Review

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Efficacy of Heterologous Immunization and Hybrid Immunity as Vaccination Strategies During the COVID-19 Pandemic: A Narrative Review of the Literature

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Abstract

Background: During the COVID-19 pandemic, achieving herd immunity became the main objective to minimize mortality, severe COVID-19 and the emergence of new SARS-CoV-2 variants. New vaccination strategies, heterologous immunity and hybrid immunity, emerged as partial solutions to the health emergency. **Aim:** To conduct a narrative review of the literature on the efficacy of new vaccination strategies against SARS-CoV-2/COVID-19 and their potential use in public health. **Methods:** A selective and strategic literature search was conducted in PubMed, MEDLINE, Embase, Web of Knowledge, Scopus, CINAHL, LILACS, ScieELO and Cochrane databases. The terms 'COVID-19, SARS-CoV-2, Vaccines, Heterologous immunity, Hybrid immunity'; and Boolean operators (AND, OR, NOT) were used. In the English language, during the years 2020 - 2024. **Results and conclusions:** Novel immunization strategies have been shown to be effective and safe for the control of SARS-CoV-2 infection and its triggering pathology COVID-19. Heterologous immunity can be used to supplement and boost immunisation schemes against SARS-CoV-2. Mixing two platforms exerts a synergism in the immune response that provides protection against SARS-CoV-2 strains. The immunological mechanisms underlying the observed benefits are still under investigation. Hybrid immunity was also shown to be effective and safe. Prior infection and subsequent vaccinations provide a humoral response capable of neutralizing SARS-CoV-2 variants. This new knowledge serves as a basis for responding to future health emergencies associated with immunopreventable pathologies. Recent evidence of developments in the field of vaccinology.

Keywords: SARS-CoV-2; COVID-19; vaccines; immunity; heterologous immunity; hybrid immunity

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1. Introduction

Despite the strong global socioeconomic impact of the COVID-19 pandemic, it was possible to evolve during adversity in terms of new prophylactic vaccine proposals. In particular, the design and development of new platforms such as: vaccines with viral vectors and vaccines with nucleic acids (mRNA), without historical precedent to date. New immunization strategies were also innovated as alternative solutions to meet the needs arising from the imbalance between the supply and demand of biologicals, as well as the accelerated emergence of new variants of interest and/or concern of SARS-CoV-2; especially in countries with limited access to the products in question [1].

Current scientific evidence has shown that the best public health strategy for the control of infectious diseases, whether contagious or not, is through vaccination [2]. Therefore, prophylactic vaccines and mass immunization strategies are the most effective tool to mitigate the COVID-19 pandemic [3]. Globally, achieving herd immunity would minimize COVID-19 mortality, the risk of developing severe COVID-19, and the emergence of new variants of interest or concern. To date, it is not known how many booster doses are enough to achieve long-term immunity, just as the effectiveness of the new vaccination strategies that emerged during the SARS-CoV-2 pandemic is unknown. Consequently, there is a knowledge gap that aims to be addressed through this review, with the purpose of cementing knowledge that favors the construction of future research work in the basic and clinical context, with regard to immunization against SARS-CoV-2/COVID-19.

SARS-CoV-2, identified in late 2019, is a highly transmissible coronavirus that triggered the COVID-19 pandemic, representing an unprecedented challenge to global public health. Among the seven known human coronaviruses, some cause mild disease (229E, OC43, NL63, and HKU1), while others, such as SARS-CoV, MERS-CoV, and SARS-CoV-2, are highly pathogenic [4]. The outbreak in China reached its epidemic peak in February 2020, with more than 3,000 new cases confirmed daily. To control the spread, China implemented drastic measures, such as locking down the city of Wuhan and restricting all outdoor activities, resulting in a steady decline in new cases [5].

Given the magnitude of the pandemic, vaccination has emerged as the most effective tool for the prevention and long-term control of COVID-19. Various vaccine platforms have been developed, including recombinant vectors, DNA, mRNA in lipid nanoparticles, inactivated viruses, live attenuated viruses and protein subunits [6]. By October 2020, around 174 vaccine candidates had been reported, and 51 were in human clinical trials [7]. This rapid development of vaccines marks a milestone in medicine, establishing solid foundations for long-term immunization strategies, essential to control the virus and prevent future outbreaks.

