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MINI-REVIEW

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Limitations of neutralizing antibody titers in COVID-19 vaccine efficacy trials and a call for additional correlates of protection

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ABSTRACT

The coronavirus disease (COVID-19) pandemic accelerated development of various vaccine platforms. Among them, mRNA vaccines played a crucial role in controlling the pandemic due to their swift development and efficacy against virus variants. Despite the success of these vaccines, recent studies highlight challenges in evaluating vaccine efficacy, especially in individuals with prior COVID-19 infection. Weakened neutralizing antibody responses after additional doses are observed in these populations, raising concerns about using neutralizing antibody titers as the sole immune correlate of protection. While neutralizing antibodies remain the primary endpoint in immunogenicity trials, they may not fully capture the immune response in populations with widespread prior infection or vaccination. This review explores reduced neutralizing antibody responses in previously infected individuals, and their impact on vaccine efficacy evaluation. It also offers recommendations for improving efficacy assessment, stressing incorporation of additional immune markers such as cell-mediated immunity to enable more comprehensive understanding of vaccine-induced immunity.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to rapid development of various vaccine platforms, including adenovirus-vector vaccines, recombinant protein vaccines, and mRNA vaccines.[1] Among them, mRNA vaccines played a critical role in mitigating the pandemic due to their rapid development and early authorization for emergency use. The success of mRNA vaccines in combating the ongoing emergence of COVID-19 variants has reinforced their potential as a tool for addressing not only the current epidemic but also future pandemics. This potential has been recognized by initiatives like the Coalition for Epidemic Preparedness Innovations (CEPI) and its '100 Days Mission,' which aims to develop mRNA vaccines within 100 days of an emerging pandemic.[2] Additionally, many countries are actively working to secure domestic mRNA vaccine production capability.

The rapid approval of vaccines manufactured by Moderna, Pfizer-BioNTech, AstraZeneca, and Janssen in late 2020 and early 2021 was supported by large-scale efficacy trials that demonstrated substantial increases in neutralizing antibody titers, a key marker of immunogenicity;[3–6] however, as the pandemic progressed and vaccination campaigns intensified, disparities in vaccine distribution emerged, with some nations prioritizing domestic need over international supply, leading to what has been termed "vaccine nationalism." In this context, continued development of additional COVID-19 vaccines and the need for domestic vaccine production became increasingly important. Given the logistical and ethical challenges associated with conducting traditional efficacy trials, particularly in highly vaccinated populations, comparative immunogenicity trials have become the standard for evaluating new vaccines.[7] These trials often rely on neutralizing antibody responses as the primary endpoint to demonstrate non-inferiority to previously authorized vaccines.

Recent studies, however, report that individuals with a history of COVID-19 infection may not experience a significant increase in neutralizing antibody titer following booster vaccination, and in some cases, titers may even decline.[8–14] In light of the fact that a large portion of the global population has now either been infected with COVID-19 or completed their primary vaccination course,[15,16] these findings raise questions about the limitations of using neutralizing antibody titers as the sole immune correlate of protection.

This review aims to explore the phenomenon of reduced neutralizing antibody responses in individuals with prior COVID-19 infection or a history of vaccination. We will examine the mechanisms underlying this diminished response and discuss the implications for identifying appropriate immune correlates of protection for future development of COVID-19 vaccines.

COVID-19 vaccination and seroprevalence of SARS-CoV-2

In 2020, various COVID-19 vaccines based on different platforms were approved (Table 1).[1] Since many studies demonstrate that primary vaccination against SARS-CoV-2 reduces

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Table 1. Emergency use authorization for COVID-19 vaccines developed by global pharmaceutical companies.

