Appendix I. Pharmacotherapy Article

Exploring the Variants of COVID-19 and Their Consequences

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On March 11th, 2020, the World Health Organization (WHO) declared the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) outbreak a global pandemic. The world has come to know the coronavirus disease 2019 as COVID-19. The acronym, COVID-19, is derived from the following words: corona 'CO', virus 'VI', and disease 'D'. The COVID-19 lineage is linked to the same family of viruses that cause Severe Acute Respiratory Syndrome (SARS) and some types of the common cold. COVID-19 statistics have been compared with previous viruses that are in the *Coronaviridae* family of viruses (Figure 1).[1] When you evaluate the number of infected cases and deaths, COVID-19 is still an ongoing problem that has not been controlled. As of today, the total number of cases of COVID-19 worldwide are 194 million and deaths from COVID-19 are 4.16 million.[2] There are several contributing factors to the continuing rise in mortality rates. The most evident factors are the number of unvaccinated individuals and the rise of COVID-19 variants.

On December 11th, 2020, the U.S. Food and Drug Administration issued the first emergency use authorization (EUA) for a vaccine for the prevention of COVID-19 caused by SARS-CoV-2. The first vaccination against COVID-19 was introduced by Pfizer on December 11th, 2020, which was shortly followed by Moderna's COVID-19 vaccine on December 18th, 2020. Both vaccines became available for selected patients with certain comorbidities such as asthma, COPD, and diabetes, as well as the elderly population. As seen in Figure 2 below, there is an evident trend illustrated when you look at the number of deaths due to COVID-19.[3] First, we saw a spike in COVID-19 deaths from November to December 2020 that reflects the holiday season where families congregated to celebrate the New Year. Around the end of December 2020, the vaccine was introduced to the public. There was a significant decrease in deaths after the projected 2nd dose of the vaccine around January to February 2021, with a steady decline in mortality rate.

On July 27th, 2021, the CDC recommended that everyone in areas with high COVID-19 infection rates wear masks in public indoor spaces regardless of vaccination status. There is mountain of evidence that masks help stop the spread of coronavirus due to the barrier concept of a layer between you and the virus in the air that can aid in preventing transmission of the disease. This mask mandate is necessary, though rare breakthrough COVID-19 infections can occur in people who are fully vaccinated due to the emerging Delta variant. If the vaccinated individuals have a breakthrough infection, the incidence of hospitalization or death is considerably lower compared to unvaccinated individuals. Furthermore, herd immunity is another method to protect those who cannot receive the vaccine due to certain medical conditions such as autoimmune disorders. Vaccinated patients confer herd immunity, whereas individuals who received immunity from a previous COVID-19 infection do not. This illustrates the necessity to attain herd

immunity in order to protect the members of our society who cannot receive the COVID-19 vaccine.