Between July and October 2021, was recommended to increase the protection against COVID-19 for immunocompromised people due to the evolution of the pandemic and the emergence of new variants of SARS-CoV-2 [8]. Vaccination is crucial, with various platforms available, such as viral vector, protein subunit, RNA and DNA vaccines, enhancing the immune response [9]. It is vital to continue immunization, monitor complications, develop new vaccines and optimize immunoadjuvants to ensure safety and efficacy, especially in vulnerable populations such as immunocompromised, pregnant and elderly [10].

The aim of this narrative review is to show the latest evidence on the efficacy of new vaccination strategies against SARS-CoV-2/COVID-19 and their potential use in public health. A selective and strategic literature search was conducted in PubMed, MEDLINE, Embase, Web of Knowledge, Scopus, CINAHL, LILACS, ScieELO and Cochrane databases. The terms ‘COVID-19, SARS-CoV-2, Vaccines, Heterologous immunity, Hybrid immunity’; and Boolean operators (AND, OR, NOT) were used. English-language articles published between 2020 and 2024 were included.

2. Heterologous Immunization

Heterologous immunization (HI) refers to the vaccination strategy that uses different types of vaccines (platforms) for the first and second doses, including booster doses; to improve the immune response or respond to the needs of the mismatch between supply and demand of biologicals [11]. The strategy has been proposed as an option to provoke stronger and longer-lasting immunity, in

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those vaccines with moderate vaccine efficacy (less than 70%). Strategic Advisory Group of Experts on Immunization (SAGE) considers two doses of different covid vaccines (heterologous) included in the emergency use list, constitute a complete primary vaccination. For countries that use HI regimens, World Health Organization (WHO) has made recommendations to ensure that such regimens have equivalent or favorable actual immunogenicity or vaccine efficacy compared to homologous regimens [12].

HI has previously been used in experimental studies of vaccines against various pathogens in animal models (non-human primates) and in some cases in humans [13]. The current evidence has been supported by studies carried out against the human immunodeficiency virus (experimental models), the hepatitis C virus, the pseudorabies virus, hepatitis B, human papillomavirus, and influenza virus, among others. Therefore, the heterologous vaccination strategy is not new and benefits have been demonstrated in immune response mechanisms. However, evidence has also documented some disadvantages or limitations with this vaccination strategy [14]. For example, prior immunization with a chimeric vaccine against yellow fever and Japanese encephalitis reduced the seroconversion rate and the neutralizing antibody titer against an anthrax vaccine administered 30 days later [15]. The use of HI between flaviviruses can generate the synthesis of non-neutralizing antibodies that would favor the phenomenon of "*Antibody-Dependent Enhancement*", documented in cases of severe dengue [16]. Therefore, further research is needed to fully understand the potential impact of HI on vaccine efficacy and safety.

2.1. Heterologous Immunization in the Context of Vaccination Against SARS-CoV-2/COVID-19

In the context of the COVID-19 pandemic, the WHO has authorized the HI strategy as an alternative solution to the mismatch between the supply and demand of biologicals in some populations, with the aim of make more flexible, maintain and increase vaccine coverage against SARS-CoV-2. The effectiveness of HI has been demonstrated in clinical trials and its administration to the community, for example, heterologous booster vaccination of adenovirus-vectored vaccines (ChAdOx1 nCoV-19 or Ad26.COV 2-S) followed by vaccines mRNA (BNT162b2 or mRNA-1273) induced stronger immune responses and provided greater efficacy than the homologous vaccine with ChAdOx1 nCoV-19 [17]. The results observed in the Com-COV2 and COV-BOOST clinical trials demonstrated that HI with ChAdOx1 nCoV-19 and NVXCoV2373 induced a greater humoral and cellular response than homologous vaccination with ChAdOx1 nCoV-19 [18,19].

The WHO, in its interim guidelines for the use of vaccines against COVID-19, recommends that after the administration of a first dose of the Pfizer vaccine, any of the two anticovid viral vector vaccines included in the WHO emergencies list can be used (Janssen or AstraZeneca Vaxzervia/COVISHIELD), depending on the availability of one or the other [20]. The Pfizer vaccine can also be used as a second dose after any of the COVID-19 vaccines that appear on the WHO emergency list, whether inactivated (Sinopharm, Sinovac or Bharat) or viral vector (Janssen or AstraZeneca Vaxzervia/COVISHIELD). Pfizer vaccines can also be used as a booster dose after having administered any of the anti-covid vaccines included in the WHO emergency use list [21]. SAGE considers two doses of different COVID-19 vaccines listed for emergency use to constitute a complete primary vaccination [22].

