Current Insights into Covid-19 Vaccination

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ABSTRACT

Almost a year after the worldwide appearance of the coronavirus (SARS-CoV-2), several novel vaccines of diverse platforms have been successfully developed and administered. Two mRNA vaccines represented a new type of vaccine that comprised of synthetic mRNA molecules containing the code sequence necessary to build the SARS-CoV-2 spike protein. These mRNA vaccines almost single handedly carried the brunt of the US COVID-19 immunization strategy during the past three years. The known and potential benefits of COVID-19 vaccination outweigh the risks and adverse complications. The ongoing COVID-19 pandemic has stimulated unprecedented research on aspects of the vaccines' ability to reduce the risk of severe infection and death. Likewise, basic immunological studies are pivotal to unraveling the potential and long-term effects of the vaccines as well as to be able to make adjustments to new vaccine development. As the circulating virus strain continues to evolve, updated vaccines will be critical to protecting the population, particularly the elderly and immune compromised.

Keywords COVID-19, Vaccination, IgG4 and mRNA, Long COVID, Myocarditis

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INTRODUCTION

Going into the fourth year of COVID-19, vaccination has become the vanguard of protective measures to manage the disease, as many countries in the world have all but given up on mass mitigation schemes such as masking, regular testing, lockdowns and other government mandates. The initial vaccines released in the fall of 2020, both adenovirus and mRNA vaccine platforms, displayed a remarkable efficacy in preventing severe infections requiring hospitalizations and deaths.[1] Presently, the population's immune situation is vastly different from what it was in 2019 when SARS-CoV-2 first emerged, most people now have been vaccinated against the virus, been infected with it (once or several times), or both. What we do recognize now is that immune responses do build up, but primarily against getting significant or severe infection and not against getting reinfected in the future. It is clear that for many, if not most, people, COVID-19 no longer carries the same risks of adverse outcomes as it did in the early months of the pandemic. It is vital for all of us to be fully aware that we are entering a new phase of this global outbreak, but it is a little bit too early to call that the pandemic is behind us and that it is time to let go of caution and resume prepandemic life. We have to realize that even though cases of COVID-19 are still lower or milder compared to earlier years, it is still quite disruptive, can lead to longer-term post-COVID symptoms, and is very much a risk for those who do not have the same intact immune systems as others.

Bivalent Covid-19 Vaccine With a Caveat

A couple of years after the start of COVID-19 vaccination, our frenzy for the COVID-19 vaccines has been restrained for two reasons. Firstly, the

safeguard against infection for the original strain of SARS-CoV-2 the vaccines were intended for had decreased heavily, and many people were susceptible to reinfection only months later. Secondly, virus mutations emerged and spread much more rapidly than most expected, resulting in little protection against newer mutated SARS-CoV-2 strains. A specific new variant, called Omicron, was detected in late 2021.[2] The Omicron variant contained an alarming number of mutations found mostly in the spike protein of the virus, which is the primary target of neutralizing antibodies. Public health officials were worried that the variant strain posed a serious threat to the efficacy of existing COVID-19 vaccines and commercially available monoclonal antibody preparations. Given the ability to use mRNA technology to respond quickly to the Omicron variant, bivalent vaccines were planned and created to counter this threat. Last October 2022, Pfizer and Moderna started rolling out the new bivalent vaccine containing equal amount of mRNA directed against the original or ancestral strain of SARS-CoV-2 and the Omicron subvariants (BA.4 and BA.5).[3] The US Food and Drug Administration (FDA) authorized the bivalent vaccines with an understanding that they would target Omicron subvariants BA.4 and BA.5, which at that time had accounted for more than 95% of circulating SARS-CoV-2 strains.

