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Reactions to SARS-CoV-2: The Effectiveness of the Body's Immunological Memory

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ABSTRACT

Coronavirus Disease 2019 (COVID-19), caused by SARS-CoV-2, is a worldwide pandemic which resulted in significant morbidity and mortality. After being exposed to SARS-CoV-2 infection, some patients (especially elderly patients) begin to develop severe COVID-19. Infected individuals begin to produce hyper-inflammatory responses in the body. These responses build immunological memory, which helps to determine one's protection against reinfection, disease risk, and vaccine efficacy. This research paper aims to answer the question of whether immunological memory against COVID-19 is retained in individuals after contraction of the virus. Through a compilation of multiple research studies, a clear correlation was made between coronavirus pathogens and antibody/memory cell responses. The original hypothesis, which focused on the efficacy of immune memory against COVID-19, was partially supported by the results. While it was found that immunological memory after the virus is present, there are limitations to the testing group. This research's purpose is to help readers understand the body's immune response system and its role in controlling COVID-19 infection. With this information, other researchers can further study and develop treatments for future deadly infections/diseases similar to COVID-19.

Introduction

Coronaviruses (CoVs) refer to a family of highly diverse, single stranded, enveloped, and single stranded RNA viruses (Sharma et. al., 2020). Coming from the previous SARS and MERS viruses, SARS-CoV-2 virus caused a worldwide pandemic in late 2019, and had a great effect on the lives of many across the world. As of January 2023, the COVID-19 pandemic has affected more than 650 million individuals worldwide, with over 6.6 million fatalities (WHO). Compared to other hCoVs, SARS-CoV, MERS-CoV, and SARS-CoV-2 have a greater propensity to infect the lower respiratory tract, resulting in the development of severe conditions such as acute respiratory distress syndrome (ARDS), acute lung injury (ALI), septic shock, and multi-organ failure. The case fatality ratio (CFR) associated with these infections is also high (Zhu, Z., Lian, X., Su, X. *et al.*, 2020). SARS-CoV was initially identified in Foshan, China in 2002, and then it was transmitted to Hong Kong in 2003, from where it circulated worldwide (Zhu, Z., Lian, X., Su, X. *et al.*, 2020). A decade after the decline in cases of the SARS-CoV outbreak, a more lethal hCoV emerged, namely MERS-CoV. This virus originated in Jordan and spread throughout the Middle East. On the other hand, SARS-CoV-2 was initially detected in Wuhan, China in December 2019 and quickly spread throughout the country before aggressively infecting people all over the world. SARS-CoV-2 is the first hCoV to cause a pandemic and widespread concern on a global scale (Zhu, Z., Lian, X., Su, X. *et al.*, 2020).

In an effort to prevent further global morbidity and mortality, multiple effective vaccines have been developed and administered worldwide. There are now 17 different vaccinations being administered worldwide that have been licensed by national regulatory agencies, 7 of which have received approval from the WHO for use in an emergency. BNT162b2 (manufactured by Pfizer-BioNTech and marketed as Comirnaty) and mRNA-

1273 (made by Moderna) are two SARS-CoV-2 vaccines based on new messenger RNA (mRNA) technology that have been granted human use licenses. The nature and duration of the evoked immune response aren't completely understood because mRNA vaccines have been licensed for use in humans. Although significant progress has been made in COVID-19 research and vaccine development, there is much that is unknown about the disease. The dreadful threats posed to humans can't be completely cured, emphasizing the urgent need to gain a deeper understanding of these lethal hCoVs and the illnesses caused by them as they continue to pose a threat to the world, especially individuals that are immunocompromised (who would take the biggest hit). This paper will go on to study blood sample tests to determine specific memory cells to coronavirus in individuals that have and have not contracted COVID-19. The original hypothesis is that patients who have contracted COVID 19 will trigger a memory cell response that will induce immunity to the infection.

Coronavirus Cell Biology

In order to understand this research paper, it is important to recognize the structure of coronavirus cells and how it infects the body. The SARS-CoV-2 virus spreads through coronavirus cells that reproduce in the bloodstream, in contrast to bacteria and fungi that can self-reproduce in various environments. Viruses are parasitic and solely focus on reproducing within cells. There are two classes of plant and animal viruses based on their genetic material: DNA or RNA molecules (King et. al., n. d.). Coronaviruses, which derive their name from their crown-like appearance, which pertains to the spike proteins extending from them, store their genetic information in RNA molecules (King et. al., n. d.) Previous outbreaks of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) are related to the SARS-CoV-2 virus.

