Vaccine efficacy against Covid-19 and its worrying variants

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ABSTRACT

Objective: To analyze the main COVID-19 vaccines available in Brazil and coverage against VOCs. Methods: 199 articles were found in PubMed, VHL and SciElo. The following were researched: Coronavirus, Vaccine, COVID-19, Evolution, Variant, Delta and Omicron. Works published in the period between 2019 and 2023. A total of 07 articles were selected. Results: The vaccine release sequence was Coronavac followed by Pfizer, Astrazeneca and Janssen with different mechanisms of action and dose schedules. Regarding VOCs, five were identified: Alpha, Beta, Delta, Gamma and Omicron. Conclusion: the pathogenicity of VOCs was increased and vaccine efficacy (IV) decreased. It is noteworthy that VE in the real scenario is affected by public health measures, individual behaviors, access to health services, and vaccine hesitancy, factors not considered in the studies.

Keywords: SARS-CoV-2 variants, Pandemic, Vaccine, Literature review.

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INTRODUCTION

In March 2020, the World Health Organization (WHO) declared a global pandemic due to the high rate of contagion by the COVID-19 virus, demonstrated by the spread of the disease in 223 countries and more than 593 million cases registered in this period of time1. In this pandemic scenario, it was important to determine public health measures to contain the transmission of the virus and, in addition to social isolation, vaccination was the differential to contain the pandemic. In this sense, research has been directed towards the development of immunizers to combat the virus2.

In this sense, since the beginning of the pandemic of the virus that causes COVID-19, several new variants have emerged, due to adaptive mutations in the viral genome that have drastically altered its ability to evade the immune system. As a result, all progress in the development of vaccines is compromised, as the vaccine efficacy achieved has been shown to be reduced in the face of genomic variations. Thus, the variants that present greater transmissibility and greater virulence were called Variants of Concern (VOCs), which, at the time of this study, have been cataloged as Alpha, Beta, Gamma, Delta and Omicron, according to the different changes in the structure of the *Spike protein* and its receptors[1].

Thus, the objective of this study is to analyze the main COVID-19 vaccines available in Brazil, as well as the coverage of the recombinant strains of the initial virus so that it can serve as a reference for health professionals or the community.

METHODS

SEARCH STRATEGY

A systematic search was carried out in the PubMed, VHL and SciElo databases for the publication of original data that answered the guiding question regarding the combination approach between the vaccines, the analysis of the interval between doses and showed the evolution in the immunization process. This systematic review was not registered and a protocol was not prepared. The following search terms were used: Coronavirus, Vaccine, COVID-19, Evolution, Variant, Delta and Omicron. The searches included works published in the period between 2019 and 2023. The reference lists of the retrieved articles were also examined for additional relevant data.