Recent studies from the Columbia and Harvard universities found that the updated bivalent COVID-19 vaccine boosters intended to protect people against arising Omicron subvariants did not appear to provide any better protection than the original monovalent vaccine did.[4-6] It failed to promote higher antibody levels or a better immune response than the original COVID-19 vaccines. While immunization and boosting protected vaccinated individuals from getting severely sick, they were not immune to COVID-19 infection. So why are these infections occurring if the bivalent vaccine was supposed to focus on both Omicron subvariants better than the original COVID-19 vaccine? The most likely explanation is due to immune imprinting phenomenon.[7] The immune systems of individuals immunized with the bivalent vaccines, all of whom had formerly been vaccinated, were primed to react to the original strain of SARS-CoV-2. Hence, the immune response was skewed towards the epitopes (antigenic determinants) shared by subvariants BA.4 and BA.5 and the original viral strain, rather than to the new epitopes on both Omicron subvariants. Moreover, an observational study of more than 50,000 Cleveland Clinic employees published recently was conducted to assess effectiveness of the bivalent booster vaccines against COVID-19 infection between September 2022 and March 2023.[8] It concluded that bivalent booster vaccines were only 30% effective in preventing infection against the Omicron subvariants. Current thinking suggests that the immune imprinting effect could be limited or lessened by vaccinating people either with latest Omicron subvariants alone in a monovalent vaccine formulation or greater quantity of the Omicron subvariant mRNA than the original viral mRNA in a bivalent vaccine.[9]

Effect of COVID-19 Vaccination on Long COVID

Long COVID is recognized as a major health burden after infection with SARS-CoV-2 and will likely cause considerable global morbidity for many years to come.[10] With a worldwide figure of COVID-19 infections of more than 500 million and a conservative prevalence of 20%-30%, more than 100 million people could be currently afflicted by Long COVID globally. Many clinical symptoms associated with Long COVID have been reported that can last for months or a few years, and the common symptoms include, but are not limited to, extreme fatigue, cognitive difficulties, gastrointestinal symptoms, headaches, myalgias, arthralgias, and dyspnea. Factors such as female sex, older age, high body mass index, severe initial disease and comorbid conditions seem to be connected with the risk of Long COVID.[11] Accordingly, COVID-19 vaccination may help prevent or reduce Long COVID by eradicating the viral reservoir lingering in patients' bodies and clearing viral remnants away or by resetting dysregulated immune responses.[12]

Current research suggests that they offer significant protection as well as possible therapeutic effects on Long COVID. Studies have consistently observed that these vaccines could avert the new onset of Long COVID as well as exacerbations for people who already have the post-COVID condition.[13] In the RECOVER (Researching Covid to Enhance Recovery) initiative study, National Institutes of Health researchers parsed through the electronic health records of more than five million patients who had been diagnosed with COVID-19 and found

that immunization with COVID-19 vaccines reduced the chance that they would develop Long COVID.[14] The study investigators suggested that having a complete round of recommended immunizations may offer the most protection against Long COVID. A meta-analysis of six studies published in December 2022 found that one or more doses of a COVID-19 vaccine were 69% successful in keeping away symptoms of Long COVID. Furthermore, a review published in February 2023 concluded that a number of study results showed a significant reduction in the incidence of Long COVID among vaccinated patients.[10] Even a single dose of the vaccine was found to be protective. Unfortunately, untrue and uncorroborated assertions made by some antivaccine groups that the vaccines themselves may cause Long COVID continue and serve as roadblocks to affirmative vaccination.

Myocarditis Following mRNA COVID-19 Vaccination

The accelerated development, application and global deployment of COVID-19 vaccines based on mRNA technology has been one of the outstanding successes of the response to the SARS-CoV-2 worldwide outbreak. Overall, their safety profile has been good with no serious adverse events detected until the reports of temporally associated cases of acute myocarditis and pericarditis after the primary series immunization of the COVID-19 mRNA vaccines. Reported cases were predominantly in young adult and adolescent males after the second dose, with the initial clinical symptom or sign clustering in the first week after inoculation.[15] According to the US Centers for Disease Control and Prevention (CDC), myocarditis and pericarditis rates are about 12.6 cases per million doses of the second-dose mRNA vaccine among individuals aged between 12 and 39 years. Even though the immunopathologic process for development of this inflammation-induced heart damage are not clear, molecular mimicry between the freely circulating spike protein and self-antigens (eventually causing adverse autoimmune conditions), induction of inflammatory cytokines (eg, IL-1ß and IL-6) by the lipid nanoparticles enveloping the fragile mRNA and preexisting impaired immune regulatory functions in certain individuals have been proposed.[16,17] The bases for male predominance in myocarditis cases are not known, but possible causes relate to sex hormone differences in immune reaction and myocarditis.[18] Almost all the patients had all symptoms and signs resolved and improvement in diagnostic markers and imaging with or without medical care. The risk of myocarditis and pericarditis after mRNA vaccination for COVID-19 has often been touted as a valid reason not to vaccinate healthy young and adolescent males against COVID-19. However, many studies found that the comparative risks of negative outcomes were worse from myocarditis from COVID-19 infection and other viral myocarditis than from vaccination in all patients older than 12 years of age.[19]

