The Recent Origin, Evolution, and Containment of RNA Viruses: MERS, SARS, and COVID-19 and their Impact on Global Healthcare: An Editorial Perspective

George P. Einstein and Orien L. Tulp*

University of Science Arts and Technology, Montserrat, BWI and the Einstein Medical Institute, North Palm Beach, Florida, USA

Corresponding Author*

Orien L. Tulp
University of Science Arts and Technology,
Montserrat, BWI and the Einstein Medical Institute,
North Palm Beach,
Florida, USA
E-mail: o.tulp@usat.edu

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Abstract

Historically, epidemics occur about three times a century and pandemics about once a century, and each time a different infectious organism has been discovered to be the culprit. In addition, those individuals who also have comorbidities often entertain the greatest risk of the most serious complications of the illness. In January 2020, a novel coronavirus, SARS-CoV-2, was identified as the cause of an outbreak of viral pneumonia of unknown origin in Hubei Province, Wuhan, China, having infected over 200 people and causing several deaths in the early phase of the outbreak. The illness, later named coronavirus disease 2019 (COVID-19), subsequently spread globally in a seemingly exponential manner and was soon determined to be the origins of a pandemic by the World Health Organization (WHO) within the first few months of its discovery and emergence. In the first three months after COVID- 19 emerged, nearly one million people were infected and 50,000 had succumbed due to complications of the illness. By six months into the outbreak the number of cases worldwide exceeded ten million and there were more than 500,000 deaths. To date, there have been roughly 62 million cases and over 800,000 deaths from COVID-19 just in the United States. One of the troubling observations about COVID-19 is that people who were infected with SARS-CoV-2, which some scientists estimate may be as high as 40%, can transmit the virus to others when asymptomatic and before they have developed overt symptoms or without ever having symptoms of disease at all. Once infected, the virus may infect multiple organs and tissues including brain, cardiovascular, pulmonary, and other organs and cause long lasting sequela. The NIH National Institute of Allergy and Infectious Diseases (NIAID) COVID-19 and others in cooperation with vaccine manufacturers research efforts have built upon earlier research on Severe Acute Respiratory Syndromes (SARS) and Middle East Respiratory Syndrome (MERS), also caused by strains of respiratory prone coronaviruses. The purpose of the present paper is to review the evolution and development of the MERS, SARS. and COVID-19 coronaviruses and their devastating impact on global healthcare resources and their delivery with the evolution of the COVID-19 pandemic.

Keywords: MERS • SARS • COVID-19 • RNA viruses • Evolution

Introduction and Overview

Middle East Respiratory Syndrome (MERS) is a viral respiratory disease that was first reported in humans in Saudi Arabia in September 2012 and had since spread to twenty-seven countries, according to the World Health Organization [1,2]. Some people infected with MERS Coronavirus (MERS-CoV) developed severe acute respiratory illness, including fever, cough, and shortness of breath. Since its emergence in 2012 through August 2021, the WHO confirmed 2,578 MERS cases and 888 deaths from the illness. Among all reported cases of MERS in people, the majority have occurred in Saudi Arabia. Only two people in the United States have tested positive for MERS-CoV, both of whom recovered [2]. They were healthcare providers who lived in Saudi Arabia, where they likely were infected before traveling to the U.S.A. according to the Centers for Disease Control (CDC). Another respiratory virus, Severe Acute Respiratory Syndrome (SARS) was first reported in Asia in February 2003, though some cases subsequently were tracked to November 2002 [3-5]. Infection with the SARS coronavirus (SARS-CoV) can cause a severe viral respiratory illness similar to that of MERS, SARS quickly spread to 26 countries after about four months before being contained. More than 8,000 people fell ill from SARS and 774 succumbed to the illness. Since 2004, there have been no new reported SARS cases. Research evidence suggests that SARS-CoV and MERS-CoV both may have originated in bats and possibly been transmitted to other intermediate host animals before being transmitted to and infecting humans [6]. SARS-CoV-2 then appears to have spread from infected civets, sometimes used as a specialized delicacy meat source to people of some geographic locales, while MERS-CoV spreads from infected dromedary camels to people [2]. Both viruses spread via airborne micro droplet transmission, including contact with contaminated surfaces as is common among known mechanisms of viral transmission [1,3-5].

