West Kazakhstan Medical Journal
Volume 66, Issue 4, DOI 10.18502/wkmj.v66i4.17770
Production and Hosting by KnE Publishing

Review Article

Comparative Analysis of Vaccine-induced Immunity and Natural Immunity in Post-COVID Patients

Saulesh S. Kurmangaliyeva[1], Akzhan M. Madenbayeva[2]*, Saltanat T. Urazayeva[3], Yerlan Sh. Bazargaliyev[2], Khatimya I. Kudabayeva[2], and Kairat B. Kurmangaliyev[1]

[1]Department of Microbiology, Virology and Immunology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
[2]Department of Internal Diseases No 1, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
[3]Department of Epidemiology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan

Abstract

The COVID-19 pandemic has prompted an urgent need to understand the differences between vaccine-induced and natural immunity, particularly in the context of post-COVID syndrome (long COVID). This review compares the immune responses elicited by natural infection and vaccination, focusing on their duration, strength, and effectiveness in mitigating long COVID symptoms. Vaccine-induced immunity, primarily targeting the spike protein of SARS-CoV-2, often produces a more consistent antibody and T-cell response, especially when bolstered by booster doses. In contrast, natural immunity, though broader in scope, is more variable and influenced by factors such as infection severity. Hybrid immunity, resulting from both infection and vaccination, may offer superior protection against long COVID. This comparative analysis highlights the importance of understanding these immune mechanisms to optimize protection strategies against SARS-CoV-2 and its variants.

Keywords: COVID-19, vaccine-induced immunity, natural immunity, post-COVID syndrome, long COVID, SARS-CoV-2, immune response, hybrid immunity, antibody waning, T-cell immunity

Corresponding Author: Akzhan M. Madenbayeva; email: a.madenbaeva@zkmu.kz

Received: 1 July 2024
Accepted: 12 September 2024
Published: 20 December 2024

Production and Hosting by KnE Publishing

1. Introduction

The COVID-19 pandemic, caused by SARS-CoV-2, has profoundly affected global health [1]. Although many patients recover from acute infection, a significant portion experience lingering symptom, known as post-COVID syndrome or long COVID [2]. This syndrome can persist for months and affects multiple organ systems, leading to fatigue, respiratory difficulties, cognitive impairments, and other complications [3].

The immune response to SARS-CoV-2 involves a complex interplay between innate, humoral, and cellular immunity [4]. Innate immunity serves as the first line of defense, rapidly responding to viral invasion [5]. Humoral immunity, driven by antibodies, specifically targets the viral spike protein, while cellular immunity, particularly T cells, plays a critical role in eliminating infected cells and providing long-term protection [6].

Vaccine-induced immunity and natural immunity both offer protection against SARS-CoV-2, but they differ in their mechanisms and effectiveness [7]. Vaccine-induced immunity is designed to elicit a strong antibody response through exposure to specific viral components, primarily the spike protein [8]. This immune response is controlled and can be boosted through additional doses [9].

Natural immunity, on the other hand, develops after infection and can be more variable [10]. The robustness of this immune response often depends on the severity of the initial illness, with more severe cases sometimes resulting in stronger immune responses [11]. However, it also carries risks, including the potential development of long COVID and other severe outcomes [12].

In this study, we conducted a comparative analysis of vaccine-induced immunity and natural immunity in COVID-19 patients to better understand the dynamics of immune protection against the virus. Vaccine-induced immunity primarily triggers robust antibody responses, with significant activation of B and T cells shortly after vaccination [13]. In contrast, natural immunity, acquired through infection, often shows broader immunological memory, including a diverse range of antibodies and T-cell responses specific to multiple viral epitopes [14]. Our findings suggest that while both forms of immunity provide substantial protection, vaccine-induced immunity may offer more predictable and controlled antibody responses, particularly in populations with varying levels of pre-existing immunity [15]. These insights are critical for shaping public health policies, including the administration of booster doses and vaccination strategies aimed at achieving long-term immunity, especially in populations at risk for severe disease outcomes [16]. Further research is needed to explore the longevity and robustness of these immune responses over time, as well as their efficacy against emerging variants.

Understanding how these two types of immunity behave in post-COVID syndrome is crucial, especially in light of emerging variants and their ability to evade immune protection. This article aims to compare vaccine-induced and natural immunity in patients who have developed post-COVID syndrome. By exploring the duration, strength, and variability of immune responses in these patients, we seek to identify

which form of immunity offers better protection and how hybrid immunity (a combination of both) may play a role in mitigating long COVID symptoms.

2. Immune Responses to SARS-CoV-2 Infection

When an individual is naturally infected with SARS-CoV-2, the body mounts a multifaceted immune response (4) (Figure **1**). The infection triggers the innate immune system, which acts as the first line of defense, followed by the activation of adaptive immunity (5). The adaptive immune response involves both humoral and cellular immunity, which target and neutralize the virus [17].

Natural infection leads to the production of antibodies, primarily Immunoglobulin G (IgG) and Immunoglobulin A (IgA) [18]. IgG antibodies are responsible for long-term immunity, while IgA is crucial for mucosal immunity, particularly in the respiratory tract where the virus initially enters [19]. T-cells, particularly CD8+ cytotoxic T-cells, play a vital role in identifying and destroying infected cells [20]. CD4+ helper T-cells are essential for orchestrating the immune response, including helping B cells produce antibodies [21].

