INFECTION-ACQUIRED VERSUS VACCINE-INDUCED IMMUNITY AGAINST COVID-19

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Tsvetelina Velikova1* https://orcid.org/0000-0002-0593-1272
1Department of Clinical Immunology, University Hospital Lozenetz, Sofia University St. Kliment Ohridski, Sofia, Bulgaria

*Corresponding author: Tsvetelina Velikova, MD, PhD, Assistant Professor, Department of Clinical Immunology, University Hospital Lozenetz, Sofia University St. Kliment Ohridski, Kozyak 1 str., 1407 Sofia, Bulgaria;
Twitter handle: @LinaMladenova E-mail: tsvelikova@medfac.mu-sofia.bg

Abstract
The course of COVID-19 depends on a dynamic interplay between SARS-CoV-2 and the host's immune system. Although it is an emerging global health issue, little is known about the specificity, safety, and duration of the immunity elicited by the virus. This hypothesis article explores the benefits of infection-acquired and vaccine-induced immunity against COVID-19, suggesting that the latter outweighs the former. Comparative studies are proposed to explain and reveal all aspects of the immune responses. Although vaccine development relies on studies of naturally acquired immune responses, there are still no comparative analyses of the natural and vaccine immunity against SARS-CoV-2. Moreover, there are scarce reports on the characteristics of both types of responses. The scientific facts about the virulence of SARS-CoV-2 affecting the immune system are of great importance for proposed comparative analyses. Various immunological methods can be employed to elucidate infection-acquired and vaccine-induced immunity against SARS-CoV-2. The safe vaccination of subjects with and without COVID-19 history may disrupt the virus spreading and end the pandemic.

Keywords: COVID-19, SARS-CoV-2, Vaccines, Immunity, Antibodies, Natural Immunity, Immune Response, Hypothesis

INTRODUCTION
Coronavirus disease 19 (COVID-19) is a result of a dynamic interplay between severe acute respiratory syndrome virus 2 (SARS-CoV-2) and the host's immune system [1]. This disease is a global public health issue. The main question at this stage of the ongoing COVID-19 pandemic relates to the risks and benefits of naturally acquired and vaccine immunity. Better understanding of immune responses to the virus is critical for elucidating the disease pathogenesis and proposing preventative measures.

Numerous studies have attempted to elucidate the role of infection-acquired virus-neutralizing antibodies in the treatment of COVID-19 [2-4]. The neutralizing antibodies were tested for their ability to engage with the S1 subunit of the SARS-CoV-2 spike protein, which comprises the human angiotensin-converting enzyme 2 (ACE2) receptor-binding domain (RBD), and neutralize all variants of the virus [5]. Although antibody production is typically mild in asymptomatic subjects, it may intensify in hospitalized patients with COVID-19 [5].
The amount of the circulating neutralizing antibodies decreases over time, indicating that long-term immunity against COVID-19 is elusive [6,7]. The available evidence suggests that the affinity maturation in germinal centers and the ability to induce long-lived specific plasmocytes are disturbed in COVID-19 [8,9].

More than 320 laboratories worldwide are currently developing vaccines capable of producing high titers of neutralizing antibodies against SARS-CoV-2 [5]. These vaccines and vaccine candidates can be grouped into four types depending on the mode of utilizing the synthetic gene [10,11]. RNA vaccines are fully synthetic products that encode the SARS-CoV-2 spike protein [12]. The synthetic gene is transmitted by a viral vector such as non-replicating adenovirus or measles virus [13]. There are also whole-based and protein-based vaccines [14,15]. All these vaccines have their benefits and drawbacks [11,16].

COVID-19 vaccines triggering defensive immune responses are essential for preventing related morbidity and mortality. Humoral and Th1-directed cellular reactions are particularly important for the defense [17-19]. While there are no specifically designed comparative studies of the infection-acquired and vaccine-induced immune responses, we can only hypothesize which type of immunity is more beneficial and safe. By adhering to the widely publicized hypothesis-formulating recommendations [20], we attempt to distinguish the benefits and risks of different approaches to COVID-19 immunity and overview the role of the infectious inoculum, degree of acquisition, retransmission and reinfection, and clinical severity.

**HYPOTHESIS**

The availability of safe and effective vaccines against SARS-CoV-2 is crucial for overcoming the pandemic. Successful vaccination campaign covering the global population may result in much desirable herd immunity and prevention of the virus transmission. Vaccine deployment can be hindered when secondary infections arise and technical issues are encountered. Herein, a hypothesis is presented about the benefits of the vaccine-induced immunity outweighing those of COVID-19-acquired immune responses. Comparative analyses are proposed to test the hypothesis and reveal implications of both types of immune responses.