COVID-19 disease infects a person through coronavirus cells that primarily enter through one's mouth, eyes, or nose. The respiratory droplets ejected when an infected individual coughs, sneezes, or talks can spread the virus to another person through inhalation or indirect contact. In poorly ventilated or crowded rooms, the virus spreads more quickly, causing an illness ranging from mild to severe (CDC, 2022). Once entered, the virus spreads to the lungs where it has its most severe effect.

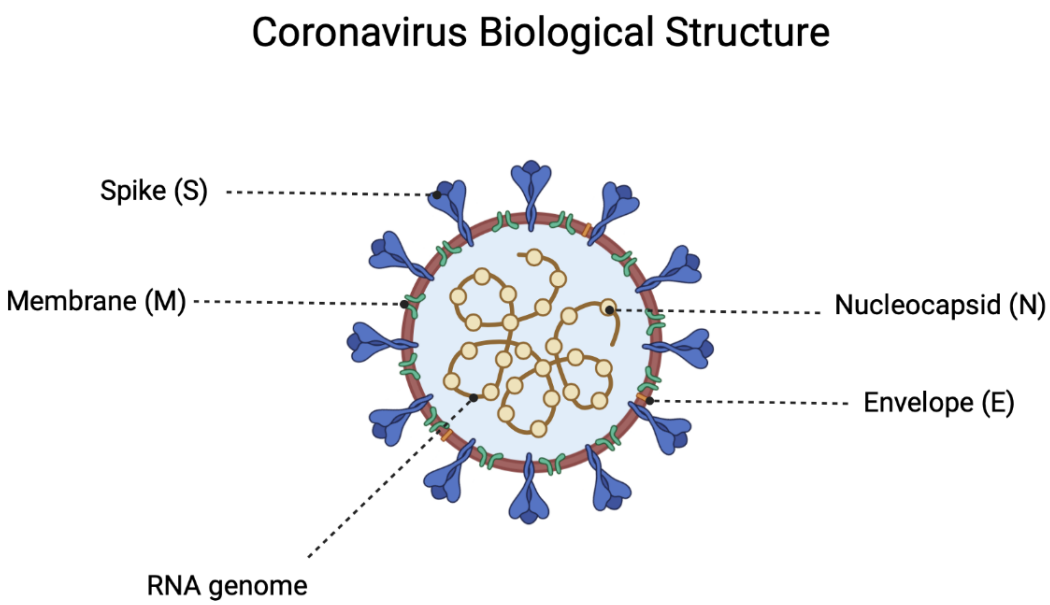

Figure 1. Depicts Coronavirus structure with viral proteins. Created and copyrighted by Abhaya Saridena.

As seen in **figure 1**, Coronavirus particles are composed of long RNA polymers that are tightly packed at the center, and are surrounded by a protective capsid made up of repeating protein molecules called coat or capsid proteins, also known as nucleocapsids in coronaviruses. Additionally, there is an outer membrane envelope made of lipids with inserted proteins that encloses the coronavirus core particle. These modified membranes, including the spike (S), membrane (M), and envelope (E) proteins (**figure 1**), are derived from the cells where the virus was most recently formed. The virus uses Angiotensin Converting Enzyme 2 (ACE2) as a receptor to infect human lung cells by binding to the spike protein. After integrating into the lung cells, the viral RNA is released into the cytoplasm, which instructs the cells to produce hundreds of thousands of viral proteins in the body (King et. al., n. d.).

Immunological Responses

It is crucial to grasp the process of the immune system before delving further into this research paper. Immunological memory refers to the immune system's swift recognition of a previously encountered antigen in the body, triggering a corresponding immunological response. This mechanism allows the body to defend itself against future reinfection (Janeway et. al., 2001). Immune cells serve as a conduit for immune memory when responding to potential viral threats. The immune system acquires the ability to neutralize the invader during the primary response. Immunity stems from the ongoing defense against the virus that is stored as immunological memory. Additionally, the immune system factors in the scale and composition of the virus to safeguard the body (Janeway et. al., 2001). In essence, the immune system's ultimate objective is to prevent viral infection.

Immune memory, derived from either prior infection or immunization, serves as the cornerstone of protection against recurrent infections. The development of the COVID-19 vaccination thus depends on immunological memory. However, even with extensive research, the immune responses observed shortly after the resolution of an infection do not provide a reliable indication of long-term memory. Therefore, the kinetics, duration, and evolution of immune memory in humans, whether in response to infection or immunization, are typically unpredictable based solely on the initial effector phase (Dan et al, 2021). Future research is necessary to advance the predictability of human immunological memory.

