Review Article

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Immune Responses to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccines: Updated Insights

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A B S T R A C T

Using a multidisciplinary approach, this review explores and investigates the relationship between immune responses, effectiveness, and results of various vaccination strategies among a range of demographics. Moreover, this review aims to aid healthcare professionals in understanding the intricacies of immune responses and their implications for future vaccine development.

In this review, we employed an electronic online database platform including the National Centre for Biotechnology Information (NCBI), the National Institute for Health and Clinical Excellence (NICE), and the World Health Organization (WHO) for evidence-based material, utilizing the keywords throughout this literature review.

This review provides a detailed framework regarding immune responses to the COVID-19 vaccine, based on demographics, age, sex, types of immunity, and immunization strategies. Such research can provide important academic support for the development of not only COVID-19 vaccines but also other vaccines.

Conclusions: Overall, immune responses tended to dwindle a few months after vaccine administration. This is because B cells block SARS-CoV-2 from infecting cells via antibodies and T cells destroy infected cells. The most efficient tool for providing long-lasting protection against SARS-CoV-2 is vaccination. Humans have developed immunity to SARS-CoV-2, particularly antibody-mediated humoral immunity. The development of vaccines across the whole family of coronaviruses that target antibody epitopes (antigenic determinants) prevents the emergence of mutant strains.

Keywords: COVID-19 vaccine, immunisation strategies, immune response, vaccinations, SARS-CoV-2.

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Although viral respiratory diseases are highly contagious and can spread rapidly, humans have evolved and developed a complex immune system to tackle this COVID-19 pandemic. The immune system is characterized by strong intrinsic, adaptive, and specific humoral and cellular immunity. SARS-CoV-2 continues to evolve and mutate, and the continuous development and research regarding its vaccines must continue to reach optimum immunization strategies. COVID-19 disease caused by the "Severe Acute Respiratory Syndrome Coronavirus 2 strain (SARS-CoV-2)" which has the ability, like other coronaviruses, to induce respiratory tract illnesses.[1]

The World Health Organization (WHO) declared this strain a new type of coronavirus in early 2020. The onset of the 2020 outbreak sparked a pandemic affecting millions worldwide. This virus affects the upper respiratory tract, encompassing the "sinuses, nose, and throat, or the lower respiratory tract, including the windpipe and lungs". Similar to other coronaviruses, transmission occurs primarily through direct person-to-person contact via the nose or mouth aerosol/droplets. The spread can be minimized using facemasks, social distancing, and handwashing.[2] Disease management can vary in severity, ranging from mild fever to extremely life-threatening conditions.[3] COVID-19 vaccinations are intended to grant acquired immunity against SARS-CoV-2, with the primary objective being the prevention of severe illness. The vaccine is grounded in invaluable research on other coronaviruses, such as the investigation of the structure and pathogenesis of Middle East Respiratory Syndrome (MERS).

Types of Immunisations

Immunization can originate from passive or active means, and these means can originate from natural or artificial sources. Natural sources are caused by intentional exposure to pathogens, whereas artificial sources are caused by medical intervention. Passive immunization (PI) refers to when a person is given antibodies against a disease rather than producing them through their own immune system. PI provides immediate short-lived immunity that usually lasts a few weeks to 3–4 months as a result of the presence of antibodies. Once the antibodies have been eliminated, the individual would no longer has immunity to the pathogen. PI can occur both naturally and artificially. A perfect example of natural passive immunity is the transfer of maternal antibodies to the child through the placenta, colostrum, and breast milk.[4]

An example of artificial passive immunity is when an individual receives antibodies in the form of an injection of pooled human immune gamma globulin and antivenin.

These injections provide temporary immunity to either a particular disease or venom".[5]

Active immunization occurs when an unimmunized individual is exposed to a pathogen. Thus, the immune system begins the process of developing immunity against this agent. In contrast to passive immunization, active immunization typically produces long-lasting immunity due to the activation of the immune system. Active immunization can occur both naturally and artificially. A great example of natural active immunity is exposure to the influenza virus. Once contracted, the body begins to develop long-term immunity against it. Active artificial immunity refers to the antibodies developed as a result of, for example, a vaccination. Herd immunity is a noteworthy concept in the domain of immunity. Although vaccination offers strong protection against targeted diseases, unfortunately, not everyone can receive it. Individuals with weakened immune systems due to conditions such as HIV infection or severe allergies to vaccine components are unable to be vaccinated. However, even these individuals can find protection, especially when they are surrounded by vaccinated individuals. In communities where vaccination rates are high, the targeted pathogens, such as COVID-19, struggle to circulate, as the majority are immune to the disease.[6]

