Viewpoint

Educating society about the unseen, but not unknown, risk factors for severe COVID-19: a step towards overcoming vaccine hesitancy through a more informed public

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Among the well-documented reasons for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine hesitancy is a lack of perceived threat of COVID-19 illness. Current public health messaging about risk factors for severe COVID-19 supports this misconception, highlighting age and underlying health conditions readily detected in the population as the primary risk factors for COVID-19-associated complications. In addition to these well-publicized risk factors, defects in the type I interferon antiviral defense system have emerged as another significant, though less visible, risk factor for severe COVID-19. Including these findings in public health messaging will promote this knowledge outside of the scientific community and increase awareness that not all COVID-19 risk factors can be readily observed in oneself and others. Efforts to improve public education about these unseen risk factors for severe COVID-19 are likely to influence attitudes towards individual risk of disease complications and may ultimately encourage SARS-CoV-2 vaccine acceptance.

From its initial isolation in January of 2020 to early July of 2021, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has accounted for over 607,000 deaths in the United States and more than 4 million deaths worldwide. Beyond these staggering numbers and the still-to-be-determined long-term health consequences for survivors of severe disease, COVID-19 has also ravaged economies, highlighted racial and ethnic disparities and inequities in healthcare, and created political divide. With these wide-ranging effects in mind, it becomes impossible to quantify the overall toll of COVID-19, a pandemic the likes of which has not been experienced in the previous 100 years. Equally unprecedented, however, has been the development, testing, and approval of multiple safe and highly efficacious SARS-CoV-2 vaccines in the United States and other countries within the span of one year,[1–4] an accomplishment that reflects not only the commitment and dedication of research scientists and healthcare professionals but also the cooperation, sense of service, and desire to achieve the common good of thousands of trial participants. These vaccines, which include lipid nanoparticle-encased mRNA (Moderna, Pfizer-BioNTech) and recombinant adenoviral vector (Johnson & Johnson/Janssen, Astrazeneca) delivery platforms, represent our means to an end for this pandemic. Despite the promise of these vaccines, however, we may now be faced with our greatest challenge of the COVID-19 pandemic to date: overcoming vaccine hesitancy in the population.

SARS-CoV-2 vaccine hesitancy has been well-documented since the onset of the COVID-19 pandemic and is particularly concerning with new variants such as the Delta and Gamma variants spreading rapidly. With the potential for these variants to acquire additional mutations that confer resistance to currently available vaccines, it is critical that we reduce the number of hosts available for virus evolution as quickly as possible. Importantly, antibodies induced by multiple SARS-CoV-2 vaccines have been shown to neutralize recently emerging variants, including the highly transmissible Delta variant that is becoming globally dominant.[5,6] Though neutralizing titers against currently circulating variants are reduced when compared to those against the original strain, they remain at levels that are protective from serious disease. Collectively, these findings demonstrate the broad immunity conferred by SARS-CoV-2 vaccination to date, while also highlighting a worrying evolutionary trajectory that could eventually result in generation of a vaccine escape variant, an outcome that would set the world back significantly in its ongoing fight to end the COVID-19 pandemic. Therefore, efforts to increase vaccine acceptance are essential to limit virus transmission and reduce the likelihood that a variant capable of escaping the currently available vaccines will emerge.

SARS-COV-2 VACCINE HESITANCY

Despite early demand for the available vaccines, there is growing concern that supply is now exceeding demand in many locations, and the proportion of individuals who ultimately take the vaccine may fall well short of what is needed to achieve herd immunity and a return to pre-COVID existence. A number of reasons have been reported