Date of WHO EUL recommendation	Developer	Product name (codename)	Vaccine platform
2020.12.31	Pfizer/BioNTech	Comirnaty (BNT162b2)	mRNA vaccine
2021.03.12	Janssen	Janssen COVID-19 vaccines (Ad26.COV2.S)	Adenovirus vector-based vaccine
2021.04.15	AstraZeneca	Vaxzevria (AZD1222)	Adenovirus vector-based vaccine
2021.04.30	Moderna	Spikevax (mRNA-1273)	mRNA vaccine

Abbreviations: EUL, emergency use listing; WHO, World Health Organization.

symptomatic infection (i.e., severe disease, hospitalization, and/or emergency department visits attributed to COVID-19), large-scale vaccination campaigns were implemented throughout the world.[3–6,17] Among the different COVID-19 vaccines, mRNA vaccines became the main platform due to their efficacy and safety; however, because studies revealed waning immunity over time after the primary course, the necessity for booster vaccination became increasingly evident.[18,19] Research showing that booster vaccination restores waning immunity and reduces hospitalization and mortality led to the recommendation that a booster dose be administered after completion of the primary course.[20,21]

Emergence of virus variants that could evade the protective effect of vaccines developed against the ancestral strain meant that new vaccine formulations were developed.[20,22] For instance, during the wave caused by the BA.4/5 strain, administration of a bivalent vaccine containing antigens from both the ancestral strain and the BA.4/5 strain was recommended. Subsequently, as the circulating variants of concern changed, it was recommended to update the vaccines annually. At present, mRNA vaccines based on the XBB.1.5. and JN.1 variants are recommended.[23,24]

As mentioned earlier, widespread administration of COVID-19 vaccines has exposed the majority of the global population to SARS-CoV-2 antigens. By December 2023, 67% of the global population had completed a primary course of COVID-19 vaccinations, and 32% had received at least one booster dose.[16] Additionally, considering that over 700 million COVID-19 cases were reported by August 2024,[15] it is likely that a significant proportion of both vaccinated and unvaccinated individuals have been infected with SARS-CoV-2 at least once. Some researchers suggest that hybrid immunity, which results from a combination of both infection and vaccination, is stronger and more durable than immunity triggered by natural infection or vaccination alone.[25,26]

Indeed, a systematic review and meta-analysis of global seroprevalence revealed that by September 2021, the global seroprevalence of SARS-CoV-2 due to infection or vaccination was 59.2%, and that the overall seroprevalence increased steeply in 2021.[27] In the case of high-income countries in the Americas and Europe, the overall seroprevalence exceeded 95% by March 2022. In addition, a cross-sectional study conducted in South Korea in August 2022 reported overall seropositivity rates of 97.6% for anti-spike protein antibodies (anti-S) and 57.1% for anti-nucleocapsid antibodies (anti-N).[28] In that study, anti-N positivity was considered to be a sign of previous natural infection; comparing this with the cumulative rate of confirmed COVID-19 cases reported to the Korean Centers for Disease Control and Preservation led to an estimation that 33.9% of COVID-19 infections were unreported. Considering the widespread vaccination campaigns and multiple epidemic waves triggered by SARS-CoV-2 variants, it is likely that the majority of people have some level of immunity against SARS-CoV-2. Furthermore, given that more people have likely experienced natural infection than is reported, it can be inferred that many people have attained durable hybrid immunity.

SARS-CoV-2 neutralizing antibodies as an immune correlate of protection

The rapid development of COVID-19 vaccine components and the swift initiation of clinical trials effectively demonstrated their efficacy against the virus, leading to early adoption in the field; however, it became necessary to understand the immune responses triggered by vaccination, and to respond swiftly to emerging viral variants that could potentially evade the protective immune response induced by the vaccine. Identifying an immunologic marker that correlates with vaccine efficacy, known as a correlate of protection, is crucial because it enables immuno-bridging studies. These studies assess vaccine efficacy by comparing new data with immune response markers from existing data, thereby avoiding the need for costly clinical trials that require long-term follow-up.