For countries that plan to use heterologous regimens in immunization programs against SARS-CoV-2, the WHO has made the following recommendations: After administering a first dose of the Moderna vaccine, either of the two anticovid viral vector vaccines can be used on the WHO emergency use list (Janssen or AstraZeneca Vaxzervia/COVISHIELD), depending on the availability of each vaccine. The Moderna vaccine can also be used as a second dose after any of the COVID-19 vaccines that appear on the WHO list for emergency use, whether inactivated (Sinopharm, Sinovac or Bharat) or viral vector (Janssen or AstraZeneca Vaxzervia/COVISHIELD). The Moderna vaccine can also be used as a booster dose after having administered any of the anti COVID-19 vaccines included in the WHO list for emergency use [23]. It is currently recommended that when two doses are administered, the same product is used for both [24].

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To date, scientific evidence has shown that heterologous COVID-19 vaccination schedules may be more immunogenic and effective than homologous schedules, depending on the specific platforms and the order in which the products are used [25]. In particular, data indicate that people who have received one dose of the Janssen vaccine followed by a second dose of a messenger RNA vaccine have higher concentrations of neutralizing antibodies than people who received two doses of the Janssen vaccine [26]. Studies also indicate that the Janssen vaccine is as effective in stimulating antibodies as a homologous schedule with the third dose of the messenger RNA vaccine when administered six months after a primary series of two doses of messenger RNA vaccine [27]. SAGE accepts full primary vaccination against COVID-19 with two heterologous doses of vaccines included in the WHO emergency use list [28].

Reproducible results have been observed with the Sinovac vaccine. To ensure equivalent or superior immunogenicity or vaccine efficacy, after a first dose of Sinovac, one of the two mRNA anti COVID-19 vaccines (Pfizer or Moderna) or one of the viral vector vaccines (AstraZeneca Vaxzevria/ Covishield or Janssen) that are included in the WHO list for emergency use, depending on the availability of each product [29].

In Thailand, the research group of Kumwichar [30] evaluated the effectiveness of a HI regimen against COVID-19, based on the mitigation of severe outcomes, specifically severe COVID-19 and death after hospitalization due to COVID-19. The researchers evaluated 8 HI schemes endorsed by the competent agencies, as mentioned: *CoronaVac/ChAdOx1, ChAdOx1/BNT162b2, CoronaVac/CoronaVac/ChAdOx1, CoronaVac/ChAdOx1/ChAdOx1, CoronaVac/ChAdOx1/BNT162b2, BBIBP-CorV/BBIBP-CorV/BNT162b2, ChAdOx1/ChAdOx1/BNT162b2 and ChAdOx1/ChAdOx1/mRNA-1273.* For comparisons, they took into account non-immunized individuals. The cohort was stratified according to vaccination status, age, sex, provincial location, month of vaccination, and outcomes. The researchers found that heterologous 2-dose vaccinations offered approximately 50% effectiveness against severe COVID-19 and death after hospitalization with COVID-19 for 2 months; however, protection decreased significantly over time. Heterologous vaccinations of 3 doses maintained an effectiveness greater than 50% against both outcomes for at least 8 months, according to logistic regression results with a temporal interaction model of durability. The immunization schedule consisting of *CoronaVac/CoronaVac/ChAdOx1* demonstrated >80% effectiveness against both outcomes, with no evidence of decreased effectiveness over time. The monthly measurement of the effectiveness of the *CoronaVac/CoronaVac/ChAdOx1* regimen against severe COVID-19 and death after hospitalization at 7 months after the last dose was 82% (95% CI: 80,3%-84%) and 86,3% (95% CI: 83,6%-84%), respectively.