by those who are hesitant about, or plan to decline, SARS-CoV-2 vaccination, including concerns over vaccine development and approval processes as well as apprehension about the potential side effects of vaccination.[7] While the scientific community appreciates the years of research and development that have gone into optimizing the aforementioned vaccine platforms, and that it is these long-term efforts that led to rapid clinical trials which ultimately demonstrated excellent vaccine safety profiles and efficacy outcomes, the presence of such concerns in the general population is in some ways understandable. On the other hand, among the reported reasons for vaccine hesitancy that I have been most struck by over the past year is a lack of perceived risk of threat from SARS-CoV-2 infection. In this regard, a recent analysis of 39 nationally representative, randomized polls conducted in the United States between August 2020 and February 2021 revealed that 24% of respondents not planning to be vaccinated are not concerned about serious complications of SARS-CoV-2 infection, and 16% believe the COVID-19 pandemic is not as serious as has been reported.[7] Another longitudinal study of public attitudes toward SARS-CoV-2 vaccination, with participants stratified by political affiliation, revealed either stable (in Democrats) or decreased (in Republicans) risk perception over time periods during which clear increases in SARS-CoV-2 infection rates and COVID-19-related hospitalizations and deaths were evident.[8]

OVERCOMING INACCURATE PERCEPTIONS OF RISK THROUGH IMPROVED EDUCATION ABOUT THE "UNSEEN" RISK FACTORS FOR COVID-19 COMPLICATIONS

While it is in some ways unfathomable to imagine how a virus that has produced a death toll surpassing 4 million worldwide in only a year and half can be seen as anything but high-risk, the broad range of presentations for COVID-19, which includes even asymptomatic cases, has indeed challenged the psyche, and empathy, of many. As an educator who has spoken to diverse audiences about COVID-19 since the onset of the pandemic, I am unfortunately not surprised by the lack of perceived risk cited above, as I cannot begin to count the number of times during the last year and a half that I've heard comments like, "The virus only causes the common cold in 99% of those it infects," or, "I don't have an underlying condition, so I'll take my chances." But it is as an educator that I also believe this mindset to be one that we can positively influence through more effective and consistent communication with the public.

While it is true that a large percentage of COVID-19 patients have not exhibited complications from their disease, the reality is that at no point in the pandemic has any one of us ever been able to accurately assess our own risk, or the risk of others with whom we interact, for severe COVID-19 illness. Of course factors that predict high risk of COVID-19 complications have been identified, and predisposing conditions linked to severe COVID-19 disease have been compiled and widely advertised by the Centers for Disease Control and Prevention, the World Health Organization, and various state and local public health agencies. While understanding each of these risk factors (which include age, obesity, chronic lung disease, and cardiovascular disease, among other underlying health conditions) is critical to identifying individuals at increased risk of COVID-19 complications, they are in and of themselves incomplete, and I reference them here not to highlight what they *do* show but instead to emphasize what they *do not* show.

Collectively, the risk factors most widely publicized to date paint a picture of conditions that we can see in, or know about, ourselves and potentially others as well. But we now also understand that there are other *unseen* risk factors that do not make it easy to identify a person's likelihood of developing COVID-19 complications simply by looking at them or inquiring about their medical history. To this point, multiple studies have described an enrichment of genomic and transcriptomic aberrations in anti-viral type I interferon pathway genes in critically ill COVID-19 patients.[9,10] In one study evaluating a cohort of 659 critically ill patients, Zhang et al. reported type I interferon pathway mutations in 3.5% of individuals, a rate nearly 2,000-fold higher than that observed in 534 patients with asymptomatic or benign SARS-CoV-2 infection.[10] Moreover, a significantly larger fraction of critically ill COVID-19 patients exhibit neutralizing autoantibodies against type I interferons, further highlighting viral escape from this pathway as a correlate of severe COVID-19 disease, albeit by an alternative mechanism. This latter means of interferon pathway antagonism has been reported in a striking 13.7% of patients with life-threatening COVID-19 (135 of 987 patients), whereas autoantibodies against type I interferons were not detected in any of the 663 patients with asymptomatic/mild disease included in this study.[11] Together, these data highlight patient-intrinsic defects in the type I interferon pathway as a correlate of severe disease in a substantial portion of critically ill COVID-19 patients. Importantly, while it is possible that COVID-19 complications in patients harboring interferon pathway defects could be exacerbated by factors such as age and other underlying health conditions, these defects are also likely to account for many of the previously unexplained critical COVID-19 cases involving otherwise apparently healthy young individuals. Indeed, the aforementioned and related studies determined that genetic aberrations in interferon pathway genes and the presence of anti-interferon autoantibodies were clinically silent conditions prior to SARS-CoV-2 infection, yet they were found to be enriched in adolescents and young adults who were later hospitalized or died as a result of COVID-19 complications.[10–12]

