New variants of SARS-CoV-2, vaccine immune response and the Brazilian reality

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a highly pathogenic β-coronavirus, is the etiologic agent of coronavirus disease 2019 (COVID-19), which gave rise to a difficult to control pandemic, especially in Brazil. Approximately 4,000 mutations have been identified in SARS-CoV-2, with the majority being redundant without having any biological effect on the virus. The aim of the present study was to objectively understand how new SARS-CoV-2 variants can affect vaccine response, in addition to highlighting the current situation in Brazil in the face of the pandemic and considering epidemiological and immunological aspects of COVID-19. The main protective correlate investigated in most vaccines is the neutralizing antibody titer induced by immunizing agents, observed in the pre-clinical phase in animals, whose action is to block the binding of the spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor, preventing infection. Up to the second half of 2021, the variants that are of greatest concern worldwide and require molecular surveillance are Alpha variant (or B.1.1.7 lineage), Beta (or B.1.351 lineage), Gamma (or P1 lineage) and Delta (or B.1.617.2 lineage). Brazil finds itself in a highly unfavorable scenario, with the circulation of variants of concern, mainly Gamma and Delta, with high fatality rates for COVID-19 and low vaccination rate. Given the still latent situation of the COVID-19 pandemic in Brazil, the lack of global planning for action strategies for non-pharmacological prevention measures, there is an imminent risk of the emergence of new variants due to the finding of susceptible hosts and the high proliferative rate of SARS-CoV-2. It is urgent to increase the genotyping of positive samples isolated from infected individuals, the speed of vaccination of the entire population and the unification of non-pharmacological preventive measures throughout the country.

Keywords

Severe acute respiratory syndrome coronavirus 2, coronavirus disease 2019, variants, vaccine, Brazil

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a highly pathogenic β-coronavirus, is the etiologic agent of coronavirus disease 2019 (COVID-19), which gave rise to a difficult to control pandemic, especially in Brazil [1]. Even though COVID-19 is an "equal opportunity" disease, its consequences in the lives of the Brazilian population increased several orders of magnitude in social differences, demonstrating the fragility of public policies. The lack of effective measures to combat the spread of the disease, caused the collapse of public and private assistance in several cities [2]. The delay in the vaccine preventive policy is noteworthy, with only 14.2% of the Brazilian population fully vaccinated by the first week of July 2021 [3].

SARS-CoV-2 infection, whose symptoms begin approximately 5 days after exposure, clinically presents in various forms, ranging from mild to severe [4], with evident tropism through the respiratory tract, causing pneumonia, severe acute respiratory syndromes and, in critical conditions, systemic involvement, with multiple functional impairments.

As a process inherent to all viruses, SARS-CoV-2 undergoes mutations in its RNA (Ribonucleic acid) genome at each replication, resulting in different biological effects, which are subjected to natural selection processes. These mutations vary from having an irrelevant or null effect (no consequences), being harmful to the virus itself (negative effect) or having positive effects. Their biological function may not be fully understood, but they may be of great epidemiological importance, given that evidence shows that some mutations are able to favor viral maintenance and increase infectivity [5]. Approximately 4,000 mutations have been identified in SARS-CoV-2, with the majority being redundant without having any biological effect on the virus [6].

Assessing the pandemic scenario, it is evident that the new variants of the new coronavirus are causing healthy and younger people to suffer severe forms of the disease. Such mutations can impact somewhat the effectiveness of emergency vaccines produced for the control of COVID-19. A global monitoring system formed by various institutes/agencies worldwide was created, called SARS-CoV-2 Interagency Group (SIG), to follow-up and monitor the emergence of new variants. Through SIG, variants are classified as of concern, of interest, and of high consequence variants [5].

Therefore, the aim of the present study was to objectively understand how new SARS-CoV-2 variants can affect vaccine response, in addition to highlighting the current situation in Brazil in the face of the pandemic and considering epidemiological and immunological aspects of COVID-19.

Immune response against natural infection

SARS-CoV-2 has in its membrane a spike (S) glycoprotein, formed by two subunits, S1 and S2. The S2 subunit has a domain called the receptor binding domain (RBD), which interacts with a transmembrane protein called angiotensin-converting enzyme 2 (ACE2) present on the surface of many cells in humans, for example, respiratory system cells, cardiac tissue cells and gut epithelial cells, among others. The formation of the RBD-ACE2 complex is essential for the processing of protein S to occur by proteolytic cleavage catalyzed by enzymes in the body, such as the furin protease, which causes a conformational change in the S2 subunit, favoring the next phase of viral penetration in the host cell [7, 8]. It is believed that this need for protein S cleavage may have made this protein unstable, and perhaps the mutations reflect a compensatory strategy to achieve the stability of this structure, which is central to the increase in virus infectivity [6].