Since the early stages of vaccine development, studies have been conducted to identify correlates of protection against SARS-CoV-2 infection; the result was adoption of neutralizing antibody levels as a highly predictive marker.[29–31] For example, one study found that a neutralization level corresponding to 20.2% of the mean convalescent level provided 50% protection against detectable COVID-19, while in cases of severe infection, a much lower level (only 3% of the mean convalescent level) was sufficient to ensure 50% protection.[31] The performance of neutralizing antibody levels as a correlate of protection has been validated across mRNA vaccines, protein subunit vaccines, and adenovirus-vector vaccines.[29–31]

Currently, neutralizing antibodies are used widely as a key parameter for evaluating vaccine efficacy. The World Health Organization (WHO), through the Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC), convenes periodically to issue statements. These statements determine the composition of vaccines based on global epidemiological data and the results of immuno-bridging studies based mainly on neutralizing antibodies;[7,32] however, the TAG-CO-VAC statement also acknowledges a fundamental limitation of the current system, i.e., reliance on neutralizing antibodies alone makes it difficult to assess other aspects of the immune response, such as cell-mediated immunity.

Attenuated neutralizing antibody responses in SARS-CoV-2-infected individuals

Since 2021, the majority of people have been exposed to the SARS-CoV-2 antigen either through natural COVID-19

infection or vaccination.[15,16] Recent investigations provide insight into the immune responses of individuals with prior COVID-19 infection or previous vaccination who then receive additional doses of a vaccine. The data suggest that prior antigen exposure may weaken the immune response, particularly induction of neutralizing antibodies.

Another study examined neutralizing antibody responses in elderly nursing home residents who received a booster dose of the Pfizer-BioNTech vaccine after completing their primary vaccination course with either the Pfizer or Moderna vaccines.[10] The data show that individuals with a history of COVID-19 infection had significantly higher baseline levels of neutralizing antibodies, as measured by a S-Fuse assay using live viruses, against both the Delta and Omicron variants than individuals without a history of COVID-19 infection. Contrary to the finding that individuals without a history of COVID-19 infection showed an expected increase in neutralizing antibodies following booster vaccination, individuals with a history of COVID-19 infection did not exhibit a marked increase in neutralizing antibodies. Many of them showed a stabilization or even a decline in levels, suggesting that prior infection might limit the additional benefit of booster vaccinations, at least in terms of viral neutralization. A study using a cytopathic effect (CPE)-based assay also highlighted differences in the neutralizing antibody responses to Pfizer's mRNA vaccine based on COVID-19 infection history.[11] For individuals without prior infection, neutralization activity reached its peak after the second dose. By contrast, those with a history of COVID-19 infection showed no significant difference in neutralization activity between the first and second doses.

Similar results were observed in another study that employed a pseudovirus neutralization assay to assess antibody responses in SARS-CoV-2-naïve and -recovered individuals after two doses of mRNA vaccine (Pfizer or Moderna).[13] That study evaluated antibody responses and memory B cell responses to the ancestral strain and the Beta variant. Unlike SARS-CoV-2-naïve individuals who required two doses of vaccine to achieve an optimal antibody response, recovered individuals showed a significant boost in anti-SARS-CoV-2 antibody (anti-spike IgG, anti-receptor binding domain IgG) concentration and the focus reduction neutralization titer of 50% ($FRNT_{50}$) after the first dose; however, antibody responses did not increase after the second dose in recovered individuals. This blunted antibody response suggests that a second dose of vaccine has little additional boosting effect on memory B cell responses. Another set of data from a phase 2 trial comparing bivalent and monovalent SARS-CoV-2 variant vaccines revealed that the geometric mean fold rise in neutralization titers among previously infected individuals was approximately one-third that in uninfected individuals.[9]

This phenomenon was also observed in studies involving vaccines based on other platforms. In a non-inferiority phase 3 clinical trial comparing the immunogenicity and safety of heterologous vaccination with Novavax's monovalent (targeting the prototype virus or BA.5 strain) or bivalent (targeting both the prototype and BA.5 strains) recombinant protein vaccines, similar findings were reported among individuals who had received at least three doses of an mRNA vaccine.[8] When comparing pseudovirus neutralization assay results based on a history of COVID-19 infection, those with a previous infection had a higher baseline geometric mean titer of neutralizing antibodies against the ancestral strain, and the BA.5 and XBB.1.5 variants, than those without prior infection. Additionally, the ratio of the neutralization titer increase following vaccination was lower in individuals with previous infection than in those without, indicating that prior infection blunted the increase in neutralization titers. This blunting effect was observed consistently across both the monovalent and bivalent vaccine groups.