COVID-19 vaccine booster doses

Throughout history, vaccinations have provided a high level of protection against viral infections, which is also true for the COVID-19 vaccine. Although the rapid development of the COVID-19 vaccine and its global distribution have helped manage the COVID-19 epidemic, there are still cases of reinfection despite vaccination. Therefore, a third or fourth booster dose of the vaccine is highly recommended. Maximizing the ability of vaccines to induce antibody formation is key to ensuring enhanced immunity and protection against viruses and their variants.[7]

Several studies have investigated whether a booster is required. A study on immunity following mRNA vaccination showed that thirty-four adults who participated presented with a decline in antibody titer formation by the vaccine approximately 200 days after the first dose. However, three months after the second dose, the antibodies formed remained elevated for an extended period.[8]

"Another study evaluated how the body handles the neutralizing antibodies formed from mRNA vaccines over 2 weeks, 1 month, 3 months, 6 months, and 9 months in healthy participants. The study showed that after 9 months of full vaccination, there was a significant decline in the level of neutralizing antibodies with a median inhibition of 66.23%, indicating that 1/5 of the participants were not fully protected against SARS-CoV-2 infection. Collectively, a booster dose is more effective in enhancing immunity in older individuals since the ability to produce antibodies is lower and the clearance of antibodies is faster than in younger individuals."[8]

Cost Effectiveness

Research has shown that COVID-19 vaccines are extremely cost-effective. This is particularly beneficial for adults aged ≥65 years, as they are among those with the highest incidence rates. For example, those aged ≥65 years old, a "single dose of the vaccine is cost saving, at an assumed $120 per dose." In terms of adults aged 50-64, the cost-effectiveness ratio of the vaccines was estimated to be $25,787 per quality-adjusted life year, with evaluations suggesting that those aged ≥50 years are responsive to changes across reasonable ranges.[9] This suggests that cost-effectiveness is lower for younger adults than for older adults. This could be due to various reasons such as vaccine effectiveness and lower hospitalization rates. Vaccinations are an extremely important part of preventing widespread COVID-19 infection in both younger and older adults, reducing the burden on

healthcare systems even if they are lower for younger adults.[10]

Immune System Overview

The immune system comprises two groups: innate and adaptive.[11]The innate immune system acts as the frontline of defense against pathogens and harmful substances. Although lacking in specification and memory, the innate immune system provides speedy and overall protection against a wide array of threats. It is composed of various physical and chemical barriers, such as intact skin, mucous membranes, and acidic environments of entry. Furthermore, physical mechanisms, such as fever, gastric acidity, and enzymes, such as lysozyme, are included. Additionally, the immune system cells contain nonspecific cells which consist of "macrophages, neutrophils, dendritic cells, natural killer (NK), cells basophils, eosinophils, mast cells" and innate lymphoid cells. The functions of these cells include phagocytosis - the engulfing and destroying of pathogens – release of inflammatory mediators to be able to employ other immune cells, exhibiting the antigen of the pathogen to ensure the activation of the adaptive immune system, and finally initiating the process of wound healing and tissue repair.[12]

Moreover, the innate immune system includes complement pathways, inflammatory responses, and pattern recognition receptors (PRRs), which work together to activate an immune response. The formation of membrane attack complexes occurs via complement pathways, which enhance defenses and promote opsonization. The inflammatory response, which is activated in response to infection or damage, is characterized by redness, heat, pain, swelling, and loss of function.[13]

Pathogen-associated molecular patterns (PAMPs), which are recognized by PRRs and are found in cell membranes, activate responses such as complement activation, cytokine release, and phagocyte activation. The innate immune system is considered a rapid, nonspecific response that lays the groundwork for the subsequent adaptive immune response.

The adaptive immune system is regarded as an advanced defense mechanism, which is characterized by specification and memory. It is composed of specialized white blood cells called lymphocytes, specifically T and B cells, and is equipped with receptors that recognize specific antigens associated with pathogens. T cells are able to identify the antigen on the infected cells, whereas B cells recognize free-floating antigens.[14]

The adaptive immune system is activated and undergoes proliferation, while T cells execute various functions, including attacking infected cells, regulating immune responses to prevent excessive inflammation or autoimmune reactions, and stimulating B cells to transform into plasma cells, which, in turn, produce antibodies. A prominent feature is immunological memory, where the memory cells persist after the initial encounter with the pathogen, allowing for quicker and more effective responses to possible future exposures to the same pathogen. Overall, the innate immune system offers a quick and non-specific response to pathogens, whereas the adaptive immune system offers a targeted defense against specific pathogens.