INCLUSION AND EXCLUSION CRITERIA

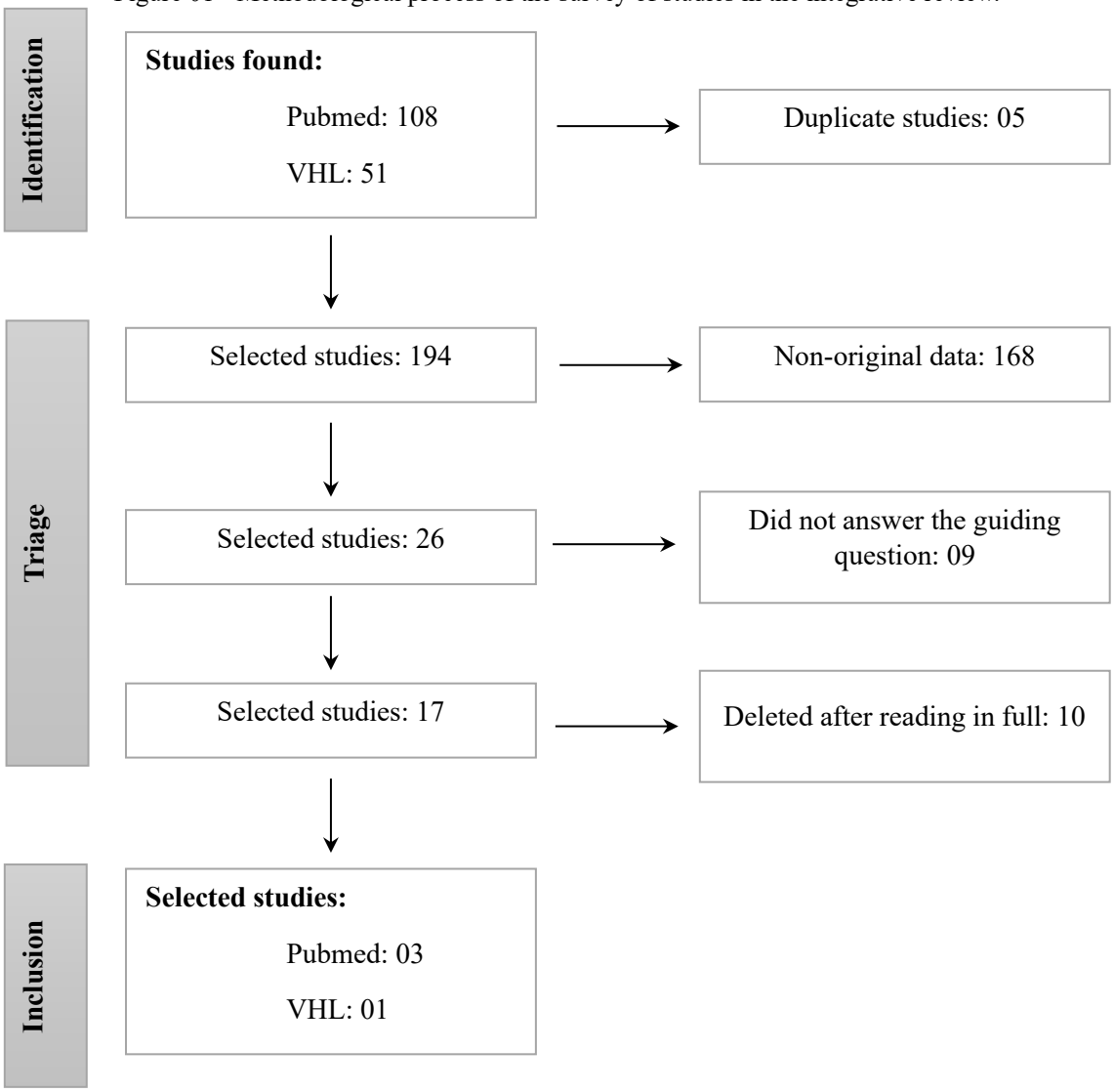
Inclusion criteria consisted of: (1) human studies; (2) original data; (3) that addressed at least one of the COVID-19 vaccines. Studies were excluded if (1) they were not in Portuguese or English; (2) if the studies did not present original data; (3) unpublished texts, such as theses and dissertations.

CHOICE OF DATA AND SEARCH RESULTS

The search of the database using the descriptors mentioned above selected 199 studies. Five of these were duplicates and have been removed. Thus, of the 194 studies, 168 were not original data and belonged to review studies. Nine studies did not meet the guiding question of this study.

After this selection, 17 studies remained for the full text to be read. Finally, a total of seven articles met the inclusion and exclusion criteria, and full-text versions were used to extract data and include them in this review. The overall research strategy is outlined in Figure 01. Vaccine leaflets were used as technical references.

Figure 01 - Methodological process of the survey of studies in the integrative review.



Source: Diagram adapted from the Prisma model.

RESULTS

After reading and applying the inclusion and exclusion criteria, 07 articles were selected, all published between 2021 and 2023, five articles in English and two in Portuguese, as described in chart 01.