The Origins of COVID-19 are Unclear

To date, the definitive origin of SARS-CoV-2 which caused the COVID-19 pandemic has not been confirmed, but it is noteworthy that coronaviruses are commonly found in bats and can be transmitted to other intermediate hosts [6]. The SARS-COV-19 virus has among the largest genomes of known viruses, and the nucleotide base sequence has some unique segments not common among other coronaviruses [7]. The scientific evidence thus far suggests that SARS-CoV-2 likely may have originally resulted from viral evolution in nature and jumped to people or through some unidentified intermediate animal host, possibly a civet, as civets often ingest bats, thereby entering the food chain as a meat delicacy common in some Asian cultures. 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, because the origins of the SARS-CoV-2 have not yet been identified, misleading and unverified allegations have been made about NIAID, Eco-Health and other entities that supported research on naturally occurring bat populations. Since the airborne micro-droplet mode of transmission is difficult to contain, the pandemic has posed considerable difficulty in public health efforts to bring about its containment. Research on coronaviruses was conducted at the Wuhan Institute of Virology in Wuhan, China, during the timeframe associated with the discovery of the original COVID-19 illness [8-10]. The naturally occurring bat coronaviruses studied through this research institute were significantly genetically different from earlier SARS-CoV-2 strains and, therefore, earlier strains have been associated with milder but not life-threatening forms of the respiratory illness, and thus could not have caused the present COVID-19 pandemic at least not in their original genomic form [11]. Although the Wuhan virology research institute used locally captured bats as a source and animal host for their coronavirus progenitors for their research, direct links between the bat viruses and SARS-CoV-2 have yet to be confirmed. By late 2020, through intensive cooperative efforts by the US government and private sectors, several vaccines had been developed using novel mRNA technology, with reported efficacy of well over 90% effectiveness against COVID-19 in their early studies [12].

Pathobiology of Coronaviruses

The coronaviruses are so named because of the lipid corona that surrounds the viral RNA core and can become spread *via* contact or *via* airborne micro-droplet transmission.Viruses sometimes referred to as viral particles, are by their nature considered to be obligate intracellular parasites, and thus any physical or chemical measures that prevent them from being take up by host cells can effectively prevent their intracellular

replication and further dissemination [13-15]. The continuity of the lipid corona is essential for an efficient viral uptake by host tissues, who also share a compatible lipid complex in their cell membranes. Disrupting the lipid corona by any means necessarily interrupts infectious potential of the viral particle from cellular entry, thereby delaying or otherwise impeding its efficient host cell uptake in a sufficient load to elicit adverse events following infection. Disinfectants including those containing chlorine (i.e., bleach) and hand sanitizers, containing alcohols, can readily disrupt the viral envelope, and as such are essential elements in inactivating the viral particles inadvertently left in airspaces by unsuspecting and often asymptomatic carriers. If chemical measures are implemented to denature the viral particles and prevent viral uptake by unsuspecting hosts, it represents one step in interrupting the life cycle of the virus, as if prevented from being taken in by host cells, it can be prevented from assessing the cellular mRNA. In contrast, the infective aspect of the COVID-19 viruses is due to the spike proteins which extend from the coronal lipid.

The spike proteins contain multiple antigenic epitopes which enable the viral particles to make contact with and recognize suitable ACE3 receptors on various tissues throughout the body [14-16]. The coronal lipids exhibit multigenerational consistent composition, while the antigenic spike proteins are the primary sites of mutation, resulting in the variant clades of differing antigenicity and clinical pathologic potential now prevalent in the global community. Because the current vaccines were developed based on the spike protein epitopes of earlier strains of COVID-19, the antibodies from those earlier forms may no longer remain fully protective against current and future variants. Presently, the omicron variant presents a special case however as while it has been found to be overwhelmingly more transmissible than earlier sub-strains, the omicron produces a milder illness that to date has not been life threatening, with no deaths reported to date [17,18]. The severity of the COVID-19 infection has been linked to the viral load presented and the host immunogenetic factors where strong correlations have been observed [19-21].

