vital capacity which is a measure of lung function, has often begun to decline to a significant degree. On the basis of the information in Table 1 and other data discussed above, 5 potential severity levels of COVID-19 can be identified, as shown in Table 2.

Some caveats concerning the data shown in Table 1 should, however, be kept in mind. The numbers shown in the table represent cases from February 12 to March 16, 2020. First, early

recognition and medical care have improved substantially since then, which could produce a drop in these numbers even in vulnerable populations. Second and even more important, the data in Table 1 are based on only ~2500 cases, whereas > 775,000 cases have now been reported in the United States (as of April 20, 2020), a number that almost undoubtedly includes more individuals at severity levels 0 or 1 of the infection because cases in the early days were first diagnosed on the basis of symptoms that were not present in infected but asymptomatic people. Because the number of cases is now so much higher, the CDC will be able to determine whether the larger numbers replicate the earlier findings shown in Table 1, which will give greater confidence in the results. Such an analysis has not yet been posted in the public domain but this will likely happen and/or the results will be shared with policymakers.

WHAT STRATEGIES HAVE BEEN EMPLOYED TO DATE AND HOW SUCCESSFUL HAVE THEY BEEN?

The most widely adopted strategies have involved the epidemiological approach of encouraging good hygiene practices and social distancing, including orders to “shelter in place” and quarantine. (Parenthetically, the term *quarantine* refers to the situation in which an individual has been in close contact with someone known to be actively shedding virus. Individuals in the quarantine may be grouped together while they continue to follow social distancing and they may use masks as an added precaution. The term *isolation* refers to the situation in which an individual is infected and is isolated from others to prevent further spread of the virus.) These strategies have met with varying degrees of success depending on the country, with smaller countries in terms of landmass and population generally doing better than large countries. Not all countries have taken these approaches, with Taiwan, Iceland, and Sweden being perhaps the most notable exceptions. While those 3 countries have not experienced the same economic consequences as have occurred with the more restrictive policies elsewhere, it is too early to tell how they will do with the spread of the illness in their populations. Taiwan seems to be doing remarkably well, relying not on sheltering the general population, but instead employing early case detection followed by establishing at-risk contacts and quarantining these individuals through the period of the risk of developing and recuperating from the illness, using extensive testing for active infection and viral shedding. However, Taiwan is considerably smaller than the United States or Europe in terms of population and landmass and has less air travel, which seeded the virus in many areas in the United States and Europe.

The common phrase used to describe the goal of this epidemiological approach is “flattening the curve.” This term refers to reducing the height of the peak of the infection, which was critical in the earliest days of the infection when a steep peak could have catastrophic consequences in terms of overwhelming the health care system and society. This approach was also a way of buying time to learn more about the disease and to find more effective ways to deal with it through developing scientifically validated treatments and, even more important, vaccines. Unfortunately, as previously mentioned, developing treatments and vaccines takes time, perhaps more

time than is available to minimize the number of people becoming infected. There is also the possibility that COVID-19 might follow the same pattern of seasonal variation as seen with seasonal strains of influenza—the onset of spring will test this possibility.

The epidemiological approach has 2 potential downsides. The most obvious is its profound effect on the economy. The other is whether it simply delays—but does not meaningfully prevent—the spread of the virus. Prescribers can consider the analogy with immediate versus delayed or extended-release formulations of drugs. While the latter produce a lower peak level, they may have the same area under the curve—in pharmacokinetics, the same area under the curve means that the amount of drug absorbed is essentially the same for the 2 formulations (ie, they are bioequivalent). In the case of the spread of the virus, it might mean that the total number of infected people will be the same but that the infections will be spread out over a longer interval. While this approach is good in terms of not overwhelming health care resources, it could: (a) prolong the economic impact, which is not without adverse consequences to the population and (b) delay the time when sufficient community immunity will have been acquired to eradicate the infection and protect the vulnerable subset of the population susceptible to experiencing serious adverse outcomes. As mentioned above, the estimate is that 50% to 66% of the population will need to have immunity to the virus to substantially reduce the spread of the virus to those who are not immune and possibly even eradicate at least the current version of the virus.⁹ This last caveat concerning the “current” version of the virus is included because some viruses mutate enough that they are no longer recognized by the immune system, as is true for the seasonal strains of influenza, which is why new vaccines are produced most years before the start of the flu season.

MIGHT RISK STRATIFICATION OF EXPOSURE BE A VIABLE STRATEGY TO MINIMIZE THE DAMAGE CAUSED BY THE VIRUS?

On the basis of the knowledge about COVID-19 obtained in recent months, it appears that a small percentage of the population (5% to 10%) is at risk for a serious infection, such as occur at severity levels 3 and 4. Moreover, that vulnerable portion of the population can be identified and can shelter until at least the current version of this virus is essentially eradicated.

During the preceding 4 months, 2 approaches have generally been suggested to deal with the current crisis: (1) continue the epidemiological approach with the focus on slowing the rate of the infection and its most serious health consequences, or (2) relax the most rigorous social restrictions to end the economic suffering. The new White House Guidelines on handling this virus announced on April 16, 2020¹³ recommend a phased movement from a shelter-in-place approach to a gradual reduction in social restrictions and an opening up of the economy. Such opening would be based on regions meeting specific criteria in terms of their ability to contain the virus, coupled with vigorous monitoring for outbreaks, followed by case monitoring, quarantine of exposed individuals, isolation of infected individuals, and increased use of testing for active disease as well as for immunity (ie, the presence of sufficient titers of antibodies against the virus in the blood). As mentioned above, this approach has been quite successful in smaller countries such as Taiwan. Testing for antibodies will also help estimate how far the country is from developing effective community immunity.