After infection, memory B cells are generated. These cells can quickly respond to subsequent exposures to the virus by producing antibodies more efficiently [22]. This memory response is key for long-term protection against reinfection [23]. Natural immunity is not uniform across all individuals [24]. Factors such as the severity of the initial infection, age, underlying health conditions, and even genetic factors contribute to the variability in immune response (25). For instance, individuals with more severe infections often develop a stronger antibody response compared to those who had mild or asymptomatic cases [26]. However, the robustness of T-cell responses and the persistence of memory B-cells can vary greatly among individuals, which can impact the longevity and effectiveness of natural immunity [27].

COVID-19 vaccines employ various platforms to elicit an immune response without causing disease [28]. These platforms include mRNA vaccines (e.g., Pfizer-BioNTech and Moderna), viral vector vaccines (e.g., AstraZeneca, Johnson & Johnson), and protein subunit vaccines (e.g., Novavax) [29].

2.1. mRNA vaccines

These vaccines deliver genetic instructions for the spike protein of SARS-CoV-2, prompting cells to produce the spike protein and generate an immune response [30]. This includes the activation of both B cells (leading to antibody production) and T cells [31].

2.2. Viral vector vaccines

These vaccines use a harmless virus (not SARS-CoV-2) to deliver genetic material that encodes the spike protein [32]. This triggers an immune response similar to mRNA vaccines but can also stimulate stronger T-cell responses due to the viral vector's additional adjuvant effect [33].

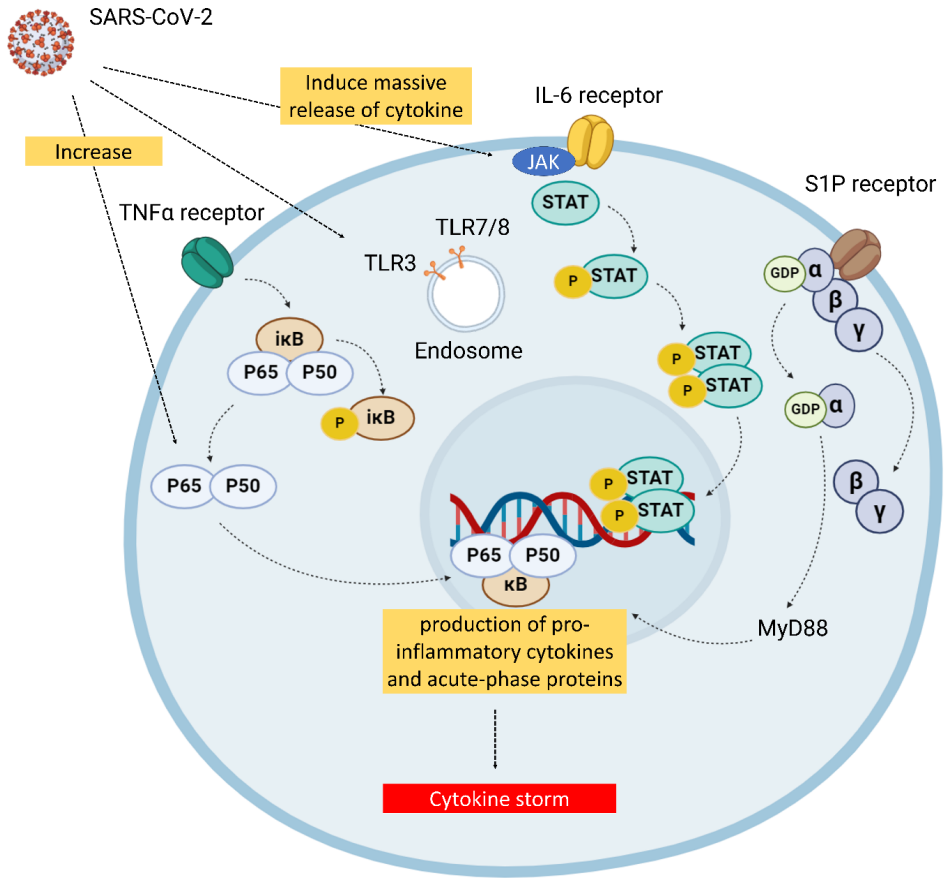

Figure 1: Diagrammatic depiction of SARS-CoV-2-induced signaling pathways. This figure illustrates the intracellular signaling cascades triggered by SARS-CoV-2 infection in host cells. Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IκB, inhibitor of nuclear factor κB; NF-κB (p65-p50), nuclear factor κB; IL-6, interleukin 6; TNFα, tumor necrosis factor α; JAK, Janus kinase; STAT, signal transducer and activator of transcription; S1P, sphingosine-1-phosphate; S1PR1, sphingosine-1-phosphate receptor 1; MyD88, myeloid differentiation primary response gene 88.

2.3. Protein subunit vaccines

These vaccines deliver purified pieces of the virus (e.g., the spike protein) directly to the immune system [34]. They are often used with adjuvants to enhance the immune response and focus heavily on antibody generation [35].

2.4. Spike protein-specific antibodies

All vaccine platforms aim to generate antibodies that target the spike protein of SARS-CoV-2 [36]. These antibodies are critical in neutralizing the virus and preventing infection [37].