Immunological memory can provide protection against clinical disease or death in various scenarios, but neutralizing antibodies at high levels are required for achieving sterilizing immunity against viruses. The immune system employs different defense mechanisms depending on the rate of infection spread and the response to memory infections. For instance, immunological memory induced by the HBV vaccine can prevent clinical hepatitis even in the absence of circulating antibodies, owing to the relatively slow progression of the disease. To develop protective immunity against severe or symptomatic secondary COVID-19, memory compartments such as circulating memory T cells and B cells can play a critical role, albeit taking several days to reactivate and generate recall T cell responses or anamnestic antibody responses. The prolonged period between the onset of symptoms and severe COVID-19 (around 19 days post-symptom onset for fatal cases) suggests that protective immunity against severe or symptomatic secondary COVID-19 may be present.

Memory B Cell Response

Lymphocytes are a vital component of our immune system and are white blood cells that come in two main types - B cells and T cells. B cells produce antibodies that can recognize and eliminate harmful foreign substances such as bacteria, viruses, and toxins. On the other hand, T cells have a critical role in identifying and destroying cells within the body that have become infected with a virus or have turned cancerous (National Human Genome Research Institute, n.d.).

Memory B cells are a crucial type of white blood cell that is involved in the immune response. These cells are generated from activated B cells after the first exposure to an infection or vaccination and can recognize and respond to the same pathogen if it is encountered again. Unlike plasma cells, which continuously produce antibodies, memory B cells can remain in the body for extended periods, even for years or decades, providing long-term immunity to particular pathogens. When a memory B cell encounters the same pathogen again, it quickly transforms into a plasma cell and produces a large quantity of antibodies to eliminate the infection. Memory B cells are therefore an essential component of the adaptive immune system, which delivers specific and long-lasting protection against pathogens.

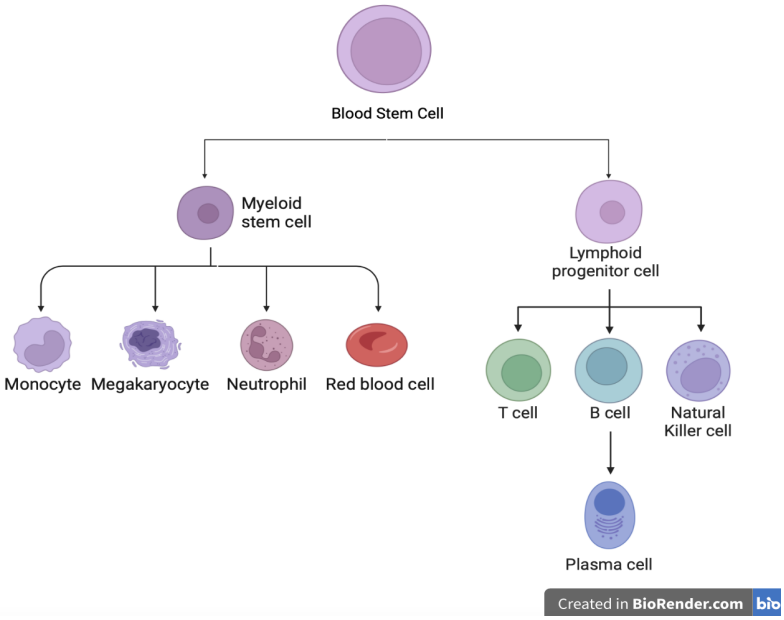

Figure 2. Demonstrates the lineage of memory cells from the body's blood cells. Created and copyrighted by Abhaya Saridena.

The pluripotent hematopoietic stem cell, or the standard blood stem cell (**figure 2**) is responsible for the development of all blood cells. It divides into two different types of cells within the bone marrow: the common myeloid progenitor cell (**figure 2**), which creates red blood cells, leukocytes, and platelets, and the common lymphoid progenitor (**figure 2**), which produces T cells and B cells (**figure 2**). B cells, also known as B lymphocytes or memory cells, are essential in the immune response to viral infections. Once activated, they carry out three main functions: presenting antigens to other immune cells, secreting cytokines, and producing antibodies.

Antigen Presentation

Regarding antigen presentation, although the most significant role of B cells is in humoral immunity (antibody-driven), inactive B lymphocytes can also serve as antigen-presenting cells (APCs). They first attach to the foreign particle or antigen and produce membrane markers as a warning signal that the T cell can detect. B lymphocytes then present these antigen-major histocompatibility complex (MHC) complexes to T cell receptors, leading to T cell activation.