The RBD portion is the main target of natural antibodies produced in the immune response against coronavirus. Neutralizing immunoglobulin G (IgG) antibodies are more specific and bind exactly to epitopes in the RBD region that interact with ACE2. However, the magnitude and duration of natural antibody responses against SARS-CoV-2 are still not well understood; it seems that they remain circulating for a period of 3 months, but interestingly, it has been observed that the levels of these natural neutralizing antibodies in patients can be extremely low [7].

In addition to the humoral immune response, driven by the effector activity of antibodies in immune neutralization and in other functions [such as complement system activation and antibody-dependent cell cytotoxicity (ADCC) induction], the cellular immune response against SARS-CoV-2 infection must be considered. In this case, it is important to know both the activation of cytotoxic CD8+ T lymphocytes, and the orchestrating

role of immunity, mediated by CD4$^+$ T lymphocytes and their subpopulations [T helper 1 (Th1) and Th17], producers of pro-inflammatory cytokines [9].

Vaccine immune response: correlates of immunity

The vaccine immune response is a controlled way of activating the body's immunity that produces a powerful and regulated inflammatory response, without causing damage to the body. As much as inflammation is necessary for the antiviral response, the intensity of inflammatory processes could compromise immune modulation, causing damage to the body. In the vaccine immune response, autoregulatory mechanisms are also activated, leading to a reduction in inflammatory intensity and generation of memory cells. To date, there are no robust results indicating which parameters would clearly act as protective correlates of the vaccine response, leading to the elimination of SARS-CoV-2 or reduction in the severity of COVID-19.

The protective immune correlates are predictors of immunity determined by assays to assess humoral and cellular immune response, which are of great importance for the evaluation of vaccine efficacy. These parameters ensure the approval of candidate vaccines for COVID-19 [10], and further provide ways to assess the effectiveness of vaccination in the population.

The neutralizing antibodies induced by immunizing agents are the main protective correlate; they are observed in the pre-clinical phase in animals [11], and their action is to block the binding of the S protein to the ACE2 receptor, preventing infection. However, there is a wide variety of antibody responses against other protein S epitopes and against other SARS-CoV-2 proteins. For vaccine immunity, it is equally important to neutralize the combined action between the antibodies and the functions performed by other polyclonal antibodies, such as activation of the classical pathway of the antibody-mediated complement system and antibody-mediated phagocytosis of monocytes [11].

Some vaccines to date with results of protection correlates in animal models, such as mRNA vaccines, with a single immunization induce a strong immune response against SARS-CoV-2, both humoral and cellular. In the cellular response, there is activation of CD4$^+$ and CD8$^+$ T cells as well as formation of long-lived plasma cells and memory B lymphocytes [12]. Uncertainties about the lifetime of the vaccine immune response and the emergence of SARS-CoV-2 variants reinforce the importance of longitudinal studies to assess the effectiveness of COVID-19 vaccines.

Recently, Naaber et al. [13] in 2021 published results on the humoral and cellular response in individuals immunized with the BNT162b2 mRNA vaccine (Pfizer-BioNTech®), who were evaluated up to 6 months post-second dose, correlating with age and side effects. The humoral response against the original strain of SARS-CoV-2 and 5 variants of concern (VOCs) was vigorous and negatively correlated with the age of those vaccinated. However, specific antibodies appeared in the first week after the second dose, but shortly thereafter, began to drop dramatically. In turn, cellular immunity against the original and variant viruses remained high for a long period of time, until 6 months of the vaccine series had been completed.

These data reinforce the hypothesis that the reduction in deaths and hospitalizations due to COVID-19 in vaccinated individuals is strongly associated with the robustness of cellular memory immunity, highlighting the need to monitor vaccine effectiveness, especially in the elderly, due to the phenomenon of immunosenescence.

These fluctuations reflect the plethora of intrinsic and extrinsic factors that determine the competence of the vaccine immune response, including with regard to the platform used. Especially in Brazil, the ChAdOx1 nCoV-19 vaccine from AstraZeneca has shown a significant reduction in hospitalizations and deaths due to COVID-19. This vaccine induced a robust cellular and humoral immunity, reaching a high percentage of seropositivity, around 91-100% of those vaccinated [14]. Effector T cells have their onset of activity at 7 days, reaching a peak on the 14th day and persisting up to 56 days after the start of vaccination, without a significant increase in response, but with the ability to rapidly expand after a secondary stimulus caused by natural infection [14].