Nithichanon [31] evaluated the effectiveness of HI schedules in a cohort of patients who had received two doses of homologous immunization with CoronaVac, prior to heterologous booster doses with nucleic acid (DNA or mRNA) vaccines. In total there were 56 participants, of which 40 had received two initial doses with CoronaVac and two booster doses with DNA or mRNA vaccines (Total dose = 4); 16 participants received an extra dose of DNA or mRNA vaccines (Total dose = 5). The results showed no difference in side effects, neutralizing antibodies, or T-cell responses for any of the heterologous vaccination schedules. However, the neutralization capacity and response of IFN-γ against the Omicron variant in participants who received 4 or 5 doses was higher. Polarization of peripheral memory T cells after stimulation in all booster groups with Omicron peptide showed an increased trend of naïve and central memory phenotypes of both CD4+ and CD8+T cells, suggesting that exposure to Omicron antigens will drive T cells into a lymphoid resident T cell phenotype. These results support the importance of ongoing vaccination programs to maximize vaccine effectiveness, especially in high-risk individuals. In addition, the number of booster doses is important for maintaining immunity.

Researchers from the University of Würzburg – Germany, evaluated the immunogenicity of homologous and heterologous vaccination schedules for mRNA vaccines (BTN162b2mRNA and mRNA-1273) in a cohort of 356 health workers [32]. The humoral immune response was evaluated through the quantification of IgG antibodies against the SARS-CoV-2 S protein, as well as the relative

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avidity index against the S protein. The cellular immune response was evaluated through the T-SPOT.® COVID test directed against SARS-CoV-2 S1 and nucleocapsid antigens, as well as interferon-gamma release assays (IGRA). The researchers also evaluated the effectiveness of hybrid immunity in those participants who had had prior vaccination infection and host-dependent factors that could influence the effectiveness of homologous and heterologous immunization schedules with mRNA vaccines. The results of the study showed that health workers who had had previous infection had a greater humoral response than individuals who only received artificial immunization, with statistically significant levels of IgG against protein S and avidity index. Strong cellular reactivity against the SARS-CoV-2 S1 antigen was also demonstrated, being higher in workers with previous infection. A negative correlation was evidenced between the time of the last dose of immunization and the cellular immune response, however, a positive correlation was observed with the humoral immune response. Of the host-dependent factors, it was evidenced that smokers had a lower antibody response against the SARS-CoV-2 S protein, regardless of the immunization schedule received. It was also evident that the cellular response was lower in the group of smoking workers. Other variables such as age, gender and body mass index did not have statistically significant results. The comparative analysis between the homologous immunization schedule (three doses of BNT162b2mRNA) and the HI schedule (two doses of BNT162b2mRNA and one dose of mRNA-1273) showed that there were no statistically significant differences in terms of the cellular response measured by the interferon-gamma release assays, however, statistically significant differences were evidenced in the production of IgG antibodies against the S protein; being higher in health workers who received a HI schedule.

Studies on the evaluation of the effectiveness of HI vs. homologous immunization have also been carried out in immunocompromised individuals, who are considered to be at high risk. It is important to note that the population in question were excluded from the initial clinical trials for the evaluation of the efficacy of vaccines against COVID-19. Pardo et al. conducted a systematic review of the literature and a meta-analysis on the effectiveness of heterologous and homologous vaccination against COVID-19 in immunocompromised people [33]. The vaccination strategies (heterologous vs homologous) showed no difference in the odds of developing anti-SARS-CoV-2 spike protein IgG (odds ratio 1.12 [95% Cl: 0.73–1.72]). Heterologous schemes also showed no difference in the production of neutralizing antibodies (odds ratio 1.48 [95% Cl: 0.72–3.05]) nor vaccine effectiveness in comparison to homologous schemes (odds ratio 1.52 [95% CI: 0.66–3.53]). Accordingly, alternative heterologous COVID-19 vaccinations have shown equivalent antibody response rates and vaccine effectiveness to homologous schemes, potentially aiding global disparity of vaccine distribution.

Table 1 summarizes the scientific evidence supporting the efficacy of HI as an immunisation strategy against COVID-19.

Table 1. Scientific evidence supporting the effectiveness of heterologous immunization as an immunization strategy against COVID-19.