Current clinical trials have demonstrated the efficiency of approved COVID-19 vaccines offering an immune defense within at least eight months [21]. The duration of vaccine-induced and infection-acquired defensive responses is comparable [22]. To date, no report has claimed the inferiority of the vaccine-induced immunity compared with infection-acquired immunity. Quite the opposite, the course of the infection may suppress the immune system and weaken post-COVID-19 immunity [23-27]. The immune response to COVID-19 varies widely across subjects, with suboptimal responses reported [28]. A number of genetic and environmental factors may confound the naturally acquired immunity against COVID-19 [29,30].

COVID-19 vaccines are more likely to elicit robust and lasting immune protection without suppressing the immune system. The immunogenicity of COVID-19 vaccines has been explored in Phase I and II clinical trials [31]. The results of these trials are diverse due to the lack of standardized testing of the neutralizing antibodies. However, COVID-19 vaccines’ potency and immunogenicity can be evaluated by comparing with average titers of the neutralizing antibodies reported in the studies of convalescent patients. The available data suggest that COVID-19 vaccines generate neutralizing antibodies at titers comparable with those reported in convalescent patients [22,32].

Importantly, SARS-CoV-2 seropositivity varies widely across countries – from 3.2% to 6.6% in the general population, and 10% in medical professionals [33]. The seroprevalence was low during the initial outbreaks of the infection, leaving most subjects susceptible to the virus. The initial wave of the pandemic resulted in detectable neutralizing antibodies in 3%-10% of the general population. However it remained unclear whether these COVID-19 survivors were immune to reinfections and whether they contributed to the global herd immunity [33]. Most probably, herd immunity is hardly achievable through contracting the disease by large population masses [34].

**HYPOTHESIS TESTING**

The widely known facts about the virulence and immune-suppressing features of SARS-CoV-2 suggest that post-infection immune responses are most likely defective. By excluding COVID-19 complicated and fatal cases and employing specific immune tests in comparative analyses, researchers may predict the likelihood of herd immunity after infections. The following is a non-exhaustive list of suggested immunological tests: measurement of SARS-CoV-2-specific T and B lymphocytes, virus-neutralizing antibodies of different immunoglobulin types, markers of mucosal immunity, activated antigen-presenting cells, Toll-like receptors, inflammatory cytokines, and chemokines. These tests...
may reveal various aspects of both infection-acquired and vaccine-induced immunity. Figure 1 schematically depicts the hierarchy of immune mechanisms and suggested immunological tests.

Studies analyzing antibody levels are prioritized in the context of immunity against SARS-CoV-2. About 90% of COVID-19 convalescent patients produce neutralizing antibodies to the virus surface spike protein [21,35]. Nonetheless, the titers of these antibodies are very low in about one-third of these patients. Younger subjects and those with less severe COVID-19 produce much lower titers [36].

In most cases, the antibody response is detectable early after COVID-19, followed by accelerated and expected waning of antibodies [6]. After an initial increase in antibody titer, it usually decreases and remains at low levels due to the sustainable activity of plasmocytes with 21-day average half-life [6].

Longitudinal studies of immune responses in COVID-19 point to the persistence of specific immune responses only in some subjects [37]. The available evidence suggests that long-lasting immunity with neutralizing antibody production is hardly achievable after the infection.

The quantity of generated antibodies depends on the use of COVID-19 vaccine platforms. Viral vectors induce antibody production at levels exceeding those in convalescent patients [22]. RNA and recombinant protein vaccines along with adjuvants amplify antibody production to a level comparable to that in convalescent patients [1].

While all current COVID-19 vaccines are administered intramuscularly, the emphasis is on the circulatory immune responses rather than those on the mucosal surfaces. Mucosal immunity plays an important role, and many intranasal vaccine formulations are being investigated [38,39]. Importantly, IgG, IgM, and IgA responses to SARS-CoV-2 are reported in both convalescence and post-vaccination periods [40,41]. To better understand specific humoral immunity, large longitudinal studies are warranted. These studies may elucidate the role of antibodies over time and predict the risk of reinfections.

