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The Impact of Re-Infection With COVID-19 on Human Immunity and Coping Strategies in The Post-Pandemic Era

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Abstract. The COVID-19 pandemic, caused by SARS-CoV-2, has led to over 6.9 million deaths as of August 2024 as a significant global health threat. While advancement of vaccines and drugs targeting SARS-CoV-2 virus has reduced severe illness, reinfection remains a significant concern. This paper explores the impact of COVID-19 reinfection on human immunity and examines possible coping strategies, particularly the advancements in plant-derived adjuvants to enhance vaccine efficacy. The virus's ability to mutate, evade immune responses, and affect immune memory highlights the importance and potential effectiveness of treatments that prolong immunity response. Plant-derived adjuvants Advax and Matrix-M have been shown to improve long term immune responses by stimulating long-lasting antibodies and cytotoxic T-cell activation. Clinical trials have demonstrated efficacy and safety in preventing symptomatic and severe COVID-19, along plant-based adjuvants reducing reinfection risks. Future research could further focus on develop precising adjuvants' formulations, exploring more plant-based compounds that could be apply in vaccine development, and conducting long-term studies to evaluate long-term immune durability and safety of the vaccines.

Keywords: COVID-19 reinfection; Reinfection prevention; SARS-CoV-2; Vaccine efficacy; Plant-derived adjuvants.

1. Introduction

Coronavirus disease appeared in December 2019. It was caused by the respiratory syndrome coronavirus-2, which is becoming an epidemic and is viewed as a worldwide health threat. As the COVID-19 pandemic continues to spread globally, it has resulted in approximately 6.9 million confirmed cases and 6.9 million deaths as of August 2024 [1]. SARS-CoV-2 enters human cells using its Spike (S) protein, which binds to the ACE2 receptor with similar affinity as the Spike protein of SARS-CoV, facilitating efficient human-to-human transmission. A distinguishing feature of SARS-CoV-2 is a furin cleavage site located between the S1 and S2 subunits of the Spike protein, which is processed during viral maturation and differentiates it from SARS-CoV and other SARS-related coronaviruses, leading covid to become a disease that spread through respiratory droplets. Consequences symptoms post-infection have shown in different severity ranging from shortness of breath to respiratory distress, and multi-organ failure. Severe complication cases include syndromes such as pneumonia and acute respiratory distress syndrome（ARDS）[2].

As the Coronavirus disease continues to develop, the population's overall immunity to coronavirus improves significantly through the development of vaccines, monoclonal antibodies, and public health measures. In recent years, the public has decreased their awareness of the severity of covid-19, it is now regarded as a health concern instead of a health crisis. However, COVID has shown in certain populations a pattern of continuous persistent infection. More than 10% of people previously infected with SARS-CoV-2 experienced reinfection over a cycle of about 18 months [3]. According to a systematic review, this review discovered while the strategies in treating the infections are alike, the reinfections are generally more severe, as shown by increased cases requiring intensive care units among reinfection patients compared to first infection patients. Reasons that prove related to the reinfection of covid involve the emergence of variants of SARS-CoV-2 including CoVs Alpha variant, Beta Variant, Gamma Variant, Delta Variant, and Omicron Variant [4]. Other causes involving

waning, incomplete or suboptimal immunity which results of Partial immunity can result from variations in immune responses or insufficient antigen exposure during the first infection [5]. Moreover, in some cases labeled as reinfections may be persistent infections with different viral strains or low-level persistent infection from the initial exposure [6]. Specific studies about the reinfection of COVID are still limited and undistinguishable compared to persistent infection.

The purpose of the essay is to elaborate on the mechanism and potential reasons for the re-infection of COVID-19, an overview from the perspectives of immunology change, and the variants of the virus. Focusing on target molecules that could provide therapeutic drug advancement in preventing the possibility of re-infection. Providing new insights and advancement in enhancing public health strategies, optimizing treatment options, and increasing long-term immunity. This research aims to contribute knowledge to decode the causes of reinfections of COVID-19, helping to shape effective prevention and treatment strategies of re-infection in the post-pandemic world.