Genetic defects in the type I interferon system have been linked to complicated infections with other viral pathogens as well.[13] Despite the clear significance of this system to antiviral immune function, however, it remains difficult to estimate the prevalence of immune-compromising interferon pathway mutations in the population because of the large number of type I interferon pathway genes that exist and the uncertain functional consequences of any given genetic aberration that might occur in these genes. Such issues also present challenges for developing diagnostic screens to identify patients at higher risk of severe COVID-19 as a result of interferon pathway gene defects. In the largest co-

hort of COVID-19 patients studied to date, predicted loss-of-function mutations in 13 type I interferon pathway genes were experimentally validated as determinants of impaired interferon signaling and found to be enriched in critically ill patients – only 0.19% of the 534 patients with asymptomatic/mild disease harbored such mutations, compared to 3.5% of the 659 critically ill patients.[10] This study did not assess interferon pathway gene mutation status in healthy controls, and while the frequency of such mutations in the asymptomatic/mild disease cohort does point to a low prevalence of these genetic aberrations in the population, it is important to note that the set of 13 genes analyzed represents only a small fraction of the genes involved in the type I interferon pathway. It is indeed likely that the integrity of other interferon pathway genes also influences patient response to SARS-CoV-2 infection. With regard to antibody-mediated autoimmune interference with type I interferon function, an analysis of 1,227 healthy individuals also revealed a low frequency of occurrence, with anti-interferon antibodies being detected in only 0.33% of cases.[11] Though the prevalence of these interferon-associated risk factors is thus relatively low in the population at large, it is important to note that these conditions are clinically silent and independent of age, meaning that anyone could unknowingly harbor these predisposing risk factors for severe COVID-19. Moreover, when put into the context of the scale of the COVID-19 pandemic, even these low frequencies equate to a significant number of patients who either have been, or still could be, impacted by severe COVID-19 complications as the result of risk factors that remain poorly publicized and unknown to many in the population.

Unfortunately, although the scientific community has appreciated the significance of the aforementioned and related studies since their original publication in the fall of 2020, their findings have not yet become part of public education campaigns to raise awareness about the diverse array of risk factors for COVID-19 complications. Going forward, it is critical that those outside the scientific community be presented with the more complete picture of COVID-19 risk factors that scientists now understand. And in sharing this message, it must be stressed that we cannot see genetic mutations the same way that we can see age. Likewise, we cannot guess that an apparently fit, healthy-looking teenager might harbor pre-existing autoimmune antibodies to components of their viral defense system the way we might guess, or even be informed, that someone suffers from obesity-related diabetes. Knowledge of these issues will allow individuals, both young and old, to make more informed choices about personal and public health, and while not all who are currently hesitant to become vaccinated are likely to be influenced by such information, perhaps those whose vaccine hesitancy is related to a lack of perceived risk will better understand the potentially unseen risk they and oth-

ers may harbor. And perhaps this understanding will promote empathy and encourage vaccine acceptance by this not-so-small population, in turn bringing vaccination rates closer to a level needed to achieve herd immunity.

CONCLUSIONS

Upon reflecting on the many tragedies wrought by the COVID-19 pandemic, I have come to appreciate more than ever just how critical science education and scientific literacy are to our global society. Indeed, outside of the loss of life we have witnessed, I believe that the politicization and distrust of science that has in many ways also "gone viral" over the last year and half will one day be recognized as the greatest tragedy of this pandemic, and society's greatest failure in the response to it. To its credit, the scientific community has acknowledged throughout the pandemic that it does not, and may never, understand the full extent of risk factors that predispose patients to severe COVID-19 disease. What it must do a better job of acknowledging now, though, is what it *does know* about COVID-19 in a way that communicates its understanding of this disease more effectively to the public. This is how we will earn better trust in science, and this is how we will end the current pandemic and be better prepared to respond to the next one.

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