Name of the study	HI Scheme	Results	Reference
Immunogenicity and Reactogenicity of Vaccine Boosters after Ad26.COV2.S Priming.	Heterologous booster vaccination of ChAdOx1 nCoV-19 or Ad26.COV 2-S vaccines BNT162b2 or mRNA-1273. +	1. Homologous or heterologous booster vaccination resulted in higher levels of S-specific binding antibodies, neutralizing antibodies, and T-cell responses than a single Ad26.COV2.S vaccination. 2. The increase in binding antibodies was significantly larger with heterologous regimens that included	SABLEROLLES RSG, et al. N Engl J Med. 2022; 386 (10):951–63. https://doi.org/10.1056/NEJMoa2116747

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		mRNA-based vaccines than with the homologous booster. 3. The mRNA-1273 booster was most immunogenic and was associated with higher reactogenicity than the BNT162b2 and Ad26.COV2.S boosters.	
Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): a single-blind, randomised, phase 2, non-inferiority trial.	First dose of ChAdOx1 nCoV-19 or BNT162b2 + mRNA-1273 [m1273] and a nanoparticle vaccine containing SARS-CoV-2 spike glycoprotein and Matrix-M adjuvant (NVX-CoV2373 [NVX], Novavax).	Heterologous second dosing with m1273, but not NVX, increased transient systemic reactogenicity compared with homologous schedules.	Stuart ASV, et al. Lancet. 2021; 399(10319):36–49. https://doi.org/10.1016/S0140-6736(21)02718-5
Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial.	Two doses of ChAdOx1 nCov-19 or BNT162b2 + third (booster) dose NVX-CoV2373 (Novavax) or Ad26.COV2.S (Janssen) or mRNA1273 (Moderna).	All study vaccines boosted antibody and neutralising responses after ChAd/ChAd initial course and all except one after BNT/BNT, with no safety concerns.	Munro APS, et al. Lancet. 2021; 398(10318):2258–76. https://doi.org/10.1016/S0140-6736(21)02717-3
Two-dose SARS-CoV-2 vaccine effectiveness with mixed schedules and extended dosing intervals: test-negative design studies from British Columbia and Quebec, Canada.	Two-dose vaccine type homologous (mRNA and ChAdOx1) + or Two-dose vaccine type heterologous (mRNA and/or ChAdOx1).	1. Two doses of any mRNA and/or ChAdOx1 combination gave substantial and sustained protection against SARS-CoV-2 hospitalization, spanning Delta-dominant circulation. 2. ChAdOx1 VE against infection was improved by heterologous mRNA series completion. A 7-8-week interval between first and second doses improved mRNA VE and may be the optimal schedule outside	Skowronski DM, et al. Clin Infect Dis. 2022 Nov 30;75(11):1980-1992. doi: 10.1093/cid/ciac290. Erratum in: Clin Infect Dis. 2023 Feb 18;76(4):778-779. doi: 10.1093/cid/ciac584. PMID: 35438175; PMCID: PMC9047203.

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		periods of intense epidemic surge.	
Comparative analysis of COVID-19 vaccine responses and third booster dose-induced neutralizing antibodies against Delta and Omicron variants	Two-dose vaccine type homologous (BNT162b2 and mRNA-1273) + Two-dose vaccine heterologous type adenovirus vector vaccines (ChAdOx1 and Janssen).	1. Two doses of BNT162b2, mRNA-1273, or a combination of ChAdOx1 adenovirus vector and mRNA vaccines administrated with a long 12-week dose interval induce equally high levels of anti-SARS-CoV-2 spike antibodies and neutralizing antibodies against D614 and Delta variant. 2. two doses of BNT162b2 with a short 3-week interval induce 2-3-fold lower titers of neutralizing antibodies than those from the 12-week interval, yet a third BNT162b2 or mRNA-1273 booster dose increases the antibody levels 4-fold compared to the levels after the second dose, as well as induces neutralizing antibody against Omicron BA.1 variant.	Belik M, et al. Nat Commun. 2022 May 5;13(1):2476. doi: 10.1038/s41467-022-30162-5. PMID: 35513437; PMCID: PMC9072399.
Immunogenicity and efficacy of heterologous ChAdOx1–BNT162b2 vaccination	ChAdOx1-S-nCoV-19 + Pfizer BNT162b2 vaccine as a booster.	1. The heterologous ChAdOx1-S-nCoV-19 and BNT162b2 combination confers better protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection than the homologous BNT162b2 and BNT162b2 combination in a real-world observational study of healthcare workers (n = 13,121). 2. Sera from heterologous vaccinated individuals displayed a stronger neutralizing activity regardless of the SARS-CoV-2 variant. 3. The ChAdOx1-S-nCoV-19 vaccine induced a weaker IgG response but a stronger T cell response than the BNT162b2 vaccine after the priming dose, which could explain the complementarity of both	Pozzetto, B., et al. Nature 600, 701–706 (2021). https://doi.org/10.1038/s41586-021-04120-y