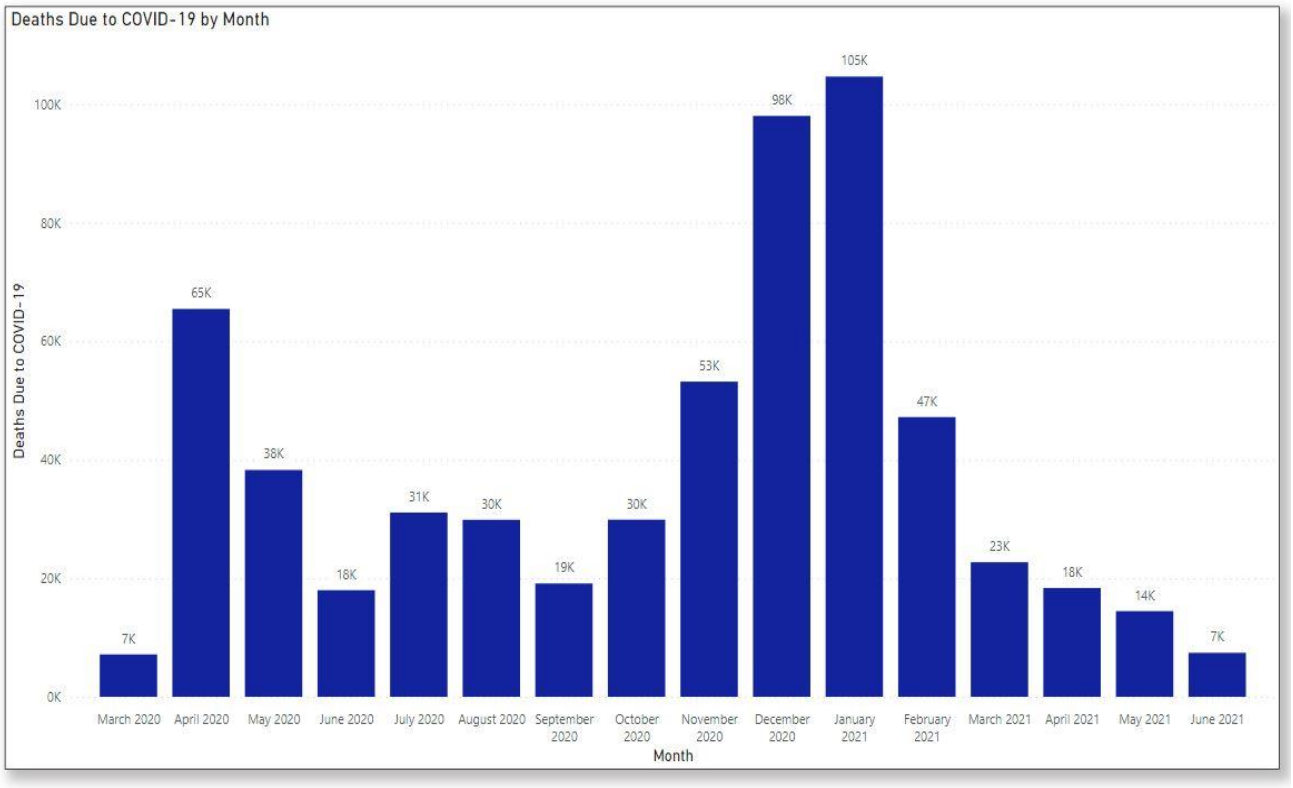
Evidence shows compelling data that vaccinated patients have a higher protection against COVID-19 infection compared to individuals who received immunity from a previous COVID-19 infection. COVID-19 vaccines have a higher antibody titer (10 times higher) than convalescent plasmas from donors who recovered from natural infection.[4] The CDC reported 6,587 COVID-19 breakthrough cases as of July 26th, including 6,239 hospitalizations and 1,263 deaths. Since the inception of the COVID-19 vaccine, 163 million people have been fully vaccinated. Furthermore, less than 0.004% of fully vaccinated people had a breakthrough case that led to hospitalization, while less than 0.001% of fully vaccinated people died from a breakthrough COVID-19 infection.[5]

Figure 1

	SARS-Cov-2	SARS-CoV	MERS-CoV
First Emergence	December 7th, 2019 Wuhan, China	November 16th, 2002 Foshan, China	April 4th, 2012 Zarqa, Jordan
Recent Status	Pandemic Ongoing	Completely Controlled	Sporadic/Continuous
Number of Infected Cases (Worldwide to date)	Above 200 million	8096	2553
Number Attributed Deaths (Worldwide)	4,270,089	774	896

Source: World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 175. 2020. https://www.who.int/docs/default-source/coronaviruse/ situation-reports/20200423-sitrep-94-covid-19.pdf?sfvrsn=b8304bf0_4. Accessed 13 July 2020

Figure 2



Source: Center Disease Control on Deaths involving coronavirus disease 2019 (COVID-19), pneumonia, and influenza reported to NCHS by time-period, jurisdiction of occurrence, sex and age group. Continuous Data. Access data 08/04/2021

Vaccine distribution is the principal driving force as to why there has been a decrease in the COVID-19 mortality rate. So why are we seeing people who have been vaccinated against SARS-CoV-2 being hospitalized for COVID-19? To answer this question, we have to investigate two fundamental concepts of viral mutation: antigenic drift and antigenic shift.

Antigenic Drift

Viruses replicate in order to spread their genetic information and infect their host. Our body's immune system can learn to identify viruses through infection or vaccination, both of which provide active immunity. Even if the parent virus clones itself and produces more viral progeny, our body has learned to identify these viral cells and activate our immune response quicker to prevent infection. However, if the parent virus introduces genetic mutations during the replication process, it can cause alterations to viral genotypes that may affect virulence, pathogenicity, or surface antigens, among other viral phenotypes.[6] When these genetic mutations alter surface antigens, our body can no longer identify the viral progeny, allowing them to evade our body's immune system and cause infection. This ability of viruses to alter their surface antigens through genetic mutations over time illustrates the concept of antigenic drift and contributes to the rise of variants in most viral species.