Authors	General Objective	Main results
Zamai L, Rocchi MBL (2021)[2]	To provide arguments of the involvement of anti-vector immunity and SARS-CoV-2 variants in the efficacy of the ChAdOx1 nCoV-19 vaccine.	This meta-analysis of 135 studies suggests that there is increased transmissibility of emerging SARS-CoV-2 variants of concern where there is prolonged close contact. Full vaccination reduced susceptibility and infectivity, but more for Alpha than for Delta and Omicron.
Aleem Aa, Akbar Samad Ab, Waqar S (2022)[1]	Describe the clinical manifestations and latest treatments in the management of COVID-19, as well as summarize the available vaccines and their effectiveness against the new variants.	It shows the date of emergence of the Variants of Concern (VOCs), as well as the Vaccine Efficacy of the immunizers BNT162b2, mRNA-1273, Ad26.COV2.S and NVX-CoV2373 against the mutations of the wild virus. In addition, it shows that mixing vaccine types increased antibodies and neutralizing responses to most major commercially available vaccines.
Madewell et al (2022)[7]	To assess how reported household SARs have changed over time and whether SARs are altered by viral variant and case, index case, and contact vaccination status.	The results suggest that emerging SARS-CoV-2 variants of concern have higher transmissibility. Full vaccination was associated with reductions in susceptibility and infectivity, particularly for Alpha compared to Delta and Omicron. It highlights the challenges of developing effective vaccines concomitantly with viral evolution.
Shao et al (2022)[6]	Systematically assess Vaccine Efficacy (VE) in the real-world setting against each clinical outcome caused by the Variants of Concern (VOCs).	Full vaccination showed high EV against the Alpha variant, moderate EV against Beta, Gamma and Delta, high EV against severe disease caused by Delta, low to moderate EV against Omicron. Booster vaccination has substantially increased EV against Delta and Omicron variants.
Maciel et al (2022)[8]	To evaluate the interval between doses of SARS-CoV-2 vaccines; interchangeability between vaccines; vaccination in adolescents and the need for better evidence.	Evidence indicates that such mixed or combined regimens of different COVID-19 vaccines can trigger immune responses even stronger and more robust than two doses of a single vaccine.
Orellana (2022)[9]	OBJECTIVE: To evaluate vaccination coverage and its relationship with changes in the pattern of hospitalizations and deaths due to COVID-19 in the elderly in Manaus, Amazonas State, Brazil.	It shows that younger individuals had more severe disease or progressed to death after the mass vaccination of the population over 60 years of age. In addition, it points out the overall reduction in the rates of hospitalization and death from the disease in the elderly. A partial regimen with the first dose of the Oxford/AstraZeneca vaccine may provide protection against symptomatic disease, however, less effective than with the Pfizer/BioNTech vaccine.
Kupek E (2021)[10]	To investigate the relationship between COVID-19 vaccination coverage and COVID-19-related mortality by age group in Brazil in 2021.	Increase in mortality rate (MT) in people aged 60 and over. People aged >70 exceeded 95% vaccination coverage, while those aged 60-69 reached 80% with the first dose of the vaccine. However, the second dose reached 26, 76, and 64% coverage in people aged 60-69, 70-79, and >80 years, respectively. About 80% of the vaccine doses administered were CoronaVac and 18% were AZD122(ChAdOx1-S). A significant reduction in MD was observed, coinciding with a high coverage (90%) of the first dose in the population of individuals aged 60 years and older.

DISCUSSION

According to the analysis of the selected articles and the available vaccine leaflets, it was possible to observe the vaccination methodology used in the immunizers for COVID 19, recommended age, number of doses, interval between doses, and the effectiveness of protection attributed to each immunizer used (Figure 02).

The coronavac vaccine, produced by the Butantan Institute, which uses inactivated virus technology, was the first immunizer approved by the National Health Surveillance Agency (Anvisa) for commercial use in Brazil. Randomized studies were conducted with children from 3 years of age to the elderly aged 60 years or older to evaluate immunogenicity and demonstrated a consistent result, with a good antibody seroconversion rate. The recommended use is two doses of the recommended immunizer, 2 to 4 weeks for adults and the elderly, and only 4 weeks for children over 3 years of age and adolescents under 18 years of age[3].

