Variants and Immunity for Non-Hospitalized COVID-19 Patients

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The continuing transmission of coronavirus disease 2019 (COVID-19) remains a world-wide 21st-century public health emergency of concern. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused greater than 600 million cases of COVID-19 and over 6 million deaths globally. COVID-19 continues to be a highly transmissible disease despite efforts by public health officials and healthcare providers to manage and control the disease. Variants identified in selected worldwide epicenters add to the complexity of vaccine efficacy, overage, and antibody titer maintenance and bioactivity. The identification of the SARS-CoV-2 variants is described with respect to evading protective efficacy of COVID-19 vaccines and breakthrough infections. Vaccines and other therapeutics have prevented millions of SARS-CoV-2 infections and thousands of deaths in the United States.

COVID-19 variants immunologic response vaccines

1. COVID-19 Public Health Variants of Concern

Since COVID-19 was discovered in Wuhan, China, [1] the coronavirus has mutated into many new variants with greater transmissibility and the ability for immune escape [2][3]. By the end of 2020, Alpha (B.1.1.7), beta (B.1.351), and gamma (P.1) variants were discovered in the United Kingdom, South Africa, and Brazil, respectively. In 2021, the dominant global variant of concern was B.1.617.2 (delta) which was discovered in the summer of 2021 in India.

This was soon replaced by the omicron variant (B.1.1.529) by the end of 2021 which emerged in Africa and is now a dominant variant of concern worldwide [4]. The dominance of the omicron variant is due to its ability to mutate over 50 times in both the spike protein and the receptor binding domain, which is the main target of neutralizing antibodies. Such escape ability contributes to its ability for neutralizing antibody escape despite prior infection, vaccination, or hybrid immunity [5][6][7]. To control the continued genetic evolution of SARS-CoV-2, the US Food and Drug Administration recently approved the use of bivalent booster vaccines to reduce the incidence of severe disease, hospitalizations, and death [8][9]. The following subvariants have been discovered and include BA.1, BA.1.1, BA.2, BA.2.12.1, BA.4, and BA.5, BF7, BQ1.1.and XBB [4][10]. The variants that have propagated the past waves are all members of the SARS-CoV-2 family that have developed subvariants that continue to increase the waves of infection.

Of the different subvariants of concern, healthcare systems around the globe should be vigilant for XBB as it has demonstrated the ability to be extremely transmissible and resistant to neutralizing antibodies greater than BA.5

[11]. Currently, XBB has been detected in 35 countries and makes up 54% of COVID-19 cases in Singapore, and 18.4% in the United States [12]. This subvariant has demonstrated increased resistance to antiviral humoral immunity from breakthrough infections by a unique evolutionary pathway [13].

Using phylogenetic analyses, Tamura, and colleagues [13] discovered that the XBB virus is a recombinant virus as two distinct genomes have merged together rather than occurring by convergent evolution (random mutation). XBB emerged from two subvariants of BA.2 (BJ.1 and BM.1.1.1). Such shared genetic material occurs on the receptor binding domain (RBD) of the viral spike protein. However, increased antiviral immunity could also be due to genetic mutations beyond the RBD. Mutations have also been observed on the N-terminal domain (NTD).

Because of omicron subvariants' immune evasive strains, the FDA advisory committee authorized the use of bivalent vaccines. Bivalent booster vaccination has been shown to increase neutralizing antibodies to the omicron variant compared to monovalent boosters [7][8][14][15]. Altarawneh and colleagues [15] reported that a third booster resulted in an approximate 60% reduced risk of infection if boosting occurred within 45 days from the previous immunization. Other studies reported that after a third mRNA immunization, decreased clinical protection and waning were observed at 4 months [15][16]. More striking, after a fourth mRNA immunization waning was reported after just 4 weeks. However, protection against the severe form of COVID-19 was clinically observed that prevented admission to the intensive care units of hospitals and deaths [11][12]. The protection conferred by hybrid immunity to SARS-CoV-2 provided the best long-term protection compared to either natural immunity or vaccination [5][14]. This finding suggests the benefits of vaccination against COVID-19-related hospitalizations and death.

2. The Innate and Adaptive Immunological Response to COVID-19

The immune system is the human body's defense against pathogens, such as bacteria, viruses, fungi, parasites, toxins, and cancer cells and consists of innate and adaptive responses [17]. Vaccines are designed to condition the immune system to protect the human body from infections due to immunologic memory.