Age

Research has found a significant and unrecognized disparity when comparing immune responses to vaccinations between individuals. One of the inconsistencies is the impact of age, particularly in infants and the elderly. Due to the low level of antibody production, immunization of infants encounters obstacles in overcoming interference with maternal antibodies. Studies conducted in the 1950s discovered variable effectiveness of vaccines like oral polio and diphtheria-tetanus-pertussis differs with age.[15] Hepatitis B vaccination in infancy results in lower long-term antibody responses than when administered later in childhood. Similarly, in the elderly, vaccine responses diminish and rapid antibody fading occurs. When the effectiveness of the COVID-19 vaccine was studied, it was found that the mRNA vaccine was effective against SARS-CoV-2 infections among 5–11-year-old children and higher in aged children. Vaccine effectiveness decreases over time, suggesting the need for booster dose schedules[15]

Immunosenescence refers to an intricate link between aging and immune dysfunction. It encompasses changes in both innate and adaptive immune cells, and responses to immune stimuli. This occurrence is characterized by reduced chemotaxis, dysregulated cytokine production, and weakened Toll-like receptor (TLR) signalling within the innate immune system, which plays a role in compromised immune function.[16]

Immunosenescence extends to adaptive immunity, compromising antigen processing and presentation to T cells, together with diminished B-cell activation, causing a

diminished immune response to both pathogens and vaccines.

The manifestation of the different variants of concern, such as the Delta (B.1.617.2) and Omicron (B.1.1.529) variants, heightened concerns among the older adults of the public regarding the effectiveness of vaccines. Research has shown a prominent decrease in the efficacy against these variants with the success of vaccines such as the AstraZeneca (AZ) vaccine, dropping from 74.5% effectiveness for the Alpha variant to just 67.0% effectiveness for the Delta variant. Likewise, the effectiveness of the Pfizer BioNTech (BNT162b2) vaccine decreased from 93.7% for the alpha variant to 88.0% for the delta variant. The decreased protection against the Omicron variants further suggests the need for ongoing observation and potential adjustments for vaccine strategies. To combat these challenges, various strategies have been developed to enhance immune responses in the elderly population. These methods include more potent adjuvants, modifications in the route of vaccine administration, and modification of vaccines to target more immunogenic antigens. Moreover, a more holistic approach, such as the integration of vaccinology with immunobiography, has favorable outcomes in shaping vaccine development in various populations.[17]

Additionally, recent advances in vaccine technology have paved the way for new approaches to enhance immunogenicity in elderly populations. Nanoparticle-based vaccines have shown favorable results in stimulating vital immune responses in the elderly population by enabling antigen uptake and presentation to the immune cells.[18] mRNA-based vaccines, such as Pfizer-BioNTech and Moderna (mRNA-1273) COVID-19 vaccines, have demonstrated efficacy in older adults, with the hope of effective vaccination among vulnerable individuals.[19] Studies have shown that older adult vaccinees have particular differences in their immune cell composition proportions and antibody responses in comparison to younger vaccinees. Although there were similar baseline hemogram parameters, older adult vaccinees presented with a lower neutrophil count and higher numbers of lymphocytes, CD56+ NK cells, and CD19+ B cells. Moreover, older adult vaccinees presented with a weaker first-dose antibody response compared to young vaccinees who had a mean age of 29.9. However, both groups showed positive responses to the booster after receiving the second vaccine dose, with no significant differences in antibody levels.[19]