However, these guidelines, at least as presented on April 16, 2020, do not take the data outlined earlier in this column into consideration. Those data suggest that individuals younger than 85 years of age without specific comorbid illnesses have little risk of developing serious illness from the current form of this virus. In this population, more rapid movement through the phases of lifting restrictions and opening up the economy seems possible, while continuing to practice good hygiene and social distancing, and simultaneously—and perhaps even more vigorously—focusing on sheltering the vulnerable population until the critical threshold for community immunity has been reached, whether through natural exposure alone or with the addition of vaccination.

This approach would have several benefits. First, it would more quickly restore the economy and thus help the entire population avoid the profound adverse societal and health effects of a serious recession or depression. Second, it would increase community immunity, which would drive down the risk for everyone, including those most susceptible to serious adverse outcomes. Third, those who develop immunity could donate antibody-enriched serum (what has been called convalescent serum) to those vulnerable individuals who develop serious adverse outcomes, which could potentially provide effective treatment while development and testing of vaccines proceed.

However, there are also downsides to this approach. First, it assumes that immunity to the COVID-19 virus will develop. Anthony Fauci, MD, the director of the National Institute of Allergies and Infectious Diseases, has been quoted as saying that he would be “willing to bet anything that people who recover are really protected against reinfection.”⁹ He has also been quoted as saying: “Ultimately, the showstopper will be obviously a vaccine.”⁹ Both statements seem almost truisms and necessary conditions to resolve this problem. Second, this approach involves risk but so, too, does either of the first 2 alternatives mentioned at the beginning of this section, but the risk with the proposed approach is arguably more calculated and nuanced. Third, individuals who are younger than 20 years old (or as old as the data indicate have minimal risk of serious adverse outcomes from the infection) and without comorbid medical illness will undoubtedly have contact with older individuals, but that is also true for the other 2 approaches. Therefore, public awareness of the need to exercise heightened concern for the vulnerable population must be understood and acted upon rather than taking a “one size fits all” approach, which is the approach that has been taken so far. That approach has led to many younger and healthy individuals incorrectly believing that they have the same risk as the vulnerable population, and, at the same time, has diminished the understanding of the need for heightened concern about the portion of the population that is at high risk. To underscore this point, in their COVID-19 surveillance report for the week of April 6-12, 2020, the World Health Organization’s Regional Office for Europe reported that 95% of those who died in Europe were 60 years of age or older.¹⁴ However, even that finding probably overfocuses on age as a surrogate for comorbid medical illness whether the patient is under or over 60 years of age.

CAVEATS

Although a tremendous amount has been learned about human infection with the SARS-CoV-2 virus, much still remains unknown. A critical next step will be to determine how many individuals in different regions of the country have been infected. That information should increasingly become available over the next weeks to months as antibody testing is done. As discussed above, that information will help determine both the infectivity of the virus (its basic reproduction number, R_0) and its fatality rate. A second major question is

whether the antibodies that are produced in response to the SARS-CoV-2 virus convey immunity to reinfection, and, if so, how long that immunity lasts. Another key question is how much of a role cell-mediated processes play in the development of immunity to the virus. The answers to these questions will determine how well giving convalescent plasma enriched with antibodies from individuals who have recovered from the virus will help treat individuals experiencing a moderate to more severe infection. That process is termed “passive immunity” to contrast it with active immunity, which refers to the production of antibodies by the immune system of an infected individual.

Moreover, in addition to the risk factors that have been identified to date and are summarized in this column, there may be other risk and protective factors yet to be identified. A key question concerns the critical aspects of the host-pathogen interaction. For example, is the sudden acute respiratory syndrome due to an excessive inflammatory response to the virus in some individuals (eg, a “cytokine storm”)? Also unknown is whether the coronavirus can develop into a low grade but continuous infection with flare-ups, as can happen with the hepatitis C virus or herpes zoster.

And how effective will vaccination be? Some vaccines against some pathogens are highly effective and their use has resulted in some illnesses essentially being eradicated. In contrast, the helpfulness of the seasonal flu vaccine varies from year to year and individual to individual.

This list of unanswered questions is not exhaustive but gives a perspective on the types of additional knowledge that are needed to combat the SARS-CoV-2 virus. The answers to these questions will be forthcoming, but this process will take time. In that interval, the information summarized here will help to mitigate the damage done by the virus, whether directly as a result of the infection or indirectly due to its effects on the economy.

CONCLUSIONS

The future is not as clear as anyone would like. This column has reviewed the great progress that has been made to date in understanding COVID-19 and possible pathways for moving forward. Perhaps the words Winston Churchill used in speaking of the Allied victory in the Battle of Egypt describe the current war with COVID-19 as succinctly as possible: “Now this is not the

end. It is not even the beginning of the end. but it is, perhaps, the end of the beginning.”¹⁵

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