Innate immunity is the first line of resistance (non-specific) to invading microbial pathogens by recruiting immune cells to the site of inflammation and infection, such as type I interferons, cytokines, neutrophils, monocytes, macrophages, and natural killer T cells [18].

Important cytokines recruited to the site of the invading pathogen include tumor necrosis factor (TNF), interleukin 1 (IL-1) and interleukin-6 (IL-6). Innate antiviral immunity is activated within hours of the invading pathogen and does not have the ability to recognize the same pathogen in future encounters [19]. It will also activate the adaptive immune response with antigen-presenting cells.

The adaptive immune response is antigen-specific and has the capability to recognize the same antigen in future encounters [20]. Adaptive immunity consists of two mechanisms- humoral and cellular immunity. With humoral

immunity (antibody-mediated immunity), antibodies attach to the spike protein of the coronavirus to eliminate the virus from the human body. With the invasion of SARS-CoV-2, cellular immunity activates B cells and antigen-specific CD8+ T cells and CD4+ T cells to eliminate infected cells and block viral replication [21]. Humoral and cellular immune mechanisms are activated with SARS-CoV-2 infection. Both mechanisms attempt to prevent severe SARS-CoV-2 infection that results in hospitalization and death [22][23]. Research has revealed that approximately 95% of individuals maintain immune memory for about eight months due to natural infection from antigen-specific antibodies, memory B-cells and T-cells.

3. COVID-19 Vaccine Effectiveness

Vaccination is the most important way to protect individuals from COVID-19-associated hospitalizations and death [24]. Transmission of SAR-CoV-2 is due to replication and shedding of the virus in the upper respiratory tract. Therefore, vaccines must direct their mechanism of action to control replication and transmission of the virus. Globally, greater than 300 vaccines have been developed in response to COVID-19 [24]. However, only 10 COVID-19 vaccines have been approved by the WHO to mitigate viral disease caused by the Wuhan ancestral (D614G) strain which was soon replaced by other variants. These vaccines represent four different vaccine platforms: messenger RNA (mRNA); adenovirus vector-based; inactivated virus and adjuvanted protein vaccines. In the United States, the 2-shot four vaccines approved for use are the following: mRNA vaccines BNT162b2 and mRNA-1273; adenovirus vector-based vaccine Ad26.CoV2. S and adjuvanted protein vaccine NVX-CoV2373. Prior to the emergence of the omicron variant, in Phase 3 clinical trials, vaccines demonstrated 94–95% clinical efficacy against COVID-19 infection except for the 1-shot Ad26.COV2. S (72% efficacy) [25][26][27][28].

In the United States, mRNA vaccines (Moderna's Spikevax mRNA-1273 and Pfizer-BioNTech; s BNT162b2) have primarily been used against the coronavirus with remarkable success [24]. In the United States, data from the Centers for Disease Control and Prevention (CDC) demonstrated that vaccination protected individuals during the delta variant surge during the winter months of 2020 and 2021 and spring of 2022 [28]. However, it was also observed that breakthrough infections were greater with the Ad26.COV2. S vaccine compared to the mRNA vaccines. The Food and Drug Administration and CDC have prohibited the use of Ad26.CoV2. S in the United States because of the number of adverse side effects observed. Vaccine-induced immune thrombotic thrombocytopenia (VITT) developed in 54 individuals and nine died [29][30]. The vaccine complication represents an incidence of three cases per one million vaccinated persons. VITT has also been reported in the United States in three patients (one died) who were vaccinated with the mRNA1272 vaccine [31][32]. Despite this adverse side effect, adenovirus vector-based vaccines are used in developing countries because of the lower cost and not requiring maintaining the vaccine at subfreezing temperatures.

Individuals in the US have immunity against SARS-CoV-2 from prior infection, vaccination, or hybrid immunity (combination of both) [33][34]. However, the SARS-CoV-2 Omicron variant (including BA.5) detected in November 2021 rapidly became the dominant circulating variant worldwide due to high transmissibility and immune evasion capability compared to the Delta variant. To better understand vaccine effectiveness data, Lin et al. [35] conducted a cohort study of 10.6 million people in the state of North Carolina who were vaccinated, and infected with the

coronavirus, and compared them with unvaccinated individuals. In their study, 67% of the population were vaccinated and 2771.364 infections with the virus were reported. They also reported that hospital admissions were 6.3% and a mortality rate of 1.0%.