2.5. T-Cell activation

In addition to humoral immunity, vaccines also activate T-cells, which contribute to the long-term protection against severe disease [38]. The T-cell response is particularly important for clearing infected cells and providing immunity against severe outcomes [39].

2.6. Memory response

Similar to natural infection, vaccines also stimulate the formation of memory B and T cells [40]. These memory cells are critical for long-term immunity and can provide protection even if antibody levels wane [41]. mRNA vaccines have been shown to produce strong antibody responses, but these antibodies may wane over time, necessitating booster doses to maintain high levels of protection, especially against emerging variants [42]. Viral vector vaccines may produce a broader immune response due to their ability to activate both humoral and cellular immunity [33]. However, their effectiveness can also diminish over time, particularly against newer variants, prompting recommendations for booster doses [32]. Booster doses play a crucial role in enhancing immunity [43]. Boosters increase the quantity of spike protein-specific antibodies and re-energize memory B and T cells, thereby prolonging protection against severe disease and reinfection [43].

In summary, while both natural and vaccine-induced immunity provide protection against SARS-CoV-2, they differ in their mechanisms, durability, and effectiveness. Vaccine-induced immunity, particularly when bolstered by booster doses, offers a more controlled and predictable response, whereas natural immunity varies depending on individual factors.

3. Comparative Analysis: Vaccine-induced Versus Natural Immunity in Post-COVID Patients

3.1. Humoral immunity

After natural infection, individuals typically develop antibodies against multiple components of the SARS-CoV-2 virus, including the spike (S) protein and nucleocapsid (N) protein [44]. The levels of these antibodies, particularly neutralizing antibodies, can vary widely depending on the severity of the infection [45]. Severe cases tend to result in higher antibody titers, whereas mild or asymptomatic cases may lead to lower and less durable responses [46].

In contrast, vaccinated individuals primarily produce antibodies against the spike protein, which is the target of most COVID-19 vaccines [47]. Studies have shown that vaccine-induced antibodies generally have a strong neutralizing capacity against the virus, especially in the early months following vaccination

[48]. However, these antibody levels also wane over time, similar to natural infection, though booster doses can restore high levels of protection [49].

While both natural infection and vaccination generate neutralizing antibodies, vaccine-induced antibodies are often more targeted toward the spike protein and have been shown to be effective against a range of variants, particularly after booster doses [50]. Natural immunity provides broader protection against different viral components, but its neutralization capacity can be more variable [10]. Overview of immune responses to SARS-CoV-2, detailing roles and differences between natural and vaccine-induced immunity are summarized in Table **1**.

Table 1: Overview of immune responses to SARS-CoV-2.

Immune Component	Role in Response	Natural Immunity	Vaccine-induced Immunity
Innate Immunity	Initial defense against pathogen.	Rapid but non-specific response; includes barriers and phagocytes.	Enhanced by vaccines; primed for quicker response.
Humoral Immunity	Antibody production to neutralize pathogens.	Antibodies produced post-infection; variable duration.	Antibodies produced by vaccination; can be boosted.
Cellular Immunity	T-cell response to infected cells.	T-cells respond to infected cells; memory cells form.	T-cells generated and activated by vaccines; enhanced with boosters.

3.2. Antibody waning over time

Antibody levels after natural infection begin to decline within a few months, although some level of protection may persist for a year or longer [51]. The rate of waning can be influenced by factors such as age, health status, and the severity of the initial infection [52]. Similar to natural infection, vaccine-induced antibody levels also decrease over time [7]. However, booster doses can significantly enhance antibody titers, particularly against new variants like Omicron [53]. The waning of vaccine-induced immunity has been well documented, necessitating ongoing booster campaigns to maintain high levels of protection [54].

3.3. Cellular immunity

3.3.1. T-cell responses

T-cell responses in naturally infected individuals can be robust, particularly in those who experienced severe disease [55]. These responses tend to be polyclonal, targeting multiple viral antigens, including the spike protein and other structural proteins like the nucleocapsid [56]. T-cell immunity has been shown to persist longer than antibody responses, providing a critical layer of defense even as antibody levels wane [57].

Vaccine-induced T-cell responses primarily focus on the spike protein, and while they may not be as broad as those from natural infection, they are highly effective at preventing severe disease [58]. Importantly, T-cell responses induced by vaccines have demonstrated cross-reactivity against multiple variants of concern, including those with significant mutations in the spike protein [59].

3.3.2. Persistence of memory T-cells

Memory T-cells generated after natural infection can persist for extended periods, potentially years, and contribute to protection against severe reinfection [60]. However, the effectiveness of these T-cells in preventing long COVID remains under investigation, as reinfections and subsequent immune responses can differ [61].

Memory T-cells induced by vaccination also show long-term persistence, especially after booster doses (58). These cells are crucial in controlling viral reactivation and preventing severe outcomes, even in the absence of high circulating antibody levels [62]. Studies suggest that vaccine-induced T-cell responses may offer better protection against severe disease compared to natural immunity alone, particularly with newer variants [63].

3.4. Long-term immunity and protection

3.4.1. Differences in long-term immunity

Long-term immunity after natural infection can be durable, particularly in those who experienced more severe illness [64]. However, the protective effect against reinfection and the development of long COVID varies widely, with some individuals experiencing recurrent symptoms or reinfections [65].