In wide use in Brazil, CoronaVac (Sinovac Biotech Laboratory), which uses the inactivated virus platform, has shown significant production of neutralizing antibodies and efficacy in reducing hospitalizations for mild, moderate and severe COVID-19 cases [15]. However, a recent comparative study showed that the seropositivity of individuals vaccinated with CoronaVac was lower compared with BNT162b2 (Pfizer-BioNTech®), especially in the group of elderly, diabetics or those with other chronic diseases [16]. In CoronaVac, the level of specific circulating antibodies against SARS-CoV-2 peaks at 3 weeks after the second dose and then drops drastically by the 16th week post-vaccination. In contrast, BNT16b2's vaccine maintains high levels of specific antibodies detectable in the blood longer.

It is important to emphasize that, in addition to the importance of the individual analysis of the effectiveness of the available vaccines, the greatest percentage reach of the population's vaccination coverage, using as a resource for this all the available approved vaccines, especially in a continental country such as Brazil, is what will ensure the success of collective immunity against COVID-19.

There is a scientific consensus that the anti-infective immunity conferred by vaccination is guaranteed by the permanence of cellular memory immunity to the detriment of the ephemerality of humoral immunity, which suffers a significant decrease over the months. However, it must be considered that the levels of neutralizing antibodies, especially after the completion of vaccine series, have undisputed actions in the specific antiviral response and overall immune activity, being important correlates of protection and monitoring markers in public health decision-making, including the need for reinforcement.

New variants of SARS-CoV-2 around the world

Here, only the VOCs will be considered, that is, those of epidemiological importance in transmission, pathogenicity, severity of the clinical picture and possible escape from natural and vaccine immunity [17]. The mutation present in the variants of current concern is N501Y, in which there is a change of asparagine (N) to tyrosine (Y) at position 501 of the coronavirus protein S (which binds to the ACE2 receptor) [6].

In May 2021, as recommended by the World Health Organization (WHO), important variants were designated by letters of the Greek alphabet to simplify scientific communication and refer to the geographical region of origin neutral [18]. Up to the second half of 2021, the variants that are of greatest concern worldwide and require molecular surveillance are Alpha variant (or B.1.1.7 lineage), Beta (or B.1.351 lineage), Gamma (or P1 lineage) and Delta (or B.1.617.2 lineage).

The Alpha variant, which was first identified in the UK and spread to 114 countries around the world in a few months, has 14 mutations, including 8 in the S protein, such as N501Y. Another mutation is P681H, which occurs in a region adjacent to the furin cleavage site, making protein S more susceptible to hydrolysis by transmembrane serine protease 2 (TMPRSS2), with a consequent increase in viral fusion [6]. Studies estimate that this variant has an infection rate of 43 to 90% higher than the preexisting variants in England [19].

The Beta variant detected in South Africa, at the end of 2020, has 7 mutations (D80A, D215G, K417N, E484K, N501Y, D614G and A701V) in the S protein, with 3 of them being in the RBD region (K417N, E484K and N501Y). It is a variant of great interest because it can confer immune escape activity and has spread to 113 countries. In individuals with low to moderate neutralizing antibody titers, due to natural infection [20] or vaccination [21], there is a reduction in the potential to neutralize the RBD region of this variant, which reflects the immune escape provided by the mutations.

The third variant of global concern is Gamma, first detected in Manaus, Brazil in November 2020, has 11 mutations in the S protein, of which 3 are in the RBD region (K417T, E484K and N501Y), 5 in the N-terminal region and 2 in the C-terminal domain of the S1 protein, near the furin cleavage site, and 1 in the S214 domain. Gamma shows 25-60% potential immune escape activity. Shortly after first detection, this variant became dominant in Brazil, making both WHO and Centers for Disease Control and Prevention (CDC) include it as a VOC. Currently, this variant has been identified in at least 36 countries, with local transmission in 5 of them, including Brazil [22].

The Delta variant is a sublineage of the B.1.617 variant, which appeared in October 2020 in India. In April and May of 2021 during a severe wave of COVID-19, the B1.617.2 variant appeared, which quickly spread across the country and around the world, becoming dominant in many countries and was designated as a VOC [23]. This variant spread to 98 countries and showed 60% greater transmission capacity compared to the Alpha variant, according to WHO [24]. Preliminary studies from England and Scotland further suggest that people infected with the Delta variant are twice as likely to be hospitalized compared to those infected with the Alpha variant [25].

It is known that the variants can decrease the protective immunity induced by vaccination, thus requiring regular monitoring of the protective correlates. An example is the B.1.351 mutation (Beta variant), which appears to reduce the neutralization of vaccine antibodies 6 to 15 times. The N501Y.V2 mutation, present in many variants, allows a rapid spread of the virus by escaping the previously established immune response. Interestingly, studies using serum from COVID-19 convalescent individuals demonstrated that the neutralizing potential was drastically reduced when it was from individuals infected with variants containing the N501Y.V2 mutation [26].