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		vaccines when used in combination. 4. The heterologous vaccination regimen could therefore be particularly suitable for immunocompromised individuals.	
Durability of the Effectiveness of Heterologous COVID-19 Vaccine Regimens in Thailand: Retrospective Cohort Study Using National Registration Data	This study focuses on 8 common heterologous vaccine sequences: CoronaVac/ChAdOx1, ChAdOx1/BNT162b2, CoronaVac/CoronaVac/ChAdOx1, CoronaVac/ChAdOx1/ChAdOx1, CoronaVac/ChAdOx1/BNT162b2, BBIBP-CorV/BBIBP-CorV/BNT162b2, ChAdOx1/ChAdOx1/BNT162b2, and ChAdOx1/ChAdOx1/mRNA-1273.	1. The 2-dose heterologous vaccinations offered approximately 50% VE against severe COVID-19 and death following hospitalization with COVID-19 for 2 months; however, the protection significantly declined over time. 2. The 3-dose heterologous vaccinations sustained over 50% VE against both outcomes for at least 8 months, as determined by logistic regression with durability time-interaction modeling. 3. The vaccine sequence consisting of CoronaVac/CoronaVac/ChAdOx1 demonstrated >80% VE against both outcomes, with no evidence of VE waning. 4. The final monthly measured VE of CoronaVac/CoronaVac/ChAdOx1 against severe COVID-19 and death following hospitalization at 7 months after the last dose was 82% (95% CI 80.3%-84%) and 86.3% (95% CI 83.6%-84%), respectively.	Kumwichar P, et al. JMIR Public Health Surveill 2024; 10:e48255 URL: https://publichealth.jmir.org/2024/1/e48255 doi: 10.2196/48255 PMID: 38441923).
A two-arm analysis of the immune response to heterologous boosting of inactivated SARS-CoV-2 vaccines	volunteers who first received two full-dose CoronaVac vaccinations + heterologous boosters with DNA- and/or mRNA-vaccines for an additional 2 doses (n = 40) or an additional 3 doses (n = 16).	1. The results showed no difference in side effects, neutralizing antibodies, or T-cell responses for any of the heterologous vaccination programs. 2. The neutralizing capacity and IFN-γ responses against the Omicron variant in volunteers who received 4 or 5 doses were improved. 3. Polarization of peripheral	Nithichanon A, et al. Sci Rep. 2023 Oct 31; 13(1):18762. doi: 10.1038/s41598-023-46053-8. PMID: 37907584; PMCID: PMC10618206.

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		memory T cells after stimulation in all booster groups with Omicron peptide showed an increased trend of naïve and central memory phenotypes of both CD4+ and CD8+ T cells, suggesting that exposure to Omicron antigens will drive T cells into a lymphoid resident T cell phenotype.	
Heterologous and homologous COVID-19 mRNA vaccination schemes for induction of basic immunity show similar immunogenicity regarding long-term spike-specific cellular immunity in healthcare workers.	homologous (three BTN162b2mRNA doses) + heterologous (mRNA-1273 as third dose building on two BTN162bmRNA doses)	1. Healthcare workers (HCWs) who had hybrid immunity due to breakthrough infections (BTIs) exhibited strong T-cell-reactivity against the Spike-S1-antigen. 2. A lasso regression model revealed a significant reduction in T-cell immune responses among smokers ($p < 0.0001$), with less significant impact observed for age, sex, heterologous vaccination, body-mass-index, Anti-Nucleocapsid T-cell reactivity, days since last COVID-19-immunization, and Anti-SARS-CoV-2-Spike-IgG. 3. Subgroup analysis revealed higher Anti-SARS-CoV-2-Spike-IgG after heterologous vaccination, similar cellular reactivity and percentages of Spike-reactive T- and B-cells were found between homologous and heterologous vaccination. 4. Anti-SARS-CoV-2-Spike-IgG concentrations and avidity significantly correlated with activated T-cells. CD4 + and CD8 + responses correlated. With each other.	Wagenhäuser I, et al. Vaccine. 2024 Aug 30; 42(21):126132. doi: 10.1016/j.vaccine.2024.07.033. Epub 2024 Jul 20. PMID: 39034219
Effectiveness of heterologous and homologous COVID-19 vaccination among immunocompromis	Heterologous and homologous vaccination schemes.	1. The vaccination strategies (heterologous vs homologous) showed no difference in the odds of developing anti-SARS-CoV-2 spike protein IgG (odds ratio	Pardo I, et al. Antimicrob Steward Healthc Epidemiol. 2024 Sep 26; 4(1):e152. doi: 10.1017/ash.2024.369. PMID: 39346662; PMCID: PMC11427957