Moreover, a study conducted on health care workers (HCWs) demonstrated that the neutralizing antibody response waned over time following mRNA vaccination.[12] The study also revealed that the pattern of neutralizing antibody responses differed depending on the history of prior SARS-CoV-2 infection. HCWs who tested negative for anti-N antibodies, suggesting no prior SARS-CoV-2 infection, exhibited maximal neutralizing antibody responses after the second dose of the mRNA vaccine. By contrast, HCWs with a history of SARS-CoV-2 infection (i.e., anti-N positive individuals) reached peak neutralizing antibody levels after the first dose of the mRNA vaccine; however, following the second dose, these individuals showed a declining trend in neutralizing antibody levels, indicating that waning of immunity had already begun. The declining neutralizing antibody response in previously infected individuals was also demonstrated in another study.[14] Neutralizing antibody levels in individuals without a history of COVID-19 did not exceed those found in convalescent sera, but increased after the second dose to surpass the levels seen in the convalescent sera. By contrast, neutralizing antibodies in individuals with a history of SARS-CoV-2 infection showed a much greater increase after the first dose of vaccine, but decreased following the second dose.

Challenges in vaccine efficacy assessment and the role of T cell-mediated immunity

China and Japan, having recently developed their own COVID-19 mRNA vaccines, opted to exclude individuals with a history of SARS-CoV-2 infection from their clinical trials.[33,34] Currently, neutralizing antibody titers are the primary measure used to assess vaccine efficacy; however, when trials include many participants with a history of COVID-19 infection, the increase in neutralizing antibody levels may appear lower than that reported by trials enrolling only COVID-19-naïve individuals. As the Omicron variant spread globally, the pool of people without prior infection decreased significantly, making it difficult to conduct trials solely with COVID-19-naïve participants.[15] Additionally, high vaccination rates worldwide mean that most of the population now has some level of immunity to SARS-CoV-2.[16] A history of infection or prior vaccination can affect the immune response to subsequent vaccine doses, often blunting the rise in neutralizing antibody titer and, in some cases, leading to a decrease in the titer.[8–14] Thus, relying exclusively on neutralizing antibody titers to compare vaccine efficacy has its limitations. Recognizing this, the WHO's TAG-CO-VAC has pointed out the need to look beyond neutralizing antibodies, suggesting

inclusion of additional measures such as cell-mediated immunity to evaluate vaccine efficacy.[7]

Indeed, T cell-mediated immunity plays a crucial role in SARS-CoV-2 infection. According to data from a cohort of healthcare workers who underwent weekly nasopharyngeal swab and blood sampling, interferon responses and virus-specific T cell responses preceded the detection of both the virus and antibody responses in non-severe COVID-19 cases.[35] A longitudinal immunologic study showed early induction of functional SARS-CoV-2-specific T cells was associated with milder disease.[36] Similarly, another study demonstrated that both the magnitude and breadth of early SARS-CoV-2-specific $CD4^+$ T cell responses correlated with milder disease.[37] Patients with mild COVID-19 exhibited a stronger T cell response in magnitude, which was also broader, as indicated by polyantigenic $CD4^+$ T cell responses that reacted to both spike and non-spike proteins. Moreover, early T cell responses, such as $CD8^+$ T cell mobilization, appear earlier than humoral response, even following vaccination.[38,39]

The role of cell-mediated immunity can also be observed in patients with impaired humoral immunity. Studies on individuals with immunocompromising conditions, or those receiving immunosuppressive treatments (particularly B cell-depleting agents such as anti-CD20 antibodies),[40] show that T cells are crucial for controlling primary SARS-CoV-2 infections. $CD4^+$ T cells facilitate humoral immunity, while both $CD4^+$ and $CD8^+$ T cells contribute to antiviral immunity through cytokine production and direct killing of infected cells. T cells are not only critical for primary SARS-CoV-2 infection but are also associated with disease severity, where timely and robust T cell responses correlate with milder disease.[41] Moreover, T cell responses tend to be more durable than neutralizing antibody responses, making them an essential component of the immune response to reinfection or repeated vaccination.[41,42]