Cytosine Secretion

Cytokines, which are signaling molecules necessary for cell-to-cell communication, are secreted by B lymphocytes. These cytokines cause cell movement and invite white blood cells in the form of phagocytes to the areas where B-cell antibodies have attached to antigens.

Antibody Production

The primary role of B cells is the production of antibodies. This process starts in the bone marrow with the development of specialized membrane receptors called B-cell receptors (BCRs) that act as locks for antigen keys. After moving to lymphoid organs, the B cells become naïve and encounter antigens that match their

receptors. Once bound, the B cell brings the antigen inside its membrane for processing, resulting in the formation of antigen-major histocompatibility complex (MHC) complexes that can be recognized by T cells. Memory cells, which have a longer lifespan, can identify the same antigen if it reappears in the future, while plasma cells react immediately by releasing antibodies that circulate throughout the bloodstream and attach to their specific antigen type.

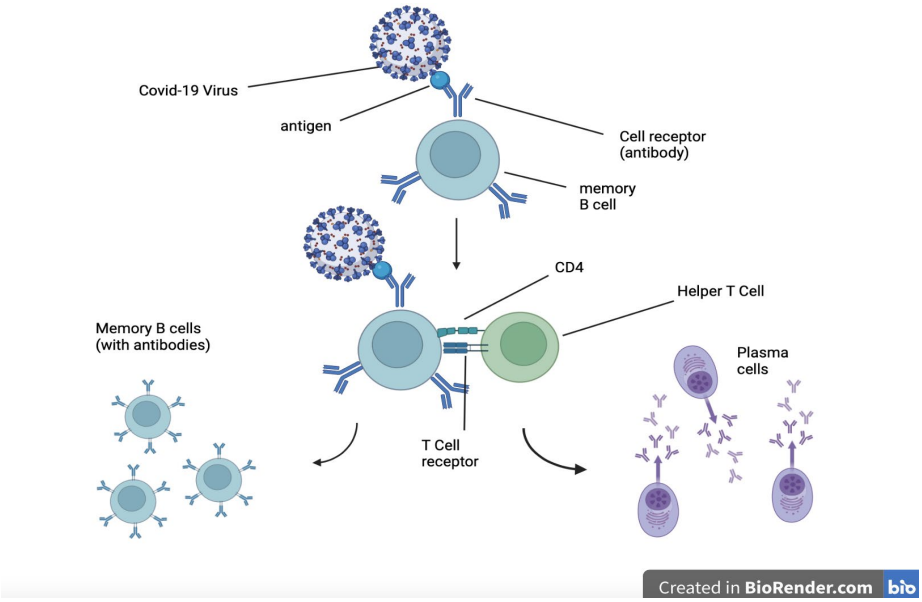

Figure 3. Process of antibody-mediated memory response to COVID-19 virus. Created and copyrighted by Abhaya Saridena.

In simple terms, during the process of a memory response to a detected COVID-19 virus, the memory B cell first recognizes an antigen on the virus through a cell receptor (**figure 3**). This is how the memory B cell gains knowledge of the virus. Then, it communicates with the helper T cell through cell receptors (**figure 3**). After this step, memory B cells rapidly proliferate, along with plasma cells (**figure 3**) aimed to target and eliminate the rest of the virus cells in the body.

B cells undergo rapid proliferation and DNA mutation within germinal centers (GCs), where they intentionally modify the DNA encoding their antigen-binding receptor's epitope-binding component to potentially increase its affinity. This process involves repeated cycles of proliferation, mutation, and selective survival of B cells with improved binding affinity to the antigen (**figure 3**). However, although mRNA vaccination has been shown to elicit an immune response primarily related to antibody production, limited information is available regarding the persistence of memory B cells, which are crucial for a rapid response to SARS-CoV-2 infection. The human memory B-cell compartment is a critical component of vaccine efficacy, as it serves as the basis for protective immunity upon encountering the pathogen, ultimately leading to the production of spike-specific antibodies by plasma cells. Therefore, assessing memory B cells provides a crucial biomarker for profiling long-term immune response efficacy, even beyond the decline of antibody titers. During their function, memory cells target viral proteins of coronaviruses that were previously introduced (Quast & Tarlinton, 2021).