Gender

Clear differences have been observed between the sexes when studying the impact of vaccines. Well-defined evidence supports the notion that, in contrast to males, females exhibit elevated antibody responses and have a higher occurrence of adverse reactions post-vaccination. Data from 1990 to 2016, focusing on females aged 19–49 years, revealed that females accounted for 83% of the incidence of anaphylactic reactions to vaccines.[20] The interactions among numerous biological mechanisms have been suggested to be the cause of sex differences in vaccine responses. Females have been found to acquire stronger and more rapid innate and adaptive immune responses than their male counterparts, which leads to their susceptibility to autoimmune diseases and a higher occurrence of negative reactions to vaccines in this group. Notably, age played a role in the analysis of vaccine responses between the sexes. While some vaccines are more effective in older females than in males, sex dimorphism in undesirable responses to certain vaccines does not necessarily narrow with age. Additionally, both hormones and genetics can affect immune responses. For example, testosterone has been shown to be related to a weakened vaccine response, whereas higher estrogen concentrations have been shown to produce a more heightened vaccine response. The relationship between genetics and their interactions with sex hormones has been linked to a clear observable difference in immunological responses between sexes. There have been found to be almost 10 time more genes on the X chromosome than on the Y chromosome. This includes a significant portion of the genes responsible for coding proteins related to the immune system. Consequently, because females are carriers of two X chromosomes, they have heightened expression of these immune-related genes and proteins, resulting in the potential for interaction with sex hormones to intensify the immune response.[21]

Comorbidities

Comorbidities are important factors that must be considered in the analysis of immune responses to vaccines, including SARS-CoV-2. Comorbidities, which are known as the presence of two or more diseases in an individual, are a critical aspect that requires thorough consideration when examining immune responses to vaccines. Those who experience comorbidities have atypical immune functioning because of their additional health conditions compared to those without comorbidities, who tend to have a typical functioning

immune system[22]. It is important to analyze the relationship between individuals with comorbidities and their immune response to the vaccine since they are often at a greater risk of developing extremely harmful and deadly outcomes if the COVID-19 virus was to be contracted, increasing the necessity for them to be vaccinated. A Taiwanese cohort of 824 subjects was used to investigate the impact of comorbidities on serological response to COVID-19 vaccination. Participants were categorized based on their health scores. More than half of them had low health scores (0–1), approximately one-third had moderate scores (2–3), and a smaller portion had higher scores (>4). The most common vaccination combination used was AstraZeneca (AZ) followed by Moderna, and the average antibody level after the third dose was measured. The factors associated with a potentially effective immune response included being over 60 years of age, being female, receiving moderna-based vaccinations (compared to AstraZeneca), receiving Pfizer-based vaccinations (compared to AstraZeneca), and having a lower number of comorbidities. As the number of comorbidities increased, antibody levels decreased. The study concluded that individuals with more health issues had a weaker immune response to three doses of the COVID-19 vaccine.

Individuals with a higher number of comorbidities had a poor serological response to three doses of COVID-19 vaccination, which suggests that their immune systems may not have responded as effectively to the standard vaccination protocol. However, this does not necessarily imply that stronger vaccines are required. These results could indicate that these individuals may require additional substitutions to enhance their immune responses. For example, this could include alternative vaccination schedules, additional doses, or improvement of existing vaccines. This emphasizes the importance of tailoring the treatment plans and approaches according to the patient.[23]

Further research must be conducted to ensure the health and well-being of patients with comorbidities. Another study, with a cohort of 86 patients (who were undergoing treatment for immune-mediated inflammatory disease and were on different medications), was paired with 38 healthy individuals (controls) for comparison. After administration of the vaccine, 86% of patients and 100% of healthy controls had detectable antibodies against SARS-CoV-2, but 14% of patients, all treated with rituximab, had undetectable antibody levels. In summary, the levels of SARS-CoV-2 antibodies were significantly lower in patients than in controls, especially in those treated with rituximab.[24]

This study also evaluated the cellular response to the SARS-CoV-2 vaccine in 30 patients, 11 of whom showed a positive cellular response, which was more common in patients treated with rituximab. SARS-CoV-2 infections were reported in 43% of patients and 34% of controls after vaccination, with a low percentage (7%) of patients requiring hospitalisation, mostly those treated with rituximab.[24]

In brief, patients treated with rituximab had lower antibody levels and a lower rate of positive cellular responses to the vaccine. Severe infections after vaccination are rare, occurring primarily in patients treated with rituximab.

To improve the immune response to the COVID-19 vaccine in individuals treated with rituximab or other medications, alternative vaccination strategies and close monitoring should be implemented.

Based on research and observations, healthcare professionals who specialize in immunology and administration of vaccinations to patients must consider taking an individualized approach per individual based on their unique patient medical history.