Immune Responses to Coronaviruses

One of the unfortunate characteristics of the immune responses to coronaviruses however is the observation of an initial transient nature of the initial antibody responses a phenomenon common to other viral infections, but which improves over time [22-24]. In the 2004 SARS epidemic, residual antibodies have been detected up to 17 years after recovery from the infection, suggestive of long-term protection following natural illness from that strain of coronavirus [21,22]. In contrast, the transient immune response to COVID-19 immunization with current vaccines now appears to become diminished to low circulating concentrations within the first four to eight months following immunization or experiencing a natural infection and subsequent immune response, thereby rendering individuals potentially subject to reinfection one or more times but usually with less severe episodes during repeat infections.

The available mRNA vaccines appear to target one or more epitopes of the spike protein, while the natural immunity likely addresses the entire viral particle, which contains multiple antigenic epitopes, thereby potentially rendering a broader and potentially longer lasting immune protective response [25,26]. When first exposed to a novel virus, the normal immune response triggers the maturation of clone of short lived plasma blasts to a population of longer lasting antibody producing memory plasma cells, where 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, longer lasting B cells typically continue the humeral response in the event of a re-exposure to reinfection. The bone marrow also contributes to the long-term immune-protective phenomena *via* the formation of Bone Marrow Plasma Cells (BMPCs) where they function as a second arm of the long-term immunoreactive elements of the immune responses. Typically, the reinfections that have occurred following immunization or natural immunity *via* these processes tend to be of less severe magnitude than occurs in unvaccinated people, and therefor prior exposure either mode of exposure, vaccination, or viral exposure, offers a distinct immunologic advantage during recovery. Recent findings indicate that following active infection or immunization protective antibody levels decrease to about 10% of those observed during the peak response. In addition, it should be noted that once infected with the COVID-19 virus, it utilizes the host mRNA system where it begins to replicate rapidly, while the more biochemically host immune responses occurs more slowly, with the result that the peak viral loads tend to occur before peak antibody levels become fully available.

Complications Linked to Comorbidities and Aging

As with any viral or other infectious illness the presence of comorbidities including respiratory, cardiovascular, and other illnesses that often become more severe with advancing age where immune responses may be slower to develop may negatively complicate the COVID-19 illness and become the triggering point in the contribution to the most dire outcomes including the demise of the patient [27-29]. The presence of such complicating factors has resulted in more severe illness, longer recovery times and more disabling outcomes than have been reported in healthier patients who lack such contributing factors. The progression of COVID-19 to sequela that are now identified as 'long Covid' also occurs more commonly in the presence of the above comorbidities. While COVID-19 can infect individuals of all ages, the majority of deaths to COVID-19 to date have occurred in individuals over 60 years of age, where the development of comorbidities is typically more prevalent. When nasopharyngeal COVID viral receptor sites are taken into consideration, it is noted that not only do adults have a greater prevalence of such viral receptor sites than occur in early childhood, but immune responses also occur more slowly in older individuals, thereby facilitating a more profound kinetic pattern of viral infection in older than in younger individuals. In addition to immunization, a healthy diet containing absorbable forms of antioxidants nutrients, vitamins C and D3, zinc and other nutrient factors in addition to a healthy lifestyle is universally beneficial in minimizing the pathophysiologic impact of the COVID-19 illness [7,25,26,30-35].