Types of Antibodies

Antibodies, also known as immunoglobulins, can be classified into five groups. The first response, IgM, has the ability to cause various antigens to cluster. IgA is responsible for defending against pathogens that target

mucous membranes. IgD controls the function of receptors that signal B cell activation and is usually expressed in conjunction with IgM. IgG is the most common human immunoglobulin and can recognize and label a diverse range of pathogens for removal. IgE binds to mast cells and basophils, releasing histamine that is associated with allergies. Antibodies can use three different processes to neutralize antigens. The first process is complement fixation, where antibodies bind to foreign particles and break them down, attracting other white blood cells through chemotaxis. Another way is opsonization, where antibodies mark antigens to facilitate recognition and removal by other cells. Neutralization is a third mechanism in which antibodies block antigens from releasing toxins. Finally, agglutination occurs when antibodies cause foreign particles to clump together, making it easier for phagocytes to digest them. This is how IgM antibodies function (Janeway, 2017).

SARS-CoV-2 Circulating Antibodies

This study analyzed the immune response to COVID-19 by testing blood samples for antibodies. A total of 188 participants, including 80 male and 108 female individuals, were included in the study, with a range of symptoms from asymptomatic to severe, and most falling into the mild category. Hospitalization was required for only 7% of participants, with some needing admission to the ICU. Blood samples were collected from most participants between 6 and 240 days after the onset of symptoms, and a subset of 51 individuals provided multiple samples at different time points. The study assessed specific antibody responses to COVID-19, with the majority of participants showing seroconversion rates ranging from 91-99%. The tests focused on spike immunoglobulin G (IgG) ELISA titers in plasma, spike receptor binding domain (RBD) IgG, and nucleocapsid (N) IgG. IgG and IgA are antibodies that fight pathogenic viruses and mediate viral neutralization, while RBD is the main target of neutralizing antibodies against SARS-CoV-2.

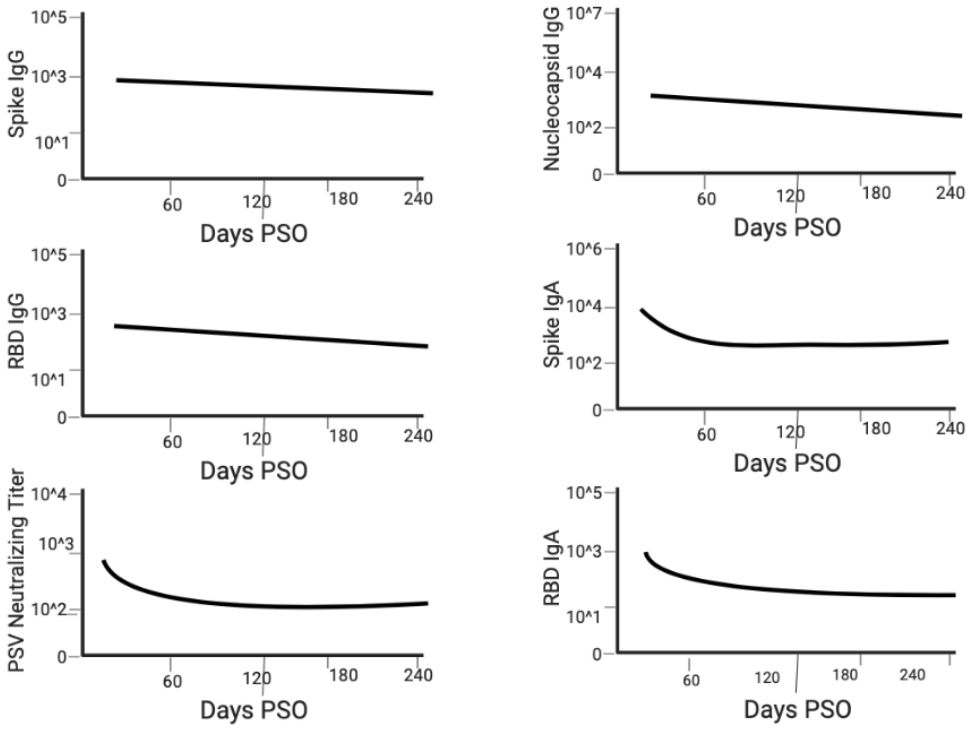

Figure 4: Shows results of antibodies targeting Coronavirus viral proteins up to 240 days post symptom onset (PSO). Created and Copyrighted by Abhaya Saridena.