Vaccinated individuals generally benefit from more consistent long-term immunity, especially when booster doses are administered [49]. Booster shots enhance both humoral and cellular immunity, reducing the risk of severe disease and long COVID [66].

3.4.2. Protection against long COVID

While both natural and vaccine-induced immunity provide protection against severe disease, the impact on long COVID remains a critical area of study [10]. Vaccination has been associated with a reduced risk of developing long COVID symptoms, especially when administered before infection [67]. Individuals with hybrid immunity (i.e., those who have been both infected and vaccinated) appear to have the best protection against long COVID, benefiting from the strengths of both immune responses [23]. Therefore,

while both natural infection and vaccination offer protective immunity against SARS-CoV-2, vaccine-induced immunity—particularly when reinforced by booster doses—tends to provide more consistent and durable protection, especially against newer variants and long COVID.

4. Clinical Implications of Immune Response Differences

4.1. Symptom profiles

The immune response to SARS-CoV-2, whether from natural infection or vaccination, significantly impacts the clinical course of post-COVID syndrome (long COVID) [68]. Studies have demonstrated that individuals with natural immunity often show a more robust and rapid antibody response when re-exposed to the virus compared to those who are vaccine-naïve [10]. However, booster vaccinations tend to level the playing field, equalizing antibody levels across individuals regardless of prior infection history [69].

These immune differences influence symptom severity and duration in long COVID [70]. For instance, vaccine-induced immunity tends to reduce the risk of severe outcomes but may not fully prevent long COVID in all cases, especially as new variants emerge [71]. Conversely, those who develop immunity through infection may experience stronger but more unpredictable long-term immune responses [72].

4.2. Treatment and management

Understanding the immune differences between naturally acquired and vaccine-induced immunity offers critical insights into personalized treatment strategies for post-COVID syndrome [73]. Targeted therapies can be developed based on the patient's immune history, whether from natural infection, vaccination, or both [74]. For instance, patients with post-vaccine immune complications may benefit from specific immunomodulating treatments [75].

Moreover, vaccination plays a pivotal role in managing long COVID by reducing the incidence of severe disease and offering protection even in breakthrough cases [76]. As research progresses, future vaccine development may focus on addressing the unique challenges posed by post-COVID syndrome, potentially targeting specific immune pathways involved in long-term symptoms [77].

5. Challenges and Limitations

5.1. Variability in data

One of the major challenges in comparing natural and vaccine-induced immunity is the variability across individual health statuses, vaccine types, and timing of infection or vaccination. The immune response to COVID-19 can vary significantly depending on factors such as age, pre-existing conditions, and

comorbidities, making it difficult to draw universal conclusions. For instance, individuals with compromised immune systems may exhibit weaker responses to both natural infection and vaccination.

Furthermore, different COVID-19 vaccines—such as mRNA-based vaccines (e.g., Pfizer-BioNTech, Moderna) and viral vector vaccines (e.g., AstraZeneca)—elicit varied immune responses. The timing between doses, the emergence of new variants, and the individual's previous exposure to SARS-CoV-2 all contribute to this complexity. Consequently, these factors make it challenging to directly compare immune responses and to predict long COVID outcomes based solely on the type of immunity acquired.

5.2. Gaps in current research

Despite extensive research on COVID-19 immunity, significant gaps remain, particularly in the context of long COVID. One critical area where more research is needed is in long-term studies that explore the durability of both natural and vaccine-induced immunity against evolving SARS-CoV-2 variants. Current studies suggest that immunity, especially from vaccines, may wane over time, but data on long-term protection and its effects on long COVID are still limited.

Our comparative analysis underscores that natural and vaccine-induced immunity both provide protection against SARS-CoV-2, but with differences in consistency and predictability. Vaccine-induced immunity, particularly with booster doses, tends to offer more reliable and durable protection, especially against newer variants and long COVID. Continued research is essential for refining vaccine strategies and managing long COVID effectively.

6. Conclusion

In comparing vaccine-induced and natural immunity among post-COVID patients, several key differences emerge. Natural immunity typically results in a broader and more variable immune response, depending on the severity of the initial infection and the individual's health status. Vaccine-induced immunity, on the other hand, tends to produce a more consistent and predictable immune response, particularly when booster doses are administered. However, both types of immunity have been associated with the development of long COVID, albeit with differences in symptom profiles and severity.

Further research is essential to optimize vaccine strategies for preventing and managing long COVID. Long-term studies are needed to assess the durability of vaccine-induced immunity, particularly in the context of emerging variants and booster campaigns. Additionally, research should focus on identifying the most effective vaccine platforms and schedules for reducing the risk of post-COVID syndrome.

These findings have important implications for public health policy. There is a need for continued vaccination efforts, especially in populations at higher risk for long COVID. Moreover, health systems should prepare for the long-term management of post-COVID syndrome, including the development of targeted therapies based on individual immune response histories.

