

Overview of the recent evolution of RNA coronaviruses: from MERS to COVID-19 and Omicron: An editorial perspective

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The purpose of the present editorial is to briefly review the evolution and development of the MERS, SARS, and COVID-19 coronaviruses. From a historical perspective, epidemics occur approximately three times a century somewhere in the world, while pandemics about once a century, and each time a different infectious organism has been discovered to be the infamous culprit.¹ In addition, those individuals who also have comorbidities often entertain the greatest risk of the most serious complications of the emerging illness.^{2,3} In January 2020 the novel coronavirus, SARS-CoV-2, was identified as the cause of an outbreak of viral pneumonia of unknown origin in Wuhan, China, having infected over 200 people and causing several deaths in the early phase of the outbreak.^{2,4} The disease was later named coronavirus disease 2019 (COVID-19), which subsequently spread globally in a seemingly exponential manner and was determined by the World Health Organization (WHO) to be the origin of a pandemic within the first few months of its emergence. In the first three months after COVID-19 emerged, nearly one million people became infected and 50,000 mostly older individuals had succumbed due to complications of the illness. By six months into the outbreak the number of cases worldwide exceeded 10 million and there were more than 500,000 deaths. To date, there have been over 45 million cases and over 6 million deaths reported globally, and 958,000 deaths from COVID-19 just in the United States alone, marking a new milestone in the pandemic.⁴⁻¹¹ While over 70% of the populations of developed countries report having been vaccinated, that figure is averages as low as 7% in undeveloped Nations.⁸⁻¹¹ Moreover, a recent report from the Lancet Researchers indicated that actual tallies are likely fluid and may be as much as three-fold greater than the above data due to widespread underreporting and pandemic fatigue among other factors.¹¹

One of the troubling observations about COVID-19 is that people who were infected with SARS-CoV-2 can transmit the virus to others when asymptomatic and often before they have developed overt symptoms of disease, and whereupon infection, the virus may infect multiple organs and tissues including brain, cardiovascular, pulmonary, and other organs in its newfound host.^{12,13} A second troubling observation is the discovery of numerous variants of the original virus, with unknown transmissibility variations in the pathophysiologic sequelae and potential for serious illness. A third troubling observation is that prior vaccination or natural immunity to COVID-19 does not fully protect individuals from reinfection only months afterward, although subsequent infections tend to be less severe than occurs in unvaccinated populations.^{6,12} The NIH National Institute of Allergy and Infectious Diseases (NIAID) COVID-19 research efforts have built upon earlier research on severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which also are caused by earlier discovered strains of coronaviruses and to compare their similarity to the emergence of SARS-CoV-2 and its emerging variants, the virus causing the COVID-19 pandemic.

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Middle East Respiratory Syndrome (MERS) is a coronavirus respiratory disease that was first reported in humans in Saudi Arabia in September 2012 and has since spread to 27 countries, according to the WHO.^{14,15} People infected with MERS develop severe acute respiratory illness, including fever, cough, and shortness of breath. The WHO confirmed 2,578 MERS cases and 888 deaths from the illness from 2012 through August 2021, most of which were in Saudi Arabia.^{16,17} Another respiratory coronavirus, severe acute respiratory syndrome (SARS) was first reported in Asia in February 2003, though some cases subsequently were tracked to November 2002.¹⁵ Like MERS, infection with the SARS coronavirus (SARS-CoV) can also cause a similar severe viral respiratory illness.^{2,17} SARS quickly spread to 26 countries within four months before being contained, causing illness over 8,000 people and 774 deaths due to the illness. Since 2004, there have been no new reported SARS cases. Research evidence suggests that SARS-CoV and MERS-CoV are genetically related, and both may have originated in bats and possibly been transmitted to other intermediate host animals before being transmitted to and infecting humans. SARS-CoV appears to have spread from bats or infected animals sometimes used as a meat source, while MERS-CoV was found to have spread from infected dromedary camels to people.^{14,15} Both viruses spread predominantly via microdroplet transmission, including contact with contaminated surfaces as is common among the known mechanisms of viral transmission.^{8,14,16}