2. COVID-19 Infection Mechanism

2.1. Structure and Pathogenesis of SARS-CoV-2

2.1.1. Viral entry and interaction with host cells

Coronaviruses belong to the family Coronaviridae under Nidovirales, which is divided into four genera: α-, β-, γ-, and δ-. Coronaviruses have the largest RNA viral genome, ranging in length from 26 to 32 kb. As a highly infectious and resistant enveloped virus, its widespread benefits from its unique cellular structure. The membrane of coronavirus is composed of four structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. For the initial phase of infection, the Spike protein contains two subunits, S1 and S2, with S1 confirming the receptor and S2 implementing the membrane fusion. This causes changes in the Spike protein, allowing the viral envelope to fuse with the host cell membrane, aided by TMPRSS2 (transmembrane protease, serine 2), a protease that breaks down proteins. This enzyme allows the Spike protein to penetrate the cell and bind with the angiotensin-converting enzyme 2 (ACE2) receptor on host cells, creating a receptor-binding domain (RBD). When SARS-CoV enters the host cells, the Nucleocapsid Protein binds with the viral RNA genome and protects the RNA from destructions by enzymes of the host cell through the production of nucleocapsid. The Membrane protein functions within the host cell to assemble the virus and initiate the process of budding, enabling the newly formed viral particles to be released from the host cell to infect other cells and spread among the host. The Envelope protein functions as a viroporin, regulating the ion balance during the process by acting as an ion channel, which maintains the operation of the SARS-CoV budding and release process.

Moreover, the Spike protein is constantly mutating. As the outermost layer, the host immune system cannot detect and identify it due to the mutations, which allow it to persist for long periods. The replication process of SARS-CoV-2, guided by viral RNA, first synthesizes viral proteins in the ribosomes of the host using RNA polymerase (RdRP) to replicate the viral RNA genome. After virions are formed, they are released from the host cell to neighboring cells and spread through the host via the bloodstream.

The initial phase of SARS-CoV-2 infection is caused by the binding process of the ACE2 receptor, an enzyme involved in regulating blood pressure and relaxing blood vessels. Once the virus binds to ACE2, it reduces the expression of this receptor on the cell surface. This downregulation of ACE2 causes the normal functions of ACE2 to become harder to operate. Since ACE2 is mainly located in the lungs, intestines, blood vessels, and kidneys, these organs express different symptoms when the Spike protein of SARS-CoV-2 binds with the ACE2 receptor. Because ACE2 is mostly concentrated in the alveoli, air sacs in the lungs that function as the location where oxygen and carbon dioxide are exchanged, significant respiratory symptoms and lung inflammation occur. Other observations of inflammatory responses distributed in different organs are also contributed to by the binding of ACE2 receptor sites [7].

2.1.2. Variants of SARS-CoV-2

Three main genomic variants have been identified, type A, type B, and type C variants. The first discovered variant type A, which is caused by the mutation of D614G in the spike protein enables the SARS-CoV-2 to improve the stability and adhesion with binding with the ACE2 receptor. Type B variants, like type A variant which also mutate in the spike protein, lead to increased binding affinity with the ACE2 receptor and improve the immune evasion mechanism by altering the antigenic properties of the virus. Type C variants can influence how efficiently the virus binds to host cells and enters them. The changes in receptor interaction or spike protein conformational changes affect viral infectivity and transmission rates.

The Spike protein plays an important role in the mutation of the virus and the production of different variants. The D614G mutation stabilizes the prefusion conformation of the Spike protein, which needs to be in the correct conformation to bind with the ACE2 receptor. This mutation also increases the binding affinity to ACE2 and this mutation of D614G enhances transmission. It has been shown that variants with the D614G mutation have become predominant in many regions, which suggests that this mutation enhances the infectiousness of the SARS-CoV-2 virus [8]. Mutations in the Spike protein can also aid in antibody evasion. The mutation of the N-terminal Domain (NTD), such as N148S, K150R, K150E, K150T, K150Q, and S151P, can lead to antibody evasion [9]. This function has been proven by observations of the distribution of mutations observed in viral populations exposed to recovered plasma, which were roughly evenly distributed between the RBD and NTD. Furthermore, in the evolution and mutation process of the Spike protein, deletions in the NTD have been observed. Deletions in the NTD, in Δ141–144 and Δ146, have been shown to alter the antigenicity of the Spike protein, which contributes to evasion from the host's immune responses [10]. Insertion mutations in the NTD, such as the residue insertion between Y248 and L249, have showcased the complete elimination of neutralization [11]. The structural plasticity of the NTD, as insertion and the introduction of additional glycosylation modes is one of the foundational mechanisms of immune escape. This characteristic causes the virus's ability to present different antigenic sites, which affect the efficacy of neutralizing antibodies and vaccine-induced immunity. Mutations in the receptor binding domain (RBD) of the Spike protein, especially at E484K, create new binding sites and change the structure of antigenic epitopes recognized by antibodies, thus decreasing the efficiency of neutralizing antibodies.