Although cell-mediated immunity is critical in any viral infection, the role of CD4+ and CD8+ T cells in the natural immunity to COVID-19 is still poorly understood. The available data suggest that virus-specific T lymphocytes are detectable in convalescent patients, but their role is unclear [42-44]. Like previous reports on SARS-CoV, studies of transferring virus-specific T cells in hACE2 transgenic mice may clarify the role of these cells [45]. Post-vaccination T-cell responses can be measured by IFNγ-releasing assays (e.g., immunospot) and intracellular cytokine staining. Multifunctional CD4+ and CD8+ T cells are often detectable after vaccinations [46]. Repetitive exposure to SARS-CoV-2 and protective immunity against reinfection are unresolved issues [47]. PCR positivity after an episode of COVID-19 may persist, with no clue whether the episode ended with complete convalescence or there is still ongoing infection. In that case, however, reinfection is unlikely [48].

Finally, it is critical to clarify the role of numerous confounding factors such as age, gender, race, ethnicity, obesity, and smoking. Understanding genetic drivers of infection and vaccine-induced humoral and cellular immunity to SARS-CoV-2 is critical. To assess the likelihood of lasting COVID-19 immunity, B-cell and T-cell reactions in infection and vaccination should be compared.

**ETHICAL CONSIDERATIONS**

Old and new diseases have emerged globally over the past decades partly due to the resistance to vaccination campaigns. Scientific data and ethical standards have often been ignored by those resisting vaccinations. Various vaccines are needed for different population groups such as newborns, children, adolescents, pregnant women, elderly subjects, and those with comorbidities. Since these groups can be prone to severe COVID-19, their involvement in vaccination campaigns should be prioritized. Most COVID-19 vaccines induce immunity to the virus spike protein without eliciting reactions to other proteins. As such, these vaccines may prevent severe COVID-19 and related deaths without inducing adverse immune reactions.

**CONCLUSION**

The hypothesis that COVID-19 vaccine immunity is more beneficial than infection-acquired immunity is based on evidence which has been rapidly accumulating over the past few months. While evidence on the safety and effectiveness of COVID-19 vaccines has been accumulating, weighing the benefits and risks of vaccine-induced and naturally acquired immune responses is advisable. More immunological studies of cell-mediated and humoral immunity are warranted to comprehensively assess different aspects of the ongoing pandemic and the globally expanding vaccination campaign.
Figure 1. Immunological, epidemiological and clinical aspects of naturally acquired and vaccine-induced immunity. Some approaches for comparatively studying of both are proposed.

How to test comparatively?

- In vitro studies
- In vivo studies
- Observational studies
- Interventional studies (Clinical trials)
- Longitudinal prospective studies

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AUTHOR CONTRIBUTIONS
TV generated the hypothesis and drafted and revised the manuscript. She takes full responsibility for the integrity of all aspects of the work.

CONFLICTS OF INTEREST
The author has completed the ICMJE Disclosure Form (http://www.icmje.org/disclosure-of-interest/; available on request). TV declares that there are no potential conflicts of interest.

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COVID-19-ГА ИНФЕКЦИЯЛЫҚ НЕМЕСЕ ВАКЦИНАЛЫҚ ИММУННОСТЬ

Резюме
Течение COVID-19 зависит от динамического взаимодействия между SARS-CoV-2 и иммунной системой организма. COVID-19 – это новая глобальная проблема здравоохранения, но нам мало, что известно о специфичности, безопасности и продолжительности иммунитета, вызываемого вирусом. В этой статье исследуется феномен инфекционного и искусственного иммунитета против COVID-19; предполагается, что последний перевешивает первый. Для объяснения и выявления всех аспектов иммунных ответов предлагается ряд сравнительных исследований. На данный момент разработка вакцины основывается на исследованиях естественных иммунных ответов, но до сих пор нет сравнительного анализа естественного и искусственного иммунитета против SARS-CoV-2, есть только скудные отчеты о характеристиках обоих типов ответов. Научные факты о вирулентности SARS-CoV-2, влияющей на иммунную систему, имеют большое значение для предлагаемого сравнительного анализа. Различные иммунологические методы могут быть использованы для выяснения иммунитета против SARS-CoV-2, инфекционного или искусственного. Безопасная вакцинация субъектов, переболевших COVID-19 и не переболевших данным инфекционным заболеванием может помочь распространению вируса и положить конец пандемии.

Ключевые слова: COVID-19, SARS-CoV-2, вакцины, иммунитет, антитела, естественный иммунитет, иммунный ответ, гипотеза