After conducting the tests, the study found that the SARS-CoV-2 spike IgG titers remained relatively stable between 20 and 240 days after symptom onset. Figure 4 displays graphs of the best fit curves for the different tests conducted, with all tests showing a continuous decay. The study also revealed that the frequencies of SARS-CoV-2 spike-specific memory B cells increased during the first 120 days and then reached a plateau. In subjects exposed to COVID-19, the frequency of spike-specific memory B cells increased from the first time point (between 36 and 163 days after symptom onset) to the second time point (between 111 and 240 days after symptom onset). Similarly, RBD-specific memory B cells showed a similar trend, with levels being undetectable in unexposed subjects, and appearing as early as 16 days after symptom onset and increasing steadily for the next 4-5 months (as shown in figure 4). Nucleocapsid-specific memory B cells also showed a similar trend to spike-specific and RBD-specific cells, steadily increasing for 4-5 months after symptom onset (as shown in figure 4).

Overall, on the basis of the observations here, development of antibodies to SARS-CoV-2 was robust, slightly decreasing over time (seen through the curves of decay in **figure 4**), but is likely long-lasting. By this study, we can assume that antibodies against COVID-19 were retained in the body for a short amount of time after COVID-19 symptoms were shown in patients. However, they were on the decline, therefore meaning the immunity isn't permanent.

SARS-CoV-2 Memory Cells

Tests were also conducted for memory B cells that were spike specific, nucleocapsid specific, and RBD specific in the blood samples.

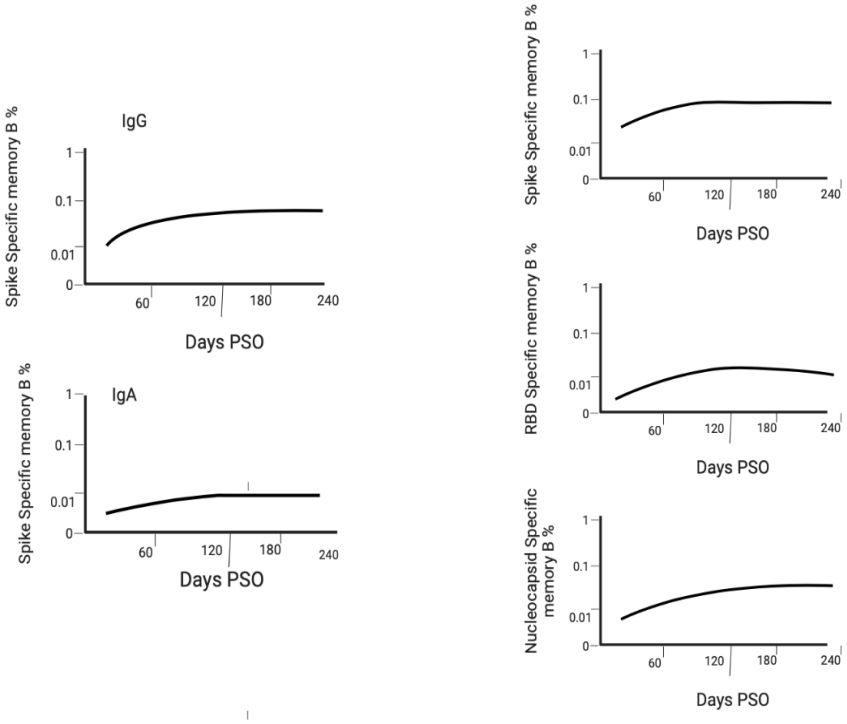

Figure 5. Graphs show spike specific, RBD specific, and Nucleocapsid specific Memory B Cell percentage in individuals who have contracted COVID-19 previously. Created and Copyrighted by Abhaya Saridena.

The blood sample tests showed that the frequencies of SARS-CoV-2 spike-specific memory B cells increased in the first 120 days and then remained stable. Spike-specific memory B cells increased from the first

to the second time point (36-163 days and 111-240 days, respectively), as seen in **figure 5**. RBD-specific memory B cells displayed similar results, appearing as early as 16 days PSO and steadily increasing for the next 4 to 5 months, with 29 out of 36 individuals having them appear at a later time point. Nucleocapsid-specific memory B cells also steadily increased for 4-5 months (**figure 5**). Overall, the data suggests that B cell memory to SARS-CoV-2 is strong and long-lasting. The graphs in **figure 5** show an increase followed by a plateau in B cell memory, indicating that memory B cell immunity is likely retained after contracting the virus.

Overall, through the observations of these blood sample tests, development of B cell memory to SARS-CoV-2 was robust and is likely long-lasting. The best fit curves for the types of tests in the graphs (**figure 5**) show an increase and then a plateau. Through this data, it can be predicted that memory B cell immunity would be retained in the body after contraction of the virus.