Funding

This research was funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. AP14870878). The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

[1] Pollard CA, Morran MP, Nestor-Kalinoski AL. The COVID-19 pandemic: A global health crisis. Physiol Genomics. 2020;52(11):549-557. https://doi.org/10.1152/physiolgenomics.00089.2020

[2] Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: Major findings, mechanisms and recommendations. Nat Rev Microbiol. 2023;21(3):133-146. https://doi.org/10.1038/s41579-022-00846-2

[3] Yong SJ. Long COVID or post-COVID-19 syndrome: Putative pathophysiology, risk factors, and treatments. Infect Dis (Lond). 2021;53(10):737-754. https://doi.org/10.1080/23744235.2021.1924397

[4] Sapir T, Averch Z, Lerman B, Bodzin A, Fishman Y, Maitra R. COVID-19 and the immune response: A multi-phasic approach to the treatment of COVID-19. Int J Mol Sci. 2022;23(15). https://doi.org/10.3390/ijms23158606

[5] Diamond MS, Kanneganti TD. Innate immunity: The first line of defense against SARS-CoV-2. Nat Immunol. 2022;23(2):165-76. https://doi.org/10.1038/s41590-021-01091-0

[6] Yaugel-Novoa M, Bourlet T, Paul S. Role of the humoral immune response during COVID-19: guilty or not guilty? Mucosal Immunol. 2022;15(6):1170-1180. https://doi.org/10.1038/s41385-022-00569-w

[7] Pooley N, Abdool Karim SS, Combadiere B, Ooi EE, Harris RC, El Guerche Seblain C, et al. Durability of vaccine-induced and natural immunity against COVID-19: A narrative review. Infect Dis Ther. 2023;12(2):367-87. https://doi.org/10.1007/s40121-022-00753-2

[8] Mengist HM, Kombe Kombe AJ, Mekonnen D, Abebaw A, Getachew M, Jin T. Mutations of SARS-CoV-2 spike protein: Implications on immune evasion and vaccine-induced immunity. Semin Immunol. 2021;55:101533. https://doi.org/10.1016/j.smim.2021.101533

[9] Krause PR, Fleming TR, Peto R, Longini IM, Figueroa JP, Sterne JAC, et al. Considerations in boosting COVID-19 vaccine immune responses. Lancet. 2021;398(10308):1377-80. https://doi.org/10.1016/S0140-6736(21)02046-8

[10] Diani S, Leonardi E, Cavezzi A, Ferrari S, Iacono O, Limoli A, et al. SARS-CoV-2-the role of natural immunity: A Narrative Review. J Clin Med. 2022;11(21). https://doi.org/10.3390/jcm11216272

[11] Silva MJA, Ribeiro LR, Lima KVB, Lima L. Adaptive immunity to SARS-CoV-2 infection: A systematic review. Front Immunol. 2022;13:1001198. https://doi.org/10.3389/fimmu.2022.1001198

[12] Marjenberg Z, Leng S, Tascini C, Garg M, Misso K, El Guerche Seblain C, et al. Risk of long COVID main symptoms after SARS-CoV-2 infection: a systematic review and meta-analysis. Sci Rep. 2023;13(1):15332. https://doi.org/10.1038/s41598-023-42321-9

[13] Luo W, Yin Q. B cell response to vaccination. Immunological Investigations. 2021;50(7):780-801.

[14] Moss P. The T cell immune response against SARS-CoV-2. Nature immunology. 2022;23(2):186-93.

[15] Torresi J, Edeling MA, Nolan T, Godfrey DI. A complementary union of SARS-CoV2 natural and vaccine induced immune responses. Frontiers in Immunology. 2022;13:914167.

[16] Saad-Roy CM, Morris SE, Metcalf CJE, Mina MJ, Baker RE, Farrar J, et al. Epidemiological and evolutionary considerations of SARS-CoV-2 vaccine dosing regimes. Science. 2021;372(6540):363-370.

[17] Hosseini A, Hashemi V, Shomali N, Asghari F, Gharibi T, Akbari M, et al. Innate and adaptive immune responses against coronavirus. Biomed Pharmacother. 2020;132:110859. https://doi.org/10.1016/j.biopha.2020.110859

[18] Clark NM, Janaka SK, Hartman W, Stramer S, Goodhue E, Weiss J, et al. Anti-SARS-CoV-2 IgG and IgA antibodies in COVID-19 convalescent plasma do not enhance viral infection. PLoS One. 2022;17(3):e0257930. https://doi.org/10.1371/journal.pone.0257930

[19] Tyagi R, Basu S, Dhar A, Gupta S, Gupta SL, Jaiswal RK. Role of immunoglobulin A in COVID-19 and influenza infections. Vaccines (Basel). 2023;11(11). https://doi.org/10.3390/vaccines11111647

[20] Tarique M, Suhail M, Naz H, Muhammad N, Tabrez S, Zughaibi TA, et al. Where do T cell subsets stand in SARS-CoV-2 infection: an update. Front Cell Infect Microbiol. 2022;12:964265. https://doi.org/10.3389/fcimb.2022.964265

[21] Kervevan J, Chakrabarti LA. Role of CD4+ T cells in the control of viral infections: Recent advances and open questions. Int J Mol Sci. 2021;22(2). https://doi.org/10.3390/ijms22020523

[22] Akkaya M, Kwak K, Pierce SK. B cell memory: Building two walls of protection against pathogens. Nat Rev Immunol. 2020;20(4):229-38. https://doi.org/10.1038/s41577-019-0244-2