Brazilian reality: vaccines and variants

With regard to anti-COVID-19 vaccines in Brazil, until June 2021, there are 4 vaccines approved by the National Health Surveillance Agency (ANVISA), which are being made available to the population through the National Immunization Plan (PNI). They are: Sinovac/Instituto Butantan CoronaVac, Oxford AstraZeneca, Pfizer BioNTech, and Janssen from Johnson & Johnson [27].

Given this situation of the spread of SARS-CoV-2 variants around the world, up to the beginning of the second half of 2021, Brazil finds itself in a highly unfavorable scenario. With the VOCs circulation in the country, added to the high fatality rates for COVID-19 and low vaccination rate (with only about 13% of the population fully vaccinated), Brazil became the epicenter of the pandemic in May 2021, occupying second place in the number of deaths caused by COVID-19 worldwide since June [28]. The socioeconomic disparities, the discrepant quantity and quality of health resources intensified the fragility of the population, and the lack of well-defined and conducted public policies made the country a favorable environment for the generation and circulation of VOCs [28].

It is estimated that the Gamma (P1) variant predominant in Brazil is 1.4 to 2.2 times more transmissible and able to evade the immune response when compared to pre-existing non-P1 variants [28]. Interestingly, studies to evaluate the effectiveness of vaccines against the variants have demonstrated the immune evasion capacity of the Gamma variant. It was observed that plasma or serum from convalescent individuals and also serum from vaccinated individuals showed a substantial loss of neutralizing antibody activity against the gamma variant [29, 30].

The impact of these mutations on other correlates of immunity must be considered, since the immune system acts in a connected and integrated way, but studies on this approach are still scarce. In a preprint study carried out in Brazil, conducted by Souza et al. [31] in 2021, it was observed that 5 months after the second dose with the CoronaVac vaccine, plasma from vaccinated individuals was not effective in neutralizing P1 variant isolates in an in vitro assay. We must consider some biases of this study, that is the small sample and *in vitro* assay, but it opens the debate on the urgent need to investigate the relationship between variants and vaccine immune efficacy. The emerging concern that needs to be discussed in this scenario of introduction of vaccines from different vaccine platforms (inactivated virus, vector, mRNA and DNA), is whether the vaccines will remain effective against these variants, after they were produced in the reality of the original variant of SARS-CoV-2.

Up to the first week of July 2021, the Ministry of Health of Brazil confirmed the notification of 15 cases of the Delta variant of SARS-CoV-2 with two deaths [27], but it should be noted that in Brazil little genotyping is performed for confirmed cases of COVID-19, so there is a high possibility that this value is underestimated, necessitating a vigorous increase in epidemiological surveillance policies.

Brazil, the United States and other countries have started the booster dose (3rd dose), but what exactly is the profile of immunity in those vaccinated and whether there will be efficacy against VOCs remain unanswered. The scientific community is still following up on studies on the effectiveness of the complete vaccine series (1st and 2nd doses), with an urgent knowledge of post-booster immunity.

Studies show that cellular immunity (T and B lymphocytes) after the complete vaccination series of COVID-19 mRNA vaccines (Pfizer BNT162b2 or Moderna mRNA-1273 SARS-CoV-2) is less affected by mutations in variant strains than humoral immunity [32]. Memory B lymphocytes reactive to SARS-CoV-2 S protein and RDB epitopes increase after the second dose, reaching stability after 3 months. From that time until the sixth month, a new significant cellular elevation is observed, due to proliferative mechanisms in the germinal center of B lymphocytes, when activated, rapidly release neutralizing antibodies.

Conclusion

Given the still latent situation of the COVID-19 pandemic in Brazil, there is an imminent risk of the emergence of new variants, due to the finding of susceptible hosts and the high proliferative rate of SARS-CoV-2. Epidemiological surveillance must be maintained due to the lack of global planning for action strategies, the insufficient rate of vaccination, and the circulation of variants with more effective transmission. It is urgent to increase the genotyping of positive samples isolated from infected individuals, the speed of vaccination of the entire population and the unification of non-pharmacological preventive measures throughout the country.

Abbreviations

ACE2: angiotensin-converting enzyme 2

COVID-19: coronavirus disease 2019

RBD: receptor binding domain

S: spike

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Th: T helper

VOCs: variants of concern

WHO: World Health Organization

Declarations

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Author contributions

MCA conceived and coordinated the study, and wrote the manuscript. LGG, VKM and HOR wrote sections in the first draft of the manuscript. All authors reviewed the manuscript for relevant intellectual content. All authors have approved the final version of the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Consent to participate

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