The Pfizer vaccine was the second approved in the country. Its mechanism of action is by synthetic messenger RNA. This vaccine was released for a target audience from 6 months of age, with a variation in the dose interval by age4. However, vaccination campaigns prioritized adults and the elderly, as efficacy studies addressed the age group over 16 years with the BNT162b2 vaccine, in the 21-day interval between doses, with 95% protection against COVID-19[1].

The ChAdOx1nCoV-19 vaccine (Astrazeneca) is an immunizer that uses an adenoviral vector, which was approved to be administered in two doses with an interval ranging from 4 to 12 weeks. In meta-analysis studies, a progressive reduction in IgG was observed with a peak at day 28 after the first dose of the vaccine. In addition, it was concluded that those vaccinated with the second dose, 84 days after the first, produced a peak of anti-SARS-CoV-2 IgG twice as high as those who received the second dose within 42 days of the initial vaccination. However, the possibility of acquiring the disease in the interval between doses was noted due to the lack of post-vaccine preventive measures. This scenario contributes to asymptomatic COVID infection and increases the number of disease transmitters. The efficacy of this immunizer for symptomatic infection was 70.4% against 28.9% for asymptomatic infection for the Alpha variant[2].

The fourth vaccine released in Brazil was Ad26.COV2.S (Jansen), which uses adenovirus serotype 26 (Ad26) vectors as a technology and has a single-dose regimen. It has been approved by ANVISA for people over 18 years of age. This immunizer was approved in the USA after a multicenter control phase study that provided an efficacy of 66.3% against the infectious[1]. This immunizer can be applied as a booster dose (second dose) after at least 2 months in case of a homologous regimen (primary Jansen vaccine) or heterologous regimen (primary mRNA vaccine)[5].

THE EMERGENCE OF VARIANTS OF CONCERN (VOCS) AND THEIR RELATIONSHIP TO THE VACCINE

Viral mutations are responsible for altering the pathogenic potential of the virus, so that even a single amino acid exchange has the potential to increase a virus's ability to evade the immune system, complicating all the progress made in developing a vaccine against it. Thus, SARS-CoV-2,

like other RNA viruses, has the propensity to evolve genetically, resulting in multiple variants that have different characteristics from ancestral strains[1].

In light of this, multiple variants of SARS-CoV-2 have been described in genetic sequencing banks, of which some are considered variants of concern (VOCs), due to their great impact on public health. Thus, studies have shown that VOCs are associated with lower neutralization by antibodies obtained both through natural infection with other strains and by vaccination, demonstrating a certain ability to avoid detection or a decrease in the effectiveness of vaccination in relation to the original strain, in addition to showing Increased transmissibility or virulence[1]. Based on the WHO epidemiological update, as of December 2021, five SARS-CoV-2 VOCs have been identified since the beginning of the pandemic, Alpha, Beta, Delta, Gamma, and Omicron, respectively in chronological order of reporting.

The Alpha variant, the first variant of concern in the chronological account, lineage B.1.1.7, was reported primarily in the United Kingdom in December 2020 based on genomic sequencing of patients who tested positive for SARS-CoV-2. That said, this variant has 17 mutations in the viral genome, eight of which are in the protein *Spike* (S), in addition to an increased affinity of this for ACE 2 receptors, resulting in increased viral binding and entry into host cells. From this point of view, the B.1.1.7 lineage was reported to be 43% to 82% more transmissible and people infected with it had greater disease severity and a higher risk of death compared to other VOCs[1].

Likewise the Alpha variant is refractory to neutralization by most monoclonal antibodies to the N-Terminal region (NTD) of the protein *Spike*, as well as relatively resistant to some monoclonal antibodies to the ancestral RBD receptor, threatening the protective efficacy of vaccines developed before their emergence. In summary, the immunizer that demonstrated the greatest efficacy for this VOCs was the ChAdOx1 nCoV-19 vaccine, produced in Brazil by the Oswaldo Cruz Foundation (FIOCRUZ)[2].

