COVID-19 Op-Ed

(U) COVID-19: Missing Puzzle Pieces, Time, and Black Swans

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COVID-19 caused by SARS-CoV-2 has become a rapidly developing epidemic across the world. Manifestations include fever, cough, pneumonia, and myalgias. The unforeseen elements include cytokine storm and multiorgan failure emanating through small vessel thromboses in the lung, kidney, skin, heart, and brain. Loss of smell or taste (anosmia and ageusia) may be prodromes or at time the limit of involvement. As of 29 May 2020, there were over 5.8 million confirmed cases and 360 thousand deaths; over 1.7 million confirmed cases and over 100 thousand deaths occurred within the United States. [1]

The Veterans Affairs (VA) Health Care System cares for over 9.2 million Veterans. Between 8 February and 26 May, over 172,000 have been tested for SARS-CoV-2, with 11,300 testing positive, 8,700 reaching convalescence [2], and 3,600 hospitalized. The VA Office of Research and Development is embedded in the covered heath care entity and is developing several intramural efforts alongside other Federal agencies to overcome this pandemic.

To treat hospitalized patients at several VA facilities, a partnership with the National Institute of Allergy and Infectious Diseases was forged to identify the combined effectiveness of the anti-viral Remdesivir and the anti-inflammatory Baricitinib. Industrial sponsorships with Regeneron in the use of the IL-6 inhibitor sarilumab and with Hoffmann-La-Roche in the use of tocilizumab also are underway. In an effort to treat the virus and detect immunity, coalitions have been established with other Federal groups to share information. Pilot studies are underway to understand the epidemiological, immunological, and clinical characteristics of patients with and without the virus.

These efforts require a backbone of data collection, sample accrual, and tracking on a national scale. One effort to address patient data is aligned with the Million Veteran Program (MVP) [3], which has been recruiting veterans as partners in a biobanking and genomic data and medical record analyses open to VA investigators through our intramural research programs. The operative approach during this pandemic is to identify and gather survey data from the 760 thousand participants on whether they have or had COVID-19, and related data associated with the disease. Improved detection and surveillance will use secondary serial sample collection.

A second effort is to fully establish a VA infectious disease-related biobank and data repository in order to contribute meaningful samples and clinical data for current and future pandemic responses. Samples will be obtained through consent and stored at the VA Office of Public Health Surveillance and Research. VA researchers and partners may request samples upon successful grant review and funding or partnerships. A robust laboratory information management system partnered with MVP will further extend the capabilities of this second biobank.

While these efforts are absolutely necessary for our success in better understanding this pandemic and others that might occur, there are several missing pieces of this puzzle that all must identify. Although there have been many successes during the current pandemic, questions remain and their answers may help current and future pandemic response. Some points to ponder are as follows:

- While a myriad of studies identify viral elements for immunogenicity, clinical testing, and the like, it appears that nearly nil studies ascertain the actual dose of virus particles to produce an infection versus immunogenicity versus mortality. Animal studies provide some insight; however, the applicability to human patients is uncertain. [4] Dose and stability of the virus under specific conditions is immensely important as it might give us a clue as to the relative risks associated with exposure to contaminated surfaces or breath.
- What is the SARS-CoV-2 genetic stability over time? Fortunately, there are public access data about the strain evolution [5]; however, infections may have occurred weeks to months ahead of the reported early December 2019
timeframe. As such, there are neither similar nor prior samples available to verify the accuracy of the December 2019 viral sequence data. With the data available, the virus appears to be relatively stable over time; however, researchers have found an ORF8 deletion. [6] In the SARS epidemic, this deletion reduced infectivity. It is uncertain if a similar effect will be seen with COVID-19. More broadly, what exactly do sequence changes mean for greater or lesser infectivity? For instance, could it be the 12 extra nucleotide bases of the furin cleavage site or presence of TMPRSS2 that impacts infectivity?

- How does human genetic variability and temporal expression affect vulnerability or resilience? While the human angiotensin-converting enzyme 2 (ACE2) receptor appears to be the location where the SARS-CoV-2 spikes bind [5], research has minimally explored the polymorphisms present with ACE2. Moreover, the temporal expression of ACE2 appears to increase with age, yet tissue types and extent are not well known. Finally, does an individual have unique, specific combination of genetic variants that could prevent infection or mark an individual as highly susceptible? The hope is that large biobanks and datasets like MVP or the NIH All of Us Program might used to analyze human genetic data to understand how genetic variability affects vulnerability to the virus. This is especially important given that there may be a second wave.

- Modeling of the disease is remarkably varied and questioned. [7] Not having a basis or standard for what is called a “COVID-19 positive patient” leads to varied results and limits the ability to cooperatively use data from other sources. Finding ground glass opacities on lung scans, RT-PCR versus next generation sequencing results are not all the same, yet different countries view the “correct” approach differently with different numbers of individuals infected using such methods. Questions seeking cogent answers are hard to find.

- Emerging technologies have been missing in this fight. The much-regarded artificial intelligence community has brought a relatively anemic response, possibly due lack of data availability, which may be solvable by large biobanks such as MVP, as discussed above, and/or inconsistent testing criteria as discussed. While image analysis of lung scans has performed quite well in this arena, the infrastructure and validation needed dwarfs its immediate utility, as does the variety of lung involvement by COVID-19. Also, the use of CRISPR technology for detection of virus by Mammoth Biosciences and Sherlock Biosciences has come onto the arena recently. Will they have the portability and bandwidth to perform tests into the millions? Where is synthetic biology at this time?

- This virus has overwhelmed both hospitals and supply chains. How should health care systems prepare for the next black swan event that require supplies and technologies for adequate response? What is the best way to network, stockpile or generate on demand items necessary for diagnoses and treatment? The lab community cascaded through low supplies of swabs, transport media, reagents for tests, and platforms to perform tests. Standards of reporting were superior; however, sharing of findings through peer review are still lacking, with many ground-breaking articles presented as preprints that only then undergo partial peer review. Who relays the commentaries to the community?

The focus should be on evaluating the quality of the response to the current situation and determining areas for improvement, and doing so in an unbiased manner. Clinical expertise armed by good science will provide strong clues, the puzzle pieces that ultimately fill in voids and lead to durable results. Communication and misinformation modulates these outcomes and saps time. Time, the Heraclitic panta rei, the “you could not step twice into the same river, for the waters are ever flowing on to you” is relentless. Is this nation ready to prepare for our next black swan event? It only takes time.

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Dr. Przygodzki’s research expertise and interests are in anatomic and clinical pathology and molecular genomics, spanning from the theoretical to practical clinically translatable arenas. He has developed unique molecular-based techniques—in particular, ones invented around the use of small archival tissue specimens typically found in pathology. He has authored numerous publications, book chapters, and books. Some of his molecular pathology research efforts led to the reclassification of two pulmonary malignancies by the World Health Organization, and have allowed him to receive national and international recognition. His current aims are targeting pharmacogenomic combinatorial analyses to help guide opioid and major depression therapies.