Are Variants Due to Antigenic Drift?

The short answer is no.

Mutations due to antigenic drift can be advantageous to the virus (such as increased virulence) or detrimental to the point where the virus is rendered inert, eventually leading to virus extinction. DNA viruses have a mutation rate of approximately 10^{-8} to 10^{-6} substitutions per nucleotide per cell infection (s/n/c) while RNA viruses have a higher mutation rate that ranges from 10^{-6} to 10^{-4} s/n/c.[7] Ultimately, larger RNA viruses will have the highest mutation rates among viruses since they will create more mutations per genome replication.

SARS-CoV-2 is a single-stranded RNA virus with one of the largest genomes of all RNA viruses (30-33 kilobases) that utilizes an RNA-dependent RNA polymerase to replicate genetic information.[8] Based on this knowledge of the virus, it should be expected that the SARS-CoV-2 virus can introduce a plethora of beneficial and detrimental mutations to its genome over time, inevitably leading to variants due to the antigenic drift theory. However, the coronavirus family contains the first known viral RNA proofreading exoribonuclease, which increases the fidelity (i.e. accuracy) of the proofreading mechanism and decreases the number of detrimental mutations.[9] This explains how SARS-CoV-2 is able to have larger and more complex genomes compared to other RNA viruses. The proofreading capability also means the virus is mutating at a slower rate, which explains why SARS-CoV-2 mutates four times slower than the influenza virus. So if antigenic drift does not contribute to variation in the SARS-CoV-2 viral genome, then what does?

Antigenic Shift

When two different strains of a similar virus infect a host, a rapid exchange of genetic material can occur resulting in a new viral subtype that comprises a mixture of the parent viral strains. Looking at the influenza viral genome, it is composed of 8 separate genomic segments.[6] If two different strains of the influenza virus infect the same host at the same time, these genomic segments from each strain can mix in a process called reassortment.[10] This can cause massive changes to the viral genome resulting in extensive alterations to virulence, pathogenicity, surface markers, and other phenotypes. If drastic changes are made to viral surface markers, our body will be unable to identify novel strains that arise from reassortment. This is one mechanism that can quickly render vaccines ineffective. Taking all of the potential phenotypic changes into consideration, one can understand the devastating consequences of viral strains undergoing an antigenic shift: global pandemics.

Think back to the H_1N_1 (Swine Flu) pandemic. An influenza virus strain that was circulating amongst European pigs was able to combine with avian and human influenza strains to create a novel influenza virus with different surface antigens that current flu vaccines could not protect against.[11] The same process is happening with the current coronavirus variants, except through a slightly different mechanism. The genome of coronaviruses are single-stranded rather than segmented like the influenza virus. Instead of going through reassortment, two similar

coronavirus genomes undergo recombination, creating a novel coronavirus genome with different viral attributes than the parent viruses.

It is important to note that the original SARS-CoV-2 strain evolved into a pandemic due to the lack of available treatment at the time of its emergence. The current Delta variant is becoming more prevalent and resistant to current therapies because of antigenic shift and recombination of the coronavirus genome, causing alterations to structural components such as the spike, envelope, or membrane.[8,12] Spike proteins help facilitate SARS-CoV-2 entry into human cells, but also serve as surface antigens that our body uses to identify the virus as a pathogen. If spike proteins are modified enough during recombination, our body's immune system may not be able to recognize a novel strain or variant, thus allowing it to replicate freely in our body and cause infection. This concept of antigenic shift and subsequent recombination of the SARS-CoV-2 virus fuels the concern requiring booster vaccines to be given to fully immunized individuals in an attempt to prevent another exacerbation in the ongoing pandemic.

As this pandemic rages on, the best defense we have against the SARS-CoV-2 virus from a healthcare perspective is vaccination. Even with vaccination though, we are not protected against all variants of the virus. Evidence has shown that we are significantly less likely to be hospitalized or experience fatal outcomes if vaccinated, but symptoms of COVID-19 infection may still be present. As pharmacists, it is paramount that we disseminate accurate information, raise awareness regarding the importance of vaccination, and aid the general public in the comprehension of the looming threat of coronavirus variants.

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