Many Viruses are Prone to Periodic Mutation

As with many viruses including influenza and the common cold, the coronaviruses are subject to periodic mutation, thereby generating multiple variants which may result in variations of symptoms of the originating COVID-19 virus [5,15,17-20]. Of concern, emerging coronavirus mutations including the recent Delta and Omicron clades may present with biochemical modifications and expansions to their antigenic epitopes, partially elude current vaccine and treatment protocols, and thus may enable the virus to continue in circulation in one or more of its variant forms. The most recent variant, the Omicron, has an even larger genome and more spike protein mutations than previous iterations, and has been reported to be over five times more transmissible than previous Delta and other variants, with over 70% of new cases appearing to be caused by this latest variant on the spike protein [17-20]. The epitope domains on the spike protein interact with the ACE2 receptor sites in host tissues, where they brings about the infectivity and pathophysiologic sequela of the virus. 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. The recent emergence and identification of the Delta, Omicron and other developing variants continue to spread globally causing respiratory and other coronavirus-related illness with unprecedented rapidity, often despite prior vaccination with any of the currently approved vaccines or with natural immunity from previous COVID-19 infection. The extent to which natural immunity acquired from previously contacting the illness may protect against variants of the originating strains or the duration of immune protection remains unclear, but a key characteristic of COVID-19 infection is the apparent functional transient nature of the initial immune response developed by the infected host. In the current wave of COVID-19 infections reported, many of those individuals who became infected report having been fully vaccinated several months prior to the current episode. In addition, since recent studies indicate that the peak magnitude of the host virus replication occurs before the antibody response can fully mature, this may enable the virus to evade the immune response early stages of the infection, likely exacerbating the magnitude of illness [23]. The extent to which the apparent imbalance between the viral replication and the host immune responses in the now recognized 'long Covid' form of the illness, where diverse chronic symptoms in cardiovascular, brain, musculoskeletal and other organ systems may persist months after the acute infection has cleared, has not been determined at the time of this writing [20,24].

Mechanism and Efficacy of Vaccination

The novel mRNA vaccines were the first such biological products to be produced using recently developed mRNA technology, and which enabled their development in record breaking time (less than one year compared to multiple years for traditional vaccine development methodology). The concept was not only innovative but conceptually simple, to develop a 'vaccine' that contained an antigenic epitope that could gain entry to a

host cell, and then capitalize on the host's intracellular mRNA biosynthetic mechanisms to produce more of the antigenic epitope, which could then stimulate the host immune responses, while avoiding the adjuvants often used in other vaccines. The vaccines so produced were found to exceed 90% efficacy in the clinical trials conducted during the early months following their administration. Antibody formation is typically highly specific to the molecular configuration of the presenting viral epitope. However, should the primary epitope molecular configurations become sufficiently altered over time in newly emerging variant clades of the virus, the newly emerging variants may not be fully recognized by the antibodies then available, enabling reinfection to occur [12,23].

On the brighter side, while prior vaccination does not appear to continue to confer full protection against emerging COVID-19 variants, and natural immunity has been proposed to result in a less serious illness than may occur in the unvaccinated members of the population likely due to the more broad spectrum nature of natural *vs* vaccine-mediated antibodies [7,25,26]. Natural immunity is formed from the naturally occurring viral particles and their multiplicity of spike proteins rather than a single epitope, and numerous studies indicate that natural immunity from prior exposure may be more comprehensive than vaccine-mediated immunity for COVID-19 in its original molecular configuration. However, it now may be necessary to develop a multivalent COVID vaccine as has been accomplished for Influenza vaccines to better enable the COVID vaccines to recognize a broader array of emerging variants now becoming prevalent. The nature of the transient intermediate nature of the immune responses in COVID-19 emphasizes the potential importance of a secondary booster immunization within the first year following an initial vaccination in an attempt to re-engage the immune response as is common for other viruses that exhibit similar immunogenic patterns, and thus is more important in older members of the population where immune responses may be compromised due to age-associated comorbidities [12,22,23]. Were an attenuated variant with lesser pathophysiologic potential such as Omicron that could produce plasma and bone marrow memory, and which could cross-react with the more severe and recent variants now emerging, it could facilitate the development of herd immunity and contribute to a global recovery from the current pandemic, and likely decrease the potential of the virus to spread to multiple organs.