The incidence of myocarditis and pericarditis is two- to three-fold higher after a second dose of the Moderna COVID-19 vaccine when compared to the Pfizer/BioNTech COVID-19 vaccine, but the overall risk has remained exceptionally low. Hence, previous findings support recommending that certain populations receives certain vaccines to maximize benefits as well as minimize possible post-immunization adverse reactions. Of interest, the risk of developing myocarditis and pericarditis was found to be lower following a booster than following a second primary dose of the COVID-19 mRNA vaccine.[20] Three possible reasons for this have been proposed. As a medical precaution, individuals who were affected by myocarditis or pericarditis after the second COVID-19 vaccine dose did not receive a third dose. Also, the timing of vaccination may be a factor. The first and second primary vaccine doses were administered approximately three to four weeks apart, but the time between the second dose and a booster was about six to twelve months. The greater risk associated with the Moderna mRNA vaccines, which have a higher mRNA dose than the Pfizer/BioNTech mRNA vaccines (100 mcg/dose vs. 30 mcg/dose, respectively), and the Moderna mRNA booster which had half of the mRNA content (50 mcg/dose) of the Moderna primary series vaccine, may be suggestive of an mRNA dose-related mechanism.

IgG4 and mRNA COVID-19 Vaccines

Before discussing IgG4 in the context of mRNA vaccines, it is first necessary to discern the phenomenon known as IgG4 class switching. The humoral part of our innate immune system shifts

towards the IgG4 isotype after continuous or repeated exposure to a protein antigen. A prospective research study among beekeepers demonstrated that initial exposure to an antigen in bee venom (ie, phospholipase A) elicited precipitating IgG1 and IgG3 isotype antibodies. However, in about six months of prolonged or repeated exposures, these antibody isotypes were replaced by IgG4 antibodies that eventually dominated the serological response. IgG4 is also the dominant isotype after allergen desensitization. IgG4's distinction as a blocking antibody stems from its decreased capacity to elicit immune system effector reactions. The development of tolerance to allergens is an essential step in the success of the allergy desensitization process.

Repeated doses of mRNA vaccines for COVID-19 result in increased proportions of anti-spike antibodies of the IgG4 isotype.[21] IgG4 antibodies are known to neutralize well and form mixed immune complexes with IgG1 and IgG3 but, in a pure condition, IgG4 might be inefficient than IgG1 and IgG3 antibodies in facilitating opsonization by phagocytes, complement fixation and NK cell-dependent elimination of infected cells. Recent studies have speculated that the described increase in IgG4 levels detected after repeated vaccination with mRNA vaccines may not be a protective mechanism; rather, it constitutes an immune tolerance mechanism to the viral spike protein that could stimulate unopposed SARS-CoV2 infection and replication by suppressing immune antiviral responses.[22,23]

Of interest, the absolute amount of vaccine-induced and spike-specific IgG1 and IgG3 remained relatively the same during those experiments.[23] In the majority of individuals tested, both IgG1 and IgG3 antibodies were still dominant. The real importance and possible role of an increased frequency of IgG4 are unclear. Despite IgG4's higher levels following repeated mRNA vaccinations, the clinical picture remains not significantly different than when levels are within normal limits. It appears that IgG4 is a possible by-product of another ongoing evolutionary process. So far, the rise in IgG4 levels has not affected COVID-19 vaccine effectiveness. Further studies are needed to clarify the relevance of this finding for future mRNA-based vaccine development and usage.

On the basis of the findings of recent peer-reviewed studies and theoretical considerations, future clinical research needs to evaluate the efficacy of temporal spreading out of mRNA vaccinations, possibly no more than once a year. Other strategies worth investigating would be the use of smaller quantities of mRNA for vaccine doses as well as the use of heterologous vaccination by boosting with non-mRNA vaccines (ie, adenovirus vector and protein-based vaccines).

The Updated Monovalent COVID-19 Vaccines of Fall 2023

As we head into the fall and winter seasons, vaccines continue to be one of the most effective and safest ways to protect ourselves against severe COVID illness and Long COVID complications. As the primary circulating SARS-CoV-2 strain continues to evolve, updated vaccines remain critical to promoting the health of the entire community and continued protection against serious complications of COVID-19.