The Beta variant, second VOC in the chronological account, B.1.351 lineage, was first reported in South Africa in December 2020, and is responsible for the second wave of infections in that country. This variant has nine mutations in the protein *Spike*, of which three are located at the RBD receptor, increasing, as in Alpha, the binding affinity for the host cell's ACE receptors. That said, the B.1.351 lineage has an increased risk of transmission and reduced neutralization by both monoclonal antibody therapy and convalescent sera and post-vaccination sera[1].

In this sense, considering the similarity of mutations in the same protein between the Alpha and Beta variants, a complete vaccination provided moderate protection against infection caused by Beta, when the vaccine efficacy (EV) for the immunizer was analyzed ChAdOx1 nCoV-19. In other words, for this immunizer, the Beta variant was neutralized, avoiding hospitalizations, in 72% of those vaccinated, while 86% of those vaccinated neutralized the Alpha6 variant.

The Delta variant, third in the chronological account, lineage B.1.617.2**,** it was initially identified in December 2020 in India and was responsible for the deadly second wave of COVID-19 infections in April 2021. On North American soil, this variant was first detected in March 2021, proving to be the most dominant strain until the end of 2021. It has ten mutations, in genes distinct from the previous variants, in the protein *Spike*[1].

In a full-schedule analysis of two doses of the mRNA, ChAdOx1 nCoV-19 and Ad26 vaccines. VOC2. S, they performed better for the B.1.617.2 variant when compared to the adenovirus vaccine. Thus, complete vaccination by means of mRNA showed a VE of 70% against infection, 84% against hospitalization, 88% against ICU admission, and 90% against death[6].

The Gamma variant, fourth in the chronological account, lineage P.1, also known as the GR/501Y variant. V3, was identified in January 2021 in Brazil. This variant harbors ten mutations in the *spike* protein, just like Delta, however, three of these mutations are located in the RBD gene. Thus, based on the WHO epidemiological update on March 30, 2021, this variant has spread to 45 countries, making it a VOC, due to its neutralization being reduced by monoclonal antibody therapies, convalescent serums, and post-vaccination sera[1].

Like the Alpha, Beta, and Delta variants, the Gamma variant was better neutralized by mRNA vector-based vaccines, with an IV of 71% against infection, 78% against hospitalization, and 81% against death in a two-dose vaccination schedule. These variants are similar both in their mutations and in their moderate vaccine efficacy compared to their ancestral strain6.

The Omicron variant, the fifth VOCs in the chronological account, also called the B.1.1.529 variant, was first identified in South Africa in November 2021. This variant has more than 30 changes in the *spike* protein, as well as in several other regions and non-structural proteins. For this reason, the Omicron variant shows a 13-fold increase in viral infectivity and is 2.8 times more infectious than the Delta variant. In addition, the Spike K417N mutation, also found in the B.1.351 variant, along with E484A is predicted to have a very disruptive effect, which makes Omicron more prone to uncovered windows of immunization between vaccines[1].

From this perspective, it is understood that the Omicron variant showed low EV, with 23% against infection, 56% against hospitalization and 82% against death. However, looking specifically at those vaccinated with mRNA vectors, there was a slight increase in VE against infection, which rose to 60%, as well as against hospitalization, which increased to 85%. In addition, it is possible to analyze the behavior of the immune response over time for the Omicron variant against the mRNA-1273, BNT162b2, ChAdOx1, Ad26.COV2.S and CoronaVac vaccines. The summarized EV, for a complete vaccination schedule of at least 2 two doses, was 44% against infection in the first month and later decreased to 6% in the sixth month. In addition, VE versus hospitalization was 71% in the first month and slowly decreased to 59% at the end of 180 days. At the same time, booster

vaccination showed a high protective effect, but also a decreasing effect against both infection and hospitalization at the end of 4 months[6].

Therefore, the infectivity and immune evasion capacity of VOCs, compared to the original strains, were shown to be increased and the VE against VOCs was lower as well as rapidly decreased over time. On the other hand, it is necessary to understand that VE performance in the real-world setting is affected by public health measures, individual self-protection behaviors, access to health services, and vaccine hesitancy, factors that may not have been considered in vaccine efficacy studies[2].

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