[23] Sette A, Crotty S. Immunological memory to SARS-CoV-2 infection and COVID-19 vaccines. Immunol Rev. 2022;310(1):27-46. https://doi.org/10.1111/imr.13089

[24] Kalk A, Sturmberg J, Van Damme W, Brown GW, Ridde V, Zizi M, et al. Surfing Corona waves - instead of breaking them: Rethinking the role of natural immunity in COVID-19 policy. F1000Res. 2022;11:337. https://doi.org/10.12688/f1000research.110593.2

[25] Oyesola OO, Souza COS, Loke P. The influence of genetic and environmental factors and their interactions on immune response to helminth infections. Front Immunol. 2022;13:869163. https://doi.org/10.3389/fimmu.2022.869163

[26] Garrido C, Hurst JH, Lorang CG, Aquino JN, Rodriguez J, Pfeiffer TS, et al. Asymptomatic or mild symptomatic SARS-CoV-2 infection elicits durable neutralizing antibody responses in children and adolescents. JCI Insight. 2021;6(17). https://doi.org/10.1172/jci.insight.150909

[27] Akhtar M, Basher SR, Nizam NN, Kamruzzaman M, Khaton F, Banna HA, et al. Longevity of memory B cells and antibodies, as well as the polarization of effector memory helper T cells, are associated with disease severity in patients with COVID-19 in Bangladesh. Front Immunol. 2022;13:1052374. https://doi.org/10.3389/fimmu.2022.1052374

[28] Bayani F, Hashkavaei NS, Arjmand S, Rezaei S, Uskokovic V, Alijanianzadeh M, et al. An overview of the vaccine platforms to combat COVID-19 with a focus on the subunit vaccines. Prog Biophys Mol Biol. 2023;178:32-49. https://doi.org/10.1016/j.pbiomolbio.2023.02.004

[29] Nagy A, Alhatlani B. An overview of current COVID-19 vaccine platforms. Comput Struct Biotechnol J. 2021;19:2508-2517. https://doi.org/10.1016/j.csbj.2021.04.061

[30] Chavda VP, Jogi G, Dave S, Patel BM, Vineela Nalla L, Koradia K. mRNA-based vaccine for COVID-19: They are new but not unknown! Vaccines (Basel). 2023;11(3). https://doi.org/10.3390/vaccines11030507

[31] Ankrah PK, Ilesanmi A, Akinyemi AO, Lasehinde V, Adurosakin OE, Ajayi OH. Clinical analysis and applications of mRNA vaccines in infectious diseases and cancer treatment. Cureus. 2023;15(10):e46354. https://doi.org/10.7759/cureus.46354

[32] Deng S, Liang H, Chen P, Li Y, Li Z, Fan S, et al. Viral vector vaccine development and application during the COVID-19 pandemic. Microorganisms. 2022;10(7). https://doi.org/10.3390/microorganisms10071450

[33] McCann N, O'Connor D, Lambe T, Pollard AJ. Viral vector vaccines. Curr Opin Immunol. 2022;77:102210. https://doi.org/10.1016/j.coi.2022.102210

[34] Cid R, Bolivar J. Platforms for production of protein-based vaccines: From classical to next-generation Strategies. Biomolecules. 2021;11(8). https://doi.org/10.3390/biom11081072

[35] Diaz-Dinamarca DA, Salazar ML, Castillo BN, Manubens A, Vasquez AE, Salazar F, et al. Protein-based adjuvants for vaccines as immunomodulators of the innate and adaptive immune response: Current knowledge, challenges, and future opportunities. Pharmaceutics. 2022;14(8). https://doi.org/10.3390/pharmaceutics14081671

[36] Martinez-Flores D, Zepeda-Cervantes J, Cruz-Resendiz A, Aguirre-Sampieri S, Sampieri A, Vaca L. SARS-CoV-2 vaccines based on the spike glycoprotein and implications of new viral variants. Front Immunol. 2021;12:701501. https://doi.org/10.3389/fimmu.2021.701501

[37] Xiaojie S, Yu L, Lei Y, Guang Y, Min Q. Neutralizing antibodies targeting SARS-CoV-2 spike protein. Stem Cell Res. 2020;50:102125. https://doi.org/10.1016/j.scr.2020.102125

[38] Hermens JM, Kesmir C. Role of T cells in severe COVID-19 disease, protection, and long term immunity. Immunogenetics. 2023;75(3):295-307. https://doi.org/10.1007/s00251-023-01294-9

[39] Moss P. The T cell immune response against SARS-CoV-2. Nat Immunol. 2022;23(2):186-93. https://doi.org/10.1038/s41590-021-01122-w

[40] Ahluwalia P, Vaibhav K, Ahluwalia M, Mondal AK, Sahajpal N, Rojiani AM, et al. Infection and immune memory: Variables in robust protection by vaccines against SARS-CoV-2. Front Immunol. 2021;12:660019. https://doi.org/10.3389/fimmu.2021.660019

[41] Bugya Z, Prechl J, Szenasi T, Nemes E, Bacsi A, Koncz G. Multiple levels of immunological memory and their association with vaccination. Vaccines (Basel). 2021;9(2). https://doi.org/10.3390/vaccines9020174