The vast preventative measures undertaken to date to control the spread of COVID-19 have not yet been successful in eradicating the pandemic, in part due to the more difficult to control elusive mode of airborne micro droplet transmission and contamination of surrounding airspace, and further complicated by the mutation-prone nature of the offending virus [14,33]. Currently over three-hundred-twelve million individuals have been infected and over five and a half million deaths have been reported world-wide, with over sixty million infections and eight-hundred-forty thousand of those illnesses and deaths in the USA alone. The global economic cost of the COVID-19 pandemic to date have been nothing short of extraordinary and includes both human tragedy and an economic loss that now tallies in untold trillions of dollars. The global pandemic, combined with the comorbidities of the most susceptible members of the population, have not only decreased the global talent and wisdom of the senior generations of all nations but has also threatened to compromise and virtually cripple the health care resources of most countries.

Special Considerations May Emerge for the Omicron Variant

The most recent clade of the COVID-19 virus has quickly become the prevalent variant in numerous geographic locations, where it appears to have displaced earlier variants in the biosphere due to its greater efficiency of transmissibility [17,18]. The Omicron may present with a more favourable outcome than earlier variants. While the Omicron is the most highly transmissible COVID-19 variant to date and has presented with a larger molecular RNA genome than earlier variants, the illness reported from Omicron is less severe than other common COVID-19 variants from which it developed. The Omicron variant was first reported in South Africa in late 2021 and has now been shown to be up to five-fold more highly transmissible than the Delta and other previous forms of the virus. During the brief duration of its current rampage, Omicron has already claimed responsibility for over one million infections in the USA, but it has resulted in less severe respiratory illness and few if any deaths directly attributed to the Omicron variant at this time [12,13,18]. Studies suggest that a periodic booster vaccine containing one or more of the antigenic epitopes is may be useful to keep the immune system sufficiently engaged and thereby able to produce immunocompetency to COVID-19. The proposed benefits of booster immunizations include producing adequate numbers and availability of circulating antibodies to minimize the impact and magnitude of reinfection to COVID-19 and including some variants, and to thereby become at the ready should re-exposure to an active viral COVID-19 threat occur. Re-exposure is more likely to occur during an active viral pandemic where local airflow in common spaces and a potentially contaminated airborne environment and opportunistic nearby surfaces occur. This indicates a need for potentially resource-intensive space reuse on a continuing basis, especially in active healthcare and other private and public environments and further depleting economic and healthcare related resources.

Conclusion

In conclusion, the coronavirus pandemic including recent variants continues to spread across the globe in an unprecedented manner. In the absence of more effective treatment protocols, including global vaccination efforts, combined with other containment measures COVID-19 and its variant clades continue to infect both unvaccinated and previously vaccinated individuals with apparent impunity. The development, distribution, and administration of multiple vaccines, although deemed highly effective in the short term, remains incomplete in resolving the global COVID-19 crisis. While natural immunity may provide a broader and more robust protection from reinfection, it has not yet received widespread acceptance, although several recent studies have reported strongly favourable results. The global impact of the COVID-19 pandemic has been extraordinary, including significant loss of lives, the financial and healthcare burdens imposed on many nations, and in the economic and industrial productivity of virtually all nations, including the wisdom and experience of the older and most susceptible generations now lost to humankind *via* the virus. Moreover, the initial transient nature of the typical immune responses to immunization or natural infection to COVID-19 poses additional logistical problems in having the capacity to immunize a sufficient proportion of the global populations in a short enough time interval, thereby enabling opportunistic viral mutation and continued spread of COVID-19 virus as logistical and other issues may impede the overall success of on-going vaccination programs. The inability to adequately immunize enough of the global populations in a brief enough timeframe has likely contributed to a compromise in the establishment of much desired widespread and herd immunity, deemed essential to end the pandemic. In addition, the inability to effect global vaccination early in the pandemic has enabled the virus to mutate into potential immunologically deceptive variants and thereby to continue to flourish globally in a virtually unfettered. Manner. The Omicron, among the most recent of the variants to emerge, has been found to be among the most highly transmissible variants with the broadest molecular genome discovered to date, but fortuitously, despite its rapid evolution in the community, has resulted in only milder, non-life-threatening forms of COVID-19 illness, indicative of an attenuation in its pathogenic potential. Only time can reveal if the naturally occurring Omicron variant may unwittingly provide the key chapter that may bring the COVID-19 pandemic to its long-sought climax.

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