Immune imprinting, a phenomenon where the immune system's first exposure to a pathogen determines future responses to related re-infections of variants, is an important factor involved in the ineffective response to variants. The variants that experience significant structural changes and mutations influence the effectiveness of the immune system in identifying and responding to the virus, as its response mainly relies on the original strain of SARS-CoV-2.

2.2. Human Immune Response

T cells are the major immune cells that respond to SARS-CoV-2 infection identify and react to specific protein structures of the virus. Research conducted on patients' peripheral blood mononuclear cells (PBMCs) has shown that both CD4 and CD8 T cells can recognize the nucleocapsid protein (N) and non-structural proteins (NSP7 and NSP13) of SARS-CoV-2. CD4 T cells recognize the N protein sequence from 81 to 95, while CD8 T cells target the sequence from 321 to 340 [12]. After identifying the target protein sequence, the immune response is carried out by a series of interferon-gamma (IFNγ) secretions, a cytokine that activates macrophage cells, enabling them to digest SARS-CoV-2 viruses, which helps the viral clearance process. T cells activate B cells, enabling the B cells to contact antigens and their segments on the surface via MHC class II molecules. Memory T cells from the SARS-CoV infection years ago still exhibit the ability to recognize SARS-CoV-2 proteins, indicating the potential for long-lasting immunity and resistance to reinfection.

B cells are a type of major immune cells that produce antibodies to neutralize pathogens during reinfection, leading to antibody-mediated responses during succeeding exposures to the virus. The

neutralizing antibodies produced by B cells target the spike protein, which mainly concentrates on the RBD on the ACE2 receptor sites, blocking the virus from binding. The production of neutralizing antibodies begins with IgM antibodies in response to initial infection, followed by IgG antibodies, which provide long-term immunity.

3. Reinfection

3.1. Potential Reasons for Reinfection

3.1.1. Virus mutations and sars-cov-2 variants

The structure of the spike protein, which regulates the SARS-CoV-2 virus binding and entrance, is constantly changing due to mutations, making it more challenging for prior immune systems to identify and react. This increases the risk of reinfection by allowing the virus to escape detection by antibodies produced from prior infections.

3.1.2. Differences in immune memory

Age, underlying medical disorders, past immunity, genetic variations, and other factors all affect the length and strength of immune memory retain, and also the degree of response to the infection. Variations in immune memory quality may affect how well B cells and T cells respond to reinfection. If the initial immune response was suboptimal or the virus presented a limited range of antigens, the resulting memory may be less effective resulting in the potential that immunity levels may not be sufficient to prevent reinfection.

3.1.3. Waning immunity

Either acquired by vaccination or spontaneous infection, immunity to SARS-CoV-2 can wane over time. Research has shown that whereas vaccinations offer a strong defense against symptomatic infection and serious disease at first, this defense may weaken a few months after the first shot. This Antibody concentration decrease is a normal immune response mechanism phenomenon. Immunological research demonstrates that memory B cells and T cells can endure and offer long-term protection against serious illness, even when plasma-neutralizing antibody levels may decline.

3.2. Mechanism of Reinfection

In certain circumstances, the SARS-CoV-2 virus can be enclosed in exosomes through cellular transport pathways, and these exosomes can persist in the host body even after recovery. A positive PCR test could happen after a while if the exosomes carrying viral RNA are released. There are more cases where the SARS-CoV-2 virus causes the body to produce antibodies, particularly neutralizing antibodies. Research indicates that the levels of these neutralizing antibodies may progressively drop within a few months of infection, which means that even those who have once been infected could become susceptible to re-infection as antibody levels decline. In individuals, the virus might not leave the body completely and might instead stay in a "latent" state. Reinfection can occur when these leftover virus particles reactivate due to changes in the body's conditions, like a decrease in immunological function.