SARS-CoV-2 Memory T Cells

Similar to memory B cells, memory T cells are a crucial component of the immune system that provide long-term protection against pathogens. They can be divided into two subtypes, central memory T cells (Tcm) and effector memory T cells (Tem), which play important roles in recognizing and eliminating infected cells. Memory T cells can also provide immunological memory against viral or bacterial infections, leading to a more rapid and effective response upon re-infection.

Memory T cells can be categorized into CD4+ or virus-specific CD8+ T cells, depending on the type of antigen they encounter. There are various subtypes of memory T cells, such as central memory T cells and effector memory T cells. Researchers analyzed blood samples obtained from individuals who had been infected with SARS-CoV-2 to investigate the long-term effects of the virus on memory T cells in the body.

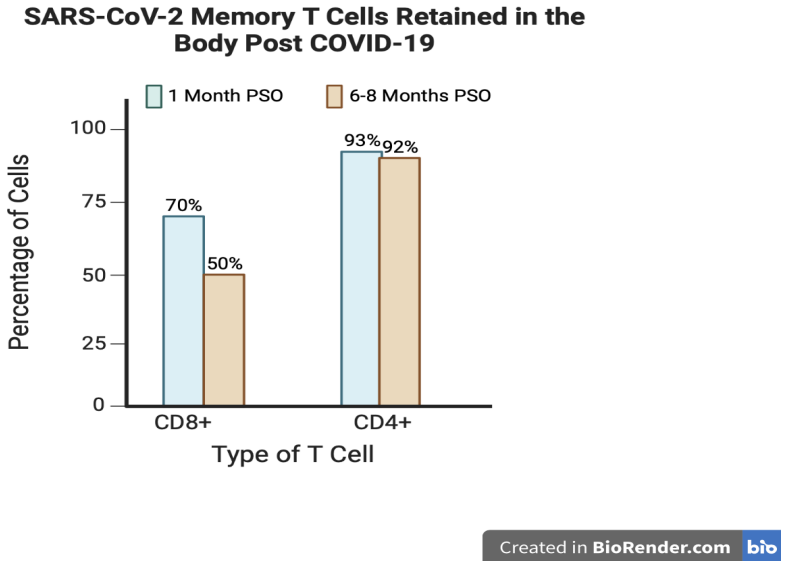

Figure 6: SARS-CoV-2 memory CD8+ cells and CD4+ cell percentage results 1 month PSO and 6-8 months PSO. Created and Copyrighted by Abhaya Saridena.

To assess the long-term impact of memory T cells in SARS-CoV-2 infected patients, blood samples were collected and analyzed. The findings, presented in Figure 6, indicate that the percentage of CD8+ cells decreased from 70% at one month post symptom onset (PSO) to 50% at 6-8 months PSO, which suggests that these cells may not have a long-lasting effect on the body's immune system against SARS-CoV-2. In contrast,

the percentage of CD4+ cells remained relatively high at 92% at 6-8 months PSO, implying that these cells may contribute to maintaining permanent memory in the body, which can strengthen the immune system's response to SARS-CoV-2.

Vaccines

Vaccines work by introducing weakened or inactive parts of a specific organism, called antigens, which stimulate an immune response in the body. Newer vaccines use the genetic blueprint for producing antigens instead of the antigen itself. These weakened versions do not cause disease but prompt the immune system to react as it would to the actual pathogen. Some vaccines require multiple doses to allow for the production of long-lived antibodies and memory cells. This prepares the body to fight the specific disease-causing organism and quickly combat it if exposed again in the future.

As of December 2022, four COVID-19 vaccines have been approved or authorized for use in the US, including Pfizer, Moderna, Novavax, and Janssen. Globally, 17 different vaccines have been authorized by national regulatory authorities, with seven approved for emergency use by the World Health Organization (WHO). The BNT162b2 vaccine from Pfizer-BioNTech and the mRNA-1273 vaccine from Moderna, which are based on novel messenger RNA (mRNA) technology, have been licensed for human use.