To date, the definitive origin of SARS-CoV-2 which caused the COVID-19 pandemic has not been definitively identified, but it is noteworthy that related coronavirus species are commonly found in bats and can be readily transmitted to other intermediate hosts.^{8,14} The SARS-CoV-2 virus has among the largest genomes of known coronaviruses, and the nucleotide base sequence has some unique segments not common among earlier known coronaviruses.⁸ The scientific evidence thus far suggests that SARS-CoV-2 likely may have originally resulted from viral evolution in nature and jumped from bats to people or through some unidentified intermediate edible animal host such as a civet, thereby potentially entering the food chain

of humans. Public health and scientific organizations are engaged in a continued international effort to uncover the confirmed origins of SARS-CoV-2, which is deemed essential to preventing future pandemics. Unfortunately, the confirmed origins of the SARS-CoV-2 have not yet been identified.¹⁸ Since the airborne microdroplet mode of viral transmission is difficult to contain via conventional measures, in addition to the emergence of numerous mutated variants including the Delta and Omicron, the pandemic has posed considerable difficulty in public health efforts to bring about its containment. Early research on coronaviruses was conducted in several labs, including the Wuhan Institute of Virology in Wuhan, China, located in close proximity to the suspected origin of the initial outbreak. The naturally occurring bat coronaviruses studied in Wuhan were found to have become significantly genetically different from earlier SARS-CoV-2 strains studied, and it was soon determined that the earlier strains were associated with more milder and not life-threatening forms of the respiratory illness than the current SARS-CoV-2, and thus could not have caused the present COVID-19 pandemic at least not likely in their original genomic form.¹⁷ By late 2020, through intensive cooperative efforts in the US government and private sectors, several vaccines were quickly developed, most with reported efficacy of well over 90% effectiveness in the initial short term studies.¹⁹ In late 2021, two oral medications have also received preliminary approval from the FDA and additional vaccines are under study.

One of the unfortunate characteristics of the immune responses to coronaviruses in humans however is the observation of an apparent transient nature of the initial antibody responses, a phenomenon also common to some other viral infections.²⁰ The transient immune response to COVID-19 now appears to become diminished to low circulating antibody concentrations within several months following immunization or a natural infection, thereby rendering individuals potentially subject to reinfection albeit it of a lesser magnitude than the initial event one or more times.¹² While the available mRNA vaccines appear to target one or more epitopes of the spike protein, the natural immunity likely addresses a broader range of the viral epitopes, thereby potentially rendering a broader and potentially longer lasting immune protective response than immunization alone, both of which origins of immunogenic stimuli may be enhanced with follow-up booster immunizations.²¹ When first exposed to a novel virus, the normal immune response triggers the maturation of clones of short lived plasmablasts and a population of longer lasting antibody producing plasma memory cells (B cells), and the newly acquired immune memory may last for decades or longer via the actions of both plasma B cells and memory cells of the bone marrow. As the viral infection becomes cleared, the longer lasting B cells typically continue the humeral response in the event of a viral re-exposure or reinfection.¹² The bone marrow also contributes to the long-term immune-protective phenomena via the formation of bone marrow plasma cells (BMPCs) where they normally function as a second arm of the long-term immunoreactive elements of the immune responses. Typically, the reinfections which have occurred following immunization or natural immunity via these processes tend to be of less severe magnitude than occurs in unvaccinated or previously exposed people, and therefore prior exposure via either mode of exposure, vaccination, or viral exposure, offers a distinct immunologic advantage during recovery.⁶ Recent findings indicate that following active infection or immunization protective antibody levels decrease to about 10% of those observed during the peak response but can respond to the re-exposure within a week of the immunodulatory event.