[42] Zhang G, Tang T, Chen Y, Huang X, Liang T. mRNA vaccines in disease prevention and treatment. Signal Transduct Target Ther. 2023;8(1):365. https://doi.org/10.1038/s41392-023-01579-1

[43] Silva-Cayetano A, Foster WS, Innocentin S, Belij-Rammerstorfer S, Spencer AJ, Burton OT, et al. A booster dose enhances immunogenicity of the COVID-19 vaccine candidate ChAdOx1 nCoV-19 in aged mice. Med. 2021;2(3):243-62 e8. https://doi.org/10.1016/j.medj.2020.12.006

[44] Wu W, Cheng Y, Zhou H, Sun C, Zhang S. The SARS-CoV-2 nucleocapsid protein: Its role in the viral life cycle, structure and functions, and use as a potential target in the development of vaccines and diagnostics. Virol J. 2023;20(1):6. https://doi.org/10.1186/s12985-023-01968-6

[45] Yan LN, Liu PP, Li XG, Zhou SJ, Li H, Wang ZY, et al. Neutralizing antibodies and cellular immune responses against SARS-CoV-2 sustained one and a half years after natural infection. Front Microbiol. 2021;12:803031. https://doi.org/10.3389/fmicb.2021.803031

[46] Pradenas E, Ubals M, Urrea V, Suner C, Trinite B, Riveira-Munoz E, et al. Virological and clinical determinants of the magnitude of humoral responses to SARS-CoV-2 in mild-symptomatic individuals. Front Immunol. 2022;13:860215. https://doi.org/10.3389/fimmu.2022.860215

[47] Dai L, Gao GF. Viral targets for vaccines against COVID-19. Nat Rev Immunol. 2021;21(2):73-82. https://doi.org/10.1038/s41577-020-00480-0

[48] Hvidt AK, Baerends EAM, Sogaard OS, Staerke NB, Raben D, Reekie J, et al. Comparison of vaccine-induced antibody neutralization against SARS-CoV-2 variants of concern following primary and booster doses of COVID-19 vaccines. Front Med (Lausanne). 2022;9:994160. https://doi.org/10.3389/fmed.2022.994160

[49] Dadras O, SeyedAlinaghi S, Karimi A, Shojaei A, Amiri A, Mahdiabadi S, et al. COVID-19 vaccines' protection over time and the need for booster doses: A systematic review. Arch Acad Emerg Med. 2022;10(1):e53. https://doi.org/10.22037/aaem.v10i1.1582

[50] Bonura F, Genovese D, Amodio E, Calamusa G, Sanfilippo GL, Cacioppo F, et al. Neutralizing antibodies response against SARS-CoV-2 variants of concern elicited by prior infection or mRNA BNT162b2 vaccination. Vaccines (Basel). 2022;10(6). https://doi.org/10.3390/vaccines10060874

[51] Swartz MD, DeSantis SM, Yaseen A, Brito FA, Valerio-Shewmaker MA, Messiah SE, et al. Antibody duration after infection from SARS-CoV-2 in the Texas coronavirus antibody response survey. J Infect Dis. 2023;227(2):193-201. https://doi.org/10.1093/infdis/jiac167

[52] Vattiatio G, Lustig A, Maclaren OJ, Plank MJ. Modelling the dynamics of infection, waning of immunity and re-infection with the Omicron variant of SARS-CoV-2 in Aotearoa New Zealand. Epidemics. 2022;41:100657. https://doi.org/10.1016/j.epidem.2022.100657

[53] Chavda VP, Apostolopoulos V. Is booster dose strategy sufficient for Omicron Variant of SARS-CoV-2? Vaccines (Basel). 2022;10(3). https://doi.org/10.3390/vaccines10030367

[54] LaJoie Z, Usherwood T, Sampath S, Srivastava V. A COVID-19 model incorporating variants, vaccination, waning immunity, and population behavior. Sci Rep. 2022;12(1):20377. https://doi.org/10.1038/s41598-022-24967-z

[55] Sekine T, Perez-Potti A, Rivera-Ballesteros O, Stralin K, Gorin JB, Olsson A, et al. Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. Cell. 2020;183(1):158-68 e14. https://doi.org/10.1016/j.cell.2020.08.017

[56] Mittal A, Khattri A, Verma V. Structural and antigenic variations in the spike protein of emerging SARS-CoV-2 variants. PLoS Pathog. 2022;18(2):e1010260. https://doi.org/10.1371/journal.ppat.1010260

[57] Pitiriga VC, Papamentzelopoulou M, Konstantinakou KE, Vasileiou IV, Sakellariou KS, Spyrou NI, et al. Persistence of T-cell immunity responses against SARS-CoV-2 for over 12 months post COVID-19 infection in unvaccinated individuals with no detectable IgG antibodies. Vaccines (Basel). 2023;11(12). https://doi.org/10.3390/vaccines11121764

[58] Wang L, Nicols A, Turtle L, Richter A, Duncan CJ, Dunachie SJ, et al. T cell immune memory after covid-19 and vaccination. BMJ Med. 2023;2(1):e000468. https://doi.org/10.1136/bmjmed-2022-000468