Vaccine-Induced Memory vs. Infection-Induced Memory

A review of multiple studies, including vaccine efficacy trials and observational studies from the US, Israel, and the United Kingdom, found no significant difference in the level of protection provided by vaccination versus protection provided by prior infection with COVID-19, including during the period when the Delta variant was prevalent. The review showed that mRNA vaccines appeared to provide higher protection in randomized controlled trials, while protection following infection appeared higher in observational studies. However, a more recent analysis of data from 187 hospitals in the US found that previously infected patients had 5.5 times higher odds of getting laboratory-confirmed COVID-19 compared to fully vaccinated patients, among more than 7,000 COVID-19-like illness hospitalizations whose prior infection or vaccination occurred 90-179 days beforehand. The authors of the study noted a potential limitation in their design, which was the possibility of missing testing that may have occurred outside of the healthcare network.

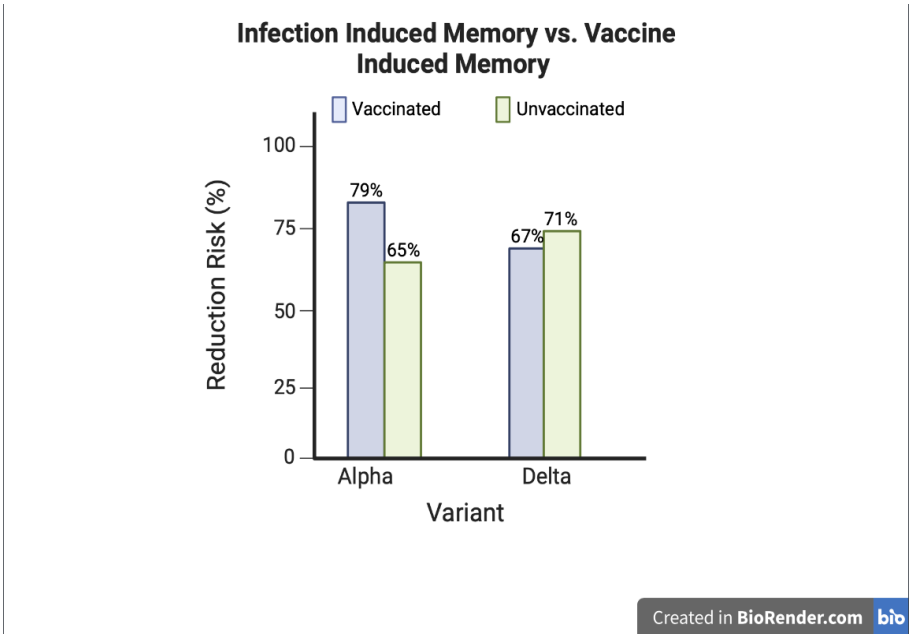

Figure 6. Comparison of reduction in risk of reinfection in infection-induced immunity and vaccine-induced immunity between Alpha and Delta variants of coronavirus. Created and Copyrighted by Abhaya Saridena.

The Office of National Statistics in the UK conducted a study that compared the risk of COVID-19 infection among people who were fully vaccinated, partially vaccinated, unvaccinated but previously infected, and unvaccinated and uninfected during two different periods. Over 26,000 positive COVID-19 test results were included in the study, which looked at the Alpha and Delta variants. The results showed that during the Alpha period, full vaccination provided the greatest protection, reducing the risk by 79% compared to 65% for partially vaccinated and unvaccinated/previously infected individuals. However, during the Delta period, full vaccination and previous infection provided equivalent protection, reducing the risk by 67% and 71%, respectively. Nonetheless, neither vaccination nor previous infection provided complete immunity (100%) against COVID-19, suggesting that the body's immunological memory is not permanently effective against the disease.

Exhaustion of Immune System

In some cases, immune memory becomes exhausted, unable to continue to fight the pathogen from the body. In these cases, the virus takes over the body, becoming too strong in population for the memory cells and antibodies to create the same number to defend and revive the body. Especially in cases of immunocompromised patients (weakened immune systems), diseases like COVID-19 that target vital organs of the body put the patients at a higher risk than others. To prevent these cases, vaccines and strong immunity is required, and is vital to protect the body and prevent reinfection or exhaustion.

Conclusion

Immunological memory in the body is important to understanding the body's reaction and vaccine creation for deadly infections, especially COVID-19. My initial hypothesis was proven to be partially correct. Through these collected blood samples, it can be concluded that up to several months after the COVID 19 infection, immune memory is retained. Circulating antibodies, memory B cells and T cells all show steady retention in the body post COVID-19 in the test groups, with intent of being long lasting. However, part of the original

hypothesis wasn't completely proved, as we cannot determine whether immunity against COVID-19 will last for long. Studying immunological memory responses in Covid-19 patients is very important, as the infection still causes global morbidity and mortality. This study will also help shape future research in understanding immune memory in humans, and preventing other diseases or similar future infections.

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