Based on the Lin et al. [35] study, several important conclusions may be made. With the low number of hospital admissions and deaths from COVID-19, vaccination is highly effective in preventing severe disease. Vaccination with boosters did not protect the public from milder infections. Further, prior infection with the coronavirus was associated with reduced risk of virus infection. For individuals with prior infection who also received the vaccine and booster, additional protection was observed from breakthrough infections. However, waning with booster vaccines occurred after 4 to 6 months.

4. Production of Novel COVID-19 Vaccines

Vaccination is the hallmark strategy to mitigate the COVID-19 pandemic through neutralizing antibody activity and plasma cell, B cell immunity, and T cell killer cells and immunological memory [36][37][38]. To bring the pandemic under control, many different new vaccines must be developed as each vaccine has different advantages and disadvantages against COVID-19. Each country with its different populations, public health care environments and age groups will be the beneficiary of different vaccine products that are developed on different platforms.

However, for at-risk populations such as the elderly and immunocompromised, the need for multiple vaccinations and boosters every 4–6 months may represent a public health challenge. Further, there is also the possibility that a new variant will emerge that will be entirely resistant to the current vaccines in preventing severe disease. The strategy to develop novel vaccines should be to produce a universal vaccine with long-lasting immunity that can be stored and transported at room temperature [36]. Such a novel COVID-19 vaccine would be similar to the influenza vaccine, where 75% of the population is expected to be protected from the influenza virus yearly and protects all age groups. Further, the novel vaccine should be a 1-dose vaccine per year based on an annual review of the current circulation of SARS-CoV-2 variants.

5. Convalescent Plasma

Passive immunity (passive antibody transfer) with convalescent plasma has been used for over 100 years in the treatment of infectious diseases until an immune response is activated in the infected patient [39][40][41]. During the 1918–1920 Spanish influenza A (H1N1) pandemic, convalescent plasma was extensively used because it was believed that plasma from donors who recovered from the influenza virus contained antibodies that may terminate viral replication and death [41][42]. This was confirmed in a meta-analysis by Luke and colleagues involving 1703 patients [41].

Before the development of antiviral and neutralizing antibody treatment during the start of the COVID-19 pandemic, the passive transfer of antibodies from the plasma of recovered patients who were infected with the coronavirus was one of the first treatments used to reduce the number of intensive care unit admissions, and ultimately death

[43][44]. This is because many treatments such as anticoagulant, antiviral and anti-inflammatory medications were inconsistent producing controversial results [45]. Further, although neutralizing anti-spike monoclonal antibody treatment has been widely used in managing COVID-19 infections, the evolution of SARS-CoV-2 variants has resulted in greater virulence, viral transmission, and resistance [46].

Early during the COVID-19 pandemic, several studies reported on the use of COVID-19 convalescent plasma. However, the results were unclear as to the benefit of passive antibody transfer [47][48]. There is now more information on the role of high titers of neutralizing antibodies in decreasing the incidence of severe disease progression, hospitalization and death if administered within 72 h since the onset of symptoms [49][50]. Further, COVID-19 convalescent plasma maintains its clinical efficacy over time with new SARS-CoV-2 variants. Therefore, there is much interest in the clinical application of COVID-19 convalescent plasma, especially for patients who are immunocompromised and not able to mount a sufficient antibody response against the coronavirus and clear the virus.

However, accessibility to post-COVID-19 patients, selection of donors, lab preparation, and distribution continue to pose challenges for the use of convalescent plasma.

In addition, several scientific organizations (i.e., CDC/IDSA, AABB) have recommended the use of COVID-19 convalescent plasma in immunocompromised patients, especially after reports of monoclonal antibody-resistant SARS-CoV-2 variants [51][52]. In a retrospective study by Joyner and colleagues [53], they determined that the hyperimmune immunoglobulin and IgG antibody levels in convalescent plasma were associated with a lower risk of death in hospitalized patients compared to plasma with lower antibody levels. In a systematic review and meta-analysis by Senefeld et al. [50] they concluded that COVID-19 convalescent plasma was associated with a mortality benefit in immunocompromised hospitalized patients. These studies agree on the decreased mortality benefit with data from observational studies and randomized trials of high-titer antibody COVID-19 convalescent plasma [54][55][56]. While most studies on COVID-19 convalescent plasma were from unvaccinated donors, Vax-Plasma is now available for clinical use from regular donors. Vax-Plasma has been shown to retain higher neutralizing antibody titers and efficacy against the SARS-CoV-2 variants [57].

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