[59] Sohail MS, Ahmed SF, Quadeer AA, McKay MR. Cross-reactivity assessment of vaccine-derived SARS-CoV-2 T cell responses against BA.2.86 and JN.1. Viruses. 2024;16(3). https://doi.org/10.3390/v16030473

[60] Jarjour NN, Masopust D, Jameson SC. T Cell Memory: Understanding COVID-19. Immunity. 2021;54(1):14-8. https://doi.org/10.1016/j.immuni.2020.12.009

[61] Yang G, Cao J, Qin J, Mei X, Deng S, Xia Y, et al. Initial COVID-19 severity influenced by SARS-CoV-2-specific T cells imprints T-cell memory and inversely affects reinfection. Signal Transduct Target Ther. 2024;9(1):141. https://doi.org/10.1038/s41392-024-01867-4

[62] Yunis J, Short KR, Yu D. Severe respiratory viral infections: T-cell functions diverging from immunity to inflammation. Trends Microbiol. 2023;31(6):644-56. https://doi.org/10.1016/j.tim.2022.12.008

[63] Zhao T, Huang X, Shu Y. Comparing the immune response and protective effect of COVID-19 vaccine under different vaccination strategies. Hum Vaccin Immunother. 2023;19(3):2273155. https://doi.org/10.1080/21645515.2023.2273155

[64] Townsend JP, Hassler HB, Sah P, Galvani AP, Dornburg A. The durability of natural infection and vaccine-induced immunity against future infection by SARS-CoV-2. Proc Natl Acad Sci U S A. 2022;119(31):e2204336119. https://doi.org/10.1073/pnas.2204336119

[65] Bosworth ML, Shenhuy B, Walker AS, Nafilyan V, Alwan NA, O'Hara ME, et al. Risk of New-Onset Long COVID Following Reinfection With Severe Acute Respiratory Syndrome Coronavirus 2: A Community-Based Cohort Study. Open Forum Infect Dis. 2023;10(11):ofad493. https://doi.org/10.1093/ofid/ofad493

[66] Korosec CS, Dick DW, Moyles IR, Watmough J. SARS-CoV-2 booster vaccine dose significantly extends humoral immune response half-life beyond the primary series. Scientific Reports. 2024;14(1):8426.

[67] Fatima S, Ismail M, Ejaz T, Shah Z, Fatima S, Shahzaib M, et al. Association between long COVID and vaccination: A 12-month follow-up study in a low- to middle-income country. PLoS One. 2023;18(11):e0294780. https://doi.org/10.1371/journal.pone.0294780

[68] Tofarides AG, Christaki E, Milionis H, Nikolopoulos GK. Effect of Vaccination against SARS-CoV-2 on Long COVID-19: A Narrative Review. Life (Basel). 2022;12(12). https://doi.org/10.3390/life12122057

[69] Ali H, Alahmad B, Al-Shammari AA, Alterki A, Hammad M, Cherian P, et al. Previous COVID-19 Infection and Antibody Levels After Vaccination. Front Public Health. 2021;9:778243. https://doi.org/10.3389/fpubh.2021.778243

[70] Bohmwald K, Diethelm-Varela B, Rodriguez-Guilarte L, Rivera T, Riedel CA, Gonzalez PA, et al. Pathophysiological, immunological, and inflammatory features of long COVID. Front Immunol. 2024;15:1341600. https://doi.org/10.3389/fimmu.2024.1341600

[71] Boufidou F, Medic S, Lampropoulou V, Siafakas N, Tsakris A, Anastassopoulou C. SARS-CoV-2 reinfections and long COVID in the post-omicron phase of the pandemic. Int J Mol Sci. 2023;24(16). https://doi.org/10.3390/ijms241612962

[72] Netea MG, Dominguez-Andres J, Barreiro LB, Chavakis T, Divangahi M, Fuchs E, et al. Defining trained immunity and its role in health and disease. Nat Rev Immunol. 2020;20(6):375-88. https://doi.org/10.1038/s41577-020-0285-6

[73] Franchi M, Pellegrini G, Cereda D, Bortolan F, Leoni O, Pavesi G, et al. Natural and vaccine-induced immunity are equivalent for the protection against SARS-CoV-2 infection. J Infect Public Health. 2023;16(8):1137-41. https://doi.org/10.1016/j.jiph.2023.05.018

[74] Fendler A, de Vries EGE, GeurtsvanKessel CH, Haanen JB, Wormann B, Turajlic S, et al. COVID-19 vaccines in patients with cancer: immunogenicity, efficacy and safety. Nat Rev Clin Oncol. 2022;19(6):385-401. https://doi.org/10.1038/s41571-022-00610-8

[75] Olivieri B, Betterle C, Zanoni G. Vaccinations and autoimmune diseases. Vaccines (Basel). 2021;9(8). https://doi.org/10.3390/vaccines9080815

[76] Asadi-Pooya AA, Nemati M, Shahisavandi M, Nemati H, Karimi A, Jafari A, et al. How does COVID-19 vaccination affect long-COVID symptoms? PLoS One. 2024;19(2):e0296680. https://doi.org/10.1371/journal.pone.0296680

[77] Mohan A, Iyer VA, Kumar D, Batra L, Dahiya P. Navigating the post-COVID-19 immunological era: Understanding long COVID-19 and immune response. Life (Basel). 2023;13(11). https://doi.org/10.3390/life13112121