The emphasis on cell-mediated immunity in vaccination, along with its potential as a correlate of protection, can be found in certain vaccine efficacy studies, with the varicella-zoster vaccine (VZV) serving as an example. In the immunologic substudy of trials on the live attenuated VZV vaccine,[43,44] cell-mediated immunity to VZV, measured by the responder cell frequency assay and interferon-gamma enzyme-linked immunosorbent (ELISpot) assay, was significantly increased in vaccine recipients. Moreover, cell-mediated immunity to VZV persisted longer than the VZV-specific antibody response and showed a stronger correlation with clinical outcomes. Likewise, in the recombinant subunit VZV vaccine trial, cell-mediated immunity, measured by intracellular cytokine staining to quantify the frequency of viral antigen-specific $CD4^+$ T cells expressing more than two activation markers, was elevated in vaccine recipients along with an increase in the VZV-specific antibody response.[45,46] Drawing insights from these VZV vaccine studies, it is essential to incorporate the measurement of cell-mediated immunity in COVID-19 vaccine research as well. Considering the long-lasting nature of cell-mediated immunity, continued tracking and analysis of immunological data could provide valuable insights into the vaccine-induced protection.

However, evaluating T cell responses to vaccination has a major limitation: the lack of standardized methods. Some studies evaluate T cell responses using cellular assay techniques such as ELISpot, intracellular cytokine staining, or activation-induced marker assays. Molecular techniques such as next generation sequencing are also used to characterize SARs-CoV-2-specific T cell receptors.[42] These methods, however, are time-consuming, costly, and not yet standardized, thereby limiting widespread use. Recently, interferon-gamma release assays targeting SARS-CoV-2 have emerged as a promising alternative.[47] Given these challenges, further studies are needed to refine the methods used to assess T cell responses. Such studies will increase our understanding of vaccine-induced immunity and provide more comprehensive tools for evaluating the efficacy of future vaccines against emerging variants. As a next step, we advocate for the organization of an international summit to establish a global strategy for defining and validating novel correlates of protection to guide phase 3 efficacy studies. This summit should prioritize the inclusion of immune markers reflective of cell-mediated immunity within vaccine evaluation frameworks, ensuring a more comprehensive understanding of immune protection beyond neutralizing antibody titers.

Conclusion

As the SARS-CoV-2 virus evolves, and both natural infection and vaccination rates increase, assessment of vaccine efficacy has become more complicated. While comparative immunogenicity trials based on neutralizing antibody levels are the primary method for evaluating immune protection, these markers have limitations, particularly in populations with prior exposure to the virus. Research shows that antibody responses in these groups tend to weaken following additional vaccination, highlighting the need to explore other immune markers such as T cell immunity, which plays a vital role in long-term protection. A more comprehensive evaluation framework that includes both humoral and cellular immunity markers in vaccine efficacy trials should be considered. However, the lack of standardized methods for assessing other immune correlates of protection remains a challenge. To address these challenges, it is time to convene an international summit to develop a global roadmap for defining new correlates of protection. This includes establishing standardized assays for measuring both humoral and cellular immunity and integrating these data into regulatory decision-making for future vaccine approval. A paradigm shift in vaccine evaluation is essential to ensure that the next generation of COVID-19 vaccines provide broad, durable, and robust protection against emerging variants and strengthens future pandemic preparedness.

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Dal-Hee Min is a professor of chemistry at Seoul National University. Her research interests encompass biotechnological multi-disciplinary topics based on the collective understanding of the surface chemistry of biochips and nanomaterials to develop chemically well-defined tools for disease diagnostics, drug development, and drug delivery.

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Author contributions statement

D-HM and WBP were responsible for the conception and design of the study. YHH, D-HM and WBP were responsible for analysis and interpretation of data; the drafting of the paper, revising it critically for intellectual content; and the final approval of the version to be published; and that all authors agree to be accountable for all aspects of the work.

Ethical statement

As this study is a review of previously published literature, ethical approval was waived.

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