Similarly, in another study, patients with cancer were found to have a higher risk of death or severe complications of COVID-19. It is critical that these patients are vaccinated against the virus. However, patients with cancer, particularly blood or lymphatic system cancers, were less likely to develop protective immunity after COVID-19 vaccination compared to others. Cancer therapies often result in immune suppression, which may explain the poor response to vaccinations. Administering booster doses of COVID-19 vaccines may enhance immunogenicity in patients with cancer, although the extent of benefits and protection remains to be fully explored. Thakkar et al. (2023) revealed that administering a third vaccine dose can trigger a protective immune response in half of cancer patients who did not develop immunity after the initial vaccination series. By examining the immune responses of 106 cancer patients who received booster shots, this study found that the third dose could maintain protection for 4-6 months and notably lower the rates of breakthrough infections. Notably, among the 18 patients with hematologic malignancies and severe immune suppression, three doses were insufficient to provide immunity; however, a fourth dose effectively boosted immunity in two-thirds of these patients, even against variants such as Omicron.[25]

Ethnic Background

Diverse cultures are another factor that must be considered when analyzing immune responses to vaccines, including the SARS-CoV-2 vaccine. Evidence indicates that people from ethnic minority backgrounds might have a higher chance of facing severe outcomes from COVID-19. South Asian HCWs presented with higher SARS-CoV-2 spike-specific antibody titers, neutralizing antibody titers, and T cell responses compared to White HCWs during the early period (14–50 days) after vaccination. Furthermore, serum neutralizing activity and T cell responses remained higher in the South Asian groups throughout the study. [26]

It is important to note that although vaccine responses by ethnicity are both limited and conflicting, research suggests that immune responses to the COVID-19 vaccine vary among different ethnic groups, with individuals of South Asian descent exhibiting higher early phase responses compared to white individuals. Factors such as culture, genetics, and diet may have contributed to these differences. Different vaccination strategies have been shown to produce different immune protection outcomes. There are three different types of vaccination strategies: booster, sequential, and hybrid strategies. Booster immunity refers to the delivery of supplementary vaccine doses following completion of the initial vaccination series. This maintains the immunity against specific pathogens. For SARS-CoV-2, the preliminary doses administered led to a decrease in effectiveness in preventing infection and disease. The literature demonstrates that COVID-19 booster doses considerably enhance immunity and provide better protection against emerging variants such as Omicron. Booster doses of mRNA vaccines following initial doses of inactivated virus vaccines has shown to significantly increase neutralising antibody levels and boost T-cell responses.[27]

Similarly, combining adenovirus vector vaccines with inactivated virus vaccines as booster doses has been shown to produce strong immune responses and improve vaccine efficacy.[28]

A delayed but significant response occurs with hybrid immunity, which plays an important role in controlling the virus and preventing severe diseases.[29]

Individuals with hybrid immunity displayed the highest level of immune protection, as the benefits of both vaccination and natural infection were combined. This immune response is vital for controlling the spread of COVID-19 and reducing the severity of the illness in affected individuals. As we begin to develop immunity to the virus, there is a potential for the virus to become endemic, similar to the pattern seen with the influenza virus (1918 H1N1). The immune response driven by B cells that produce antibodies and T cells that target infected cells plays an important role in protecting humans from SARS-CoV-2. Understanding these dynamics is essential for effective management of pandemics. [30]

Conclusion

Overall, immune responses tended to dwindle a few months after vaccine administration. However, this comes from the B cells blocking SARS-CoV-2 from infecting cells via antibodies and from T cells destroying infected cells and supporting other immune responses.

In this article, we provide a detailed framework regarding immune responses to the COVID-19 vaccine based on demographics, age, sex, types of immunity, and immunization strategies. Such research can provide important academic support for the development of not only COVID-19 vaccines but also other vaccines. Vaccination is the most cost-effective and efficient way to provide long-lasting protection against SARS-CoV-2.

Humans have developed immunity to SARS-CoV-2, particularly antibody-mediated humoral immunity. This could lead to a similar situation to that of the influenza virus; with each outbreak, the virus weakens gradually. The development of vaccines across the whole family of coronaviruses that target antibody epitopes (antigenic determinants) prevents the emergence of mutant strains. In addition, another focus regarding the immunity of the virus is centered on the development of transmucosal vaccines that can induce respiratory mucosal immunity. Although a range of aspects regarding COVID-19 immunity, its vaccines, and their immune responses have been explained, there is still a considerable disparity between the questions posed and available explanations, particularly considering the evolution of SARS-CoV-2 and new emerging variants. As a result of viral evolution, it is vital to analyze changes in cellular and humoral immune responses, their protective effects, and reactions after vaccination.

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