The transient nature of the initial immune response, combined with the more rapid chronology of the early viral replication in the infected

host likely contributes to the more serious illness often observed in older individuals, where the presence of comorbidities including respiratory, cardiovascular, and other illnesses that are typically more prevalent and often become more severe in older patients may occur more slowly with advancing age. The slower immune response may therefore negatively complicate the COVID-19 illness and become the triggering point in the comorbidities that have resulted in more severe illness, longer recovery times and more disabling outcomes than have been reported in younger and healthier patients who lack such contributing comorbidity factors. In addition to immunization, a healthy diet containing absorbable forms of antioxidants nutrients, vitamins C and D3, zinc and other essential nutrient factors in addition to a healthy lifestyle is universally beneficial in minimizing the pathophysiologic impact of the illness.⁸

As with many viruses including influenza and the common cold, the coronaviruses are also subject to periodic mutation, thereby generating multiple epigenetic forms of the virus and which variants may result in variations of symptoms observed in the originating COVID-19 virus.^{8,14,21-24} Of concern, emerging coronavirus mutations may partially elude current vaccine and treatment protocols, and thus may enable the virus to continue to remain in circulation and remain infectious. The most recent variants, the Delta and the Omicron, have an even larger genome and more spike protein mutations than previous iterations, and have been reported to be more transmissible than previous variants, with up to 70% or more of new cases appearing to be caused by this latest variant on the spike protein. The relative infectivity and contagion of each new variant poses additional challenges to public health measures and may introduce illnesses of greater or lesser magnitude than the original form of the virus. While the greater transmissibility of recent variants presents an additional public health challenge the Omicron variant in particular has often resulted in a less severe magnitude of illness, fewer hospitalizations and few if any documented deaths caused directly by the Omicron variant. The recent emergence and identification of the Delta, Omicron and other variants continue to spread globally, often despite prior vaccination and boosters with any of the currently approved vaccines or with natural immunity from previous infection.

The extent to which natural immunity acquired from previously contacting the illness may protect against emerging variants of the originating strains or the duration of vaccine or live virus induced immune protection remains unclear, but a key characteristic of coronavirus infection noted above is the transient nature of the initial immune response developed by the infected host, many of whom were considered 'fully vaccinated.'²⁵ Some recent studies indicate that the peak magnitude of the host virus replication occurs prior to the peak antibody response, thus enabling the virus to evade the immune response during the early stages of the infection, likely exacerbating the magnitude of illness especially when it occurs in the presence of comorbidities.²⁶ The extent to which the apparent chronologic imbalance between the early viral replication and the host immune responses in the 'long covid' forms of the illness, where diverse chronic symptoms in cardiovascular, brain, musculoskeletal and other organ systems may persist for months after the acute infection has cleared, has not been determined at the time of this writing.^{26,27} On the brighter side, prior vaccination or natural immunity tends to result in a less serious illness than may occur in the unvaccinated or those members of the population with natural immunity from a recovered prior infection.^{8,12} Were an attenuated variant with lesser pathophysiologic potential that could produce plasma and bone marrow memory, and which variant could immunologically cross-react with the more severe emerging variants of the virus, it could facilitate the development of a herd immunity in the community and

thus contribute to a global recovery from the current pandemic. Only time will reveal if the Omicron variant can become the attenuated form of the virus that may eventually contribute to the resolution of the Covid-19 pandemic.^{28,29}

In conclusion, the coronavirus pandemic including recent variants continues to spread across the globe in the absence of more effective treatment protocols, vaccination, boosters, or containment measures and where it continues to infect both unvaccinated, vaccinated and previously infected individuals. The global impact has been extraordinary, now exceeding 45 or more million individuals who have contracted the virus, many with comorbidities, resulting in at least six million deaths to date. This represents a significant loss of lives, severe crippling of the global financial and healthcare burdens imposed, and in the economic and industrial productivity of virtually all nations that contribute to the global economy. Moreover, the initial transient nature of the typical immune responses to immunization or natural infection in addition to the viral interaction with comorbidities poses additional unforeseen logistical problems in immunizing a sufficient proportion of the global populations in the short enough time frame, whereby logistical and other issues may impede ongoing vaccination programs, and therefore of being able to obtain an effective herd immunity as an essential element of global containment of the Covid-19 pandemic.

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Conflicts of interest

All authors declare that there is no Conflicts of interest.

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