Last May, the independent advisory committee of the FDA unanimously recommended that a new updated COVID-19 vaccine formulation offered this fall should target a predominant strain within the Omicron variant family and should no longer include a component focusing on the original strain of the virus, as last year's fall booster did. The advisory committee settled on XBB.1.5, which has been the dominant subvariant in the US for much of this year. As of September 14, 2023, the FDA approval and the CDC recommendations apply to the mRNA vaccines from Pfizer-BioNTech and Moderna. On October 3, 2023, another vaccine from Novavax was authorized by the FDA for emergency use, providing us a third choice heading into the fall and winter respiratory diseases season. Unlike the updated mRNA vaccines, the Novavax vaccine is a protein-based vaccination that uses an adjuvant to spur the immune system. Recent published data have indicated that the new updated monovalent COVID-19 vaccines could offer additional crossover protection against currently emerging subvariants EG.5 (Eris), FL.1.5.1 (Fornax) and B.2.86 (Pirola).[24,25] Considering that COVID-19 infections, hospitalizations and deaths continue to affect the US population and a rise in infections is expected this fall and winter, the updated COVID-19 vaccines increase immune protection against the currently circulating subvariants and are predicted to prevent about 400,000 hospitalizations and

40,000 deaths over the next couple of years.[26] Moreover, a research group from the University of Minnesota reported that COVID-19 vaccine-boosted participants had the least severe symptoms during COVID-19 which subsided the quickest over time in comparison with unvaccinated or unboosted study subjects.[27]

Though there is no official mandate for COVID-19 vaccination this fall, there is a broad consensus among doctors that those who would benefit most from the updated COVID-19 vaccines are people aged 65 and above, as well as those who are chronically ill, immunocompromised, pregnant or nursing home patients. The CDC's Advisory Committee on Immunization Practices recommends everyone 6 months and older get the updated COVID-19 mRNA vaccines to protect against potentially serious outcomes of COVID-19 illness this fall and winter. On the other hand, the Novavax's updated vaccine is only approved for adolescents and adults (12 years and older). The universal recommendation comes as COVID-19 cases, hospitalizations and deaths are mounting up, but still remaining much lower than the levels we had experienced through most of the COVID-19 outbreak. Many believe that the decision of whether to vaccinate against COVID-19 should be based upon the individual's age, other medical problems, relative risk from vaccines, how much and what type of COVID-19 is in the community, and the patient's and family's preference. Hence, it is now basically an individual choice.

A recent vaccine monitoring survey found that nearly half of US adults will definitely or probably get the updated monovalent COVID-19 vaccine, a pattern that is higher than previous booster campaigns but lower than the initial primary series vaccination rollout.[28] Despite solid vaccination intentions for adults, most parents are not planning to have their children vaccinated against COVID-19, despite a universal recommendation from the CDC and the American Academy of Pediatrics. Fewer than four in ten parents said they will have their children vaccinated against COVID-19.

Many concerned medical experts say that several continuing developments are behind the push for another round of immunization against COVID-19. [29] First, COVID-19 continues to be one of the most significant respiratory diseases in the US. Although the pandemic was announced to be over last May, the numbers of severe cases and hospitalizations have been slowly increasing in recent months. Second, critical spike protein mutations in the new variants could lead to immune escape from protection that had been gained through previous vaccinations and infections. The majority of the US population has some immunity due to previous vaccinations or infection, but new variants have emerged, and hospital admissions are likely to increase this fall and winter. And lastly, the immune response from previous inoculations and infections declines over time. Regardless of the CDC's recent universal recommendations, not all experts believe a new updated COVID-19 vaccine will be necessary for everyone every year, particularly young healthy people who have been previously fully vaccinated or having recovered from infections. Through a combination of the fact that many people now have some levels of immunologic protection and the fact that the Omicron subvariants as a group do not seem to cause serious disease in most healthy individuals, the role of booster or updated vaccines has also evolved.

At one time, the world hoped COVID-19 would only need a one-time vaccine, but with its ever evolving nature, it is now become understandable that it is not the case. The mutating COVID-19 virus will likely require frequently updated formulations of the vaccine to keep up our immunologic defenses and protect vulnerable populations. We may be out of the pandemic, but the virus is not gone as we head into another respiratory virus season this fall and winter.

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