3.3. Changes in Immune Response

Several major changes in immune response have been observed in the process of reinfection. cytokine storm has been observed by a significant increase of cytokines and chemokines in the serum. Increased neutrophil to lymphocyte ratio (NLR) lead to lung and organ injury. Decrease in the number of T cells (CD4 cells), CD8 cells, B cells, natural killer cells (NK cells), monocytes, eosinophils and basophils have been observed. after 3-5 months of infection, the memory T cells, CD4+ and CD8+ T cells, decrease by approximately half [13]. This reduction in the number of memory T cells makes the immune system of a reinfected patient respond less quickly to the virus than to primary infection,

especially to the variants of viruses. The significant decrease in antibody levels of lgG and lgM, further lead to reduced immune protection

3.4. Symptoms of Reinfection

According to a study of summary symptoms of 54 reinfections of patients, symptomps below have been observed.

Table 1. Symptoms of 54 Cases Reinfection of SARS-CoV-2 virus patients [14]

Symptoms	Number of cases	Percentage of Patient
Headache	19	33.90%
Dyspnea	18	32.10%
Fatigue	17	30.40%
Muscle Pain	14	25%
Rhinitis	7	12.50%
Body Pain	6	10.70%
Loss Of Taste	6	10.70%
Swallowing Pain	6	10.70%
Fatigue	4	7.10%
Nasal Congestion	4	7.10%
Chills	3	5.40%
Dizziness	3	5.40%
Joint Pain	3	5.40%
Nausea	2	3.60%
Abdominal Pain	2	3.60%
Anorexia	1	1.80%
Back Pain	1	1.80%
Muscle Fatigue	1	1.80%
Insomnia	1	1.80%
Hypoxemia	1	1.80%
Gastrointestinal Symptoms	1	1.80%
Leg Pain	1	1.80%
Edema	1	1.80%
Sneezing	1	1.80%
Fatigue	1	1.80%
Chest Pain	1	1.80%
Shivering	1	1.80%
Respiratory Failure	1	1.80%

Table 1 shows the result of the study and the percentage of patients who appear for different symptoms. This study showcases the symptoms summary from the patients who were reinfected with the SARS-CoV-2 virus and showed increased severity, reduced immunity, prolonged immune dysregulation, and neural symptoms. Further, showcases the importance of addressing the reinfection of COVID-19 through advancements in vaccines..

4. Plant-Derived Adjuvants Vaccine Advancements

4.1. Mechanism of Plant-Derived Adjuvant Vaccines

As Waning immunity is the main cause of reinfection of SARS-CoV-2 virus, the essential improvements focus mainly on maintaining long-term immune protection effect. The effect of Plant-derived adjuvant vaccines which shown effects of improving immune system responses and

maintaining the level of immunity after the first infection. Plant-derived polysaccharides, saponins, and glycoprotein extracts have gained attention as potential adjuvants due to their ability to elicit a strong and lasting immune response. Advax, Matrix-M, and mistletoe lectins are all plant-derived substances that are applied in vaccines. Among these, Advax and Matrix-M adjuvants have been found to induce long-lasting antibodies, balanced Th1/Th2 cytokine profiles, and stimulation of cytotoxic T cells which showed high rate of immunogenicity in the prevention of reinfection.

4.1.1. Advax-CpG55.2 adjuvant mechanism

Advax-CpG55.2 is a combination of delta insulin-based adjuvant and the CpG55.2 TLR9 agonist adjuvant which mimics microbial DNA. Advax enhance the formation of antigen depots at the site of injection, causing sustained antigen release which prolongs the contact and effect of antigen and the immune system. By further recruiting the dendritic cells to the injection site stimulating and balancing via MHC molecule activating T cells, it enhances both cell-mediated and humoral immunity. The activation of Th1 further stimulates the cytotoxic T lymphocytes(CTLs), which are able to eliminate SARS-CoV-2 cells. As the formation of memory B and T cells are also improved in this process, the immunity is therefore prolonged. Moreover, CpG55.2 boosts innate immunity by mimicking the unmethylated CpG motifs found in bacterial and viral DNA and activating the TLR9 which leads to an enhancement in immune activation. By Improving durability of the immune response and the effective of innate immunity response, the risk of reinfection is therefore reduced.

4.1.2. Matrix-M adjuvant mechanism

Matrix-M which is derived from saponin nanoparticles from the soapbark tree. When the adjuvant is first injected, it initializes immune cells monocytes, macrophages, dendritic cells (DCs), and neutrophils to recruit it into the injection site, activating the early immune response which fosters the antigen uptake. Then, the antigen is uptake by the antigen-presenting cells and are being sent to draining lymph nodes via the lymphatic system, which enables further transport of antigens to the T cells. CD4+ and CD8+ T Cell Activation: Once the antigens are processed in the lymph nodes, APCs present the antigen to CD4+ helper T cells (via MHC class II molecules) and CD8+ cytotoxic T cells (via MHC class I molecules). This activates both types of T cells, leading to the differentiation of CD4+ T cells into different helper subsets (Th1, Th2, and Tfh) and the formation of memory T cells, further differentiate into the T follicular helper cells (Tfh), which are essential for supporting B cell maturation in the germinal centers of lymph nodes, Stimulating cytokine release through the activation of the NLRP3 inflammasome, creating an inflammatory environment that further promotes immune cell recruitment and activation. This enhancement of antigen delivery and immune cell recruitment produced by the matrix-M adjuvant leads to a decreased possibility of reinfection.

4.1.3. Matrix-M adjuvant mechanism

NVX-CoV2373 is a protein-based COVID-19 vaccine developed by Novavax, it is made from the spike protein of the SARS-CoV-2 virus and uses a plant-derived adjuvant Matrix-M.

This study is a phase 3 randomized, placebo-controlled study that investigated the safety, immunogenicity, and efficacy of the COVID-19 vaccine NVX-CoV2373. Conducted in the UK involved approximately 400 participants who received either two doses of NVX-CoV2373 or placebo. The study aimed to explore whether the matrix-M adjuvant in NVX-CoV2373 effectively prevents reinfection of SARS-CoV-2, even when co-administered with another vaccine [15, 16].

Key findings showed that while reactogenicity symptoms was higher in the co-administration group, there was no significant increase in serious adverse events or medically attended adverse events. The immune response to the influenza vaccine remained unchanged, though there was a slight reduction in SARS-CoV-2 antibody responses. However, the efficacy of NVX-CoV2373 in preventing symptomatic COVID-19 remained high at 87.5% in the co-administered group and 89.8% in the main study population. This indicates that the matrix-M adjuvant played a key role in maintaining high efficacy rates, even in cases of co-administration with the influenza vaccine, suggesting its effectiveness in preventing SARS-CoV-2 reinfection

4.2. Advancement in Future Research

4.2.1. Enhanced formulation and dose optimization

Research should investigate the optimal formulation and dosing strategies for plant-derived adjuvants for Advax and Matrix-M. Studying how to balance adjuvant concentrations to induce the most potent immune response while minimizing side effects. Applying fine-tuning the release kinetics of antigen depots formed by adjuvants like Advax enables further improved immune memory, which will further reduce the risk of reinfection.

4.2.2. Exploration of novel plant-derived compounds

There is immense potential in the plant-derived compounds that may have more effectiveness in prolonging the immunity level. screening a wider array of plant-based substances and conducting clinical trials which combine it into the vaccine to identify novel adjuvants that may improve reinfection immunity. By studying diverse plant species with known immunostimulatory properties, researchers could uncover more effective and sufficient sources of adjuvants that can be widely apply.

4.2.3. Longitudinal studies on immune durability

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5. Conclusion

The threat of COVID-19 reinfection is a significant challenge in the post-pandemic era, as challenges on virus mutations and waning immunity decrease the effect of long-term protection of the immune system. However, advancements in vaccines, plant-derived adjuvants, such as Advax and Matrix-M, these adjuvants stimulate both humoral and cellular immune responses, and have shown effects in improving the initial immune response and maintaining a high level of immune response after certain periods which have potent effects in preventing reinfection of SARS-CoV-2 virus. Clinical trials have shown their effectiveness towards reinfection through result of preventing not only initial infections but also extending immunity, and preventing evolving variants.

Future research should focus on optimizing these adjuvants' formulations, exploring more plant-based compounds, and conducting long-term studies to evaluate long-term immune durability and safety of the vaccines.

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