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ed individuals: a systematic literature review and meta-analysis.	1.12 [95% Cl: 0.73–1.72]). 2. Heterologous schemes also showed no difference in the production of neutralizing antibodies (odds ratio 1.48 [95% Cl: 0.72–3.05]) nor vaccine effectiveness in comparison to homologous schemes (odds ratio 1.52 [95% CI: 0.66–3.53]).

Heterologous immunization (HI).

In Colombia, the vaccine group of the Colombian Consensus for Care, Diagnosis and Management of SARS-CoV-2/COVlD-19 Infection, the Colombian Association of Infectious Diseases (ACIN), and the Advisory Committee of the Ministry of Health and Social Protection, recommended the benefits of applying booster doses with a heterologous or homologous vaccine according to availability in the country, current scientific evidence and in accordance with the progress of vaccination to date [34]. Table 2 illustrates the heterologous and homologous immunization scheme recommended by the Ministry of Health and Social Protection for the Colombian population prioritized according to the availability of biologicals in the national territory [35].

Table 2. Heterologous and homologous immunization scheme in Colombia, according to the Ministry of Health and Social Protection.

Plataform			Immunization
First dose	**Second dose**	**Third dose**	
Pfizer-BioNTech (BNT162b2) (ARNm)	Pfizer-BioNTech (BNT162b2)	Pfizer-BioNTech (BNT162b2)	Homologous
		Moderna (ARNm1273)	Homologous
		Oxford/AstraZeneca (ChAdOx1-S)	heterologous
Moderna (ARNm1273) (ARNm)	Moderna (ARNm1273)	Moderna (ARNm1273)	Homologous
		Pfizer-BioNTech (BNT162b2)	Homologous
		Oxford/AstraZeneca (ChAdOx1-S)	heterologous
Oxford/AstraZeneca (ChAdOx1-S) (Vectorviral)	Oxford/AstraZeneca (ChAdOx1-S)	Oxford/AstraZeneca (ChAdOx1-S)	Homologous
		Pfizer-BioNTech (BNT162b2)	heterologous
		Moderna (ARNm1273)	heterologous
Janssen Ad26.COV2.S (Vector viral)	Janssen Ad26.COV2.S	Janssen Ad26.COV2.S	Homologous
		Pfizer-BioNTech (BNT162b2)	heterologous
		Moderna (ARNm1273)	heterologous
		Oxford/AstraZeneca (ChAdOx1-S)	Homologous
Sinovac-CoronaVac (Virus inactivated)	Sinovac-CoronaVac	Sinovac-CoronaVac	Homologous
		Pfizer-BioNTech (BNT162b2)	heterologous
		Moderna (ARNm1273)	heterologous
		Oxford/AstraZeneca (ChAdOx1-S)	heterologous

Source: Adapted and modified from the Ministry of Health and Social Protection of the Republic of Colombia website.

To date, in the national territory (Colombia), no studies evaluating the effectiveness of heterologous immunization schedules have been documented. This review precedes the experimental trials currently being carried out in our research laboratories.

3. Hybrid Immunity

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The biological concept of "Hybrid Vigor" or "Heterosis" is used in genetics for breeding and selective improvement; which provides an improvement in the characteristics of the various crosses, and offers the opportunity to obtain benefits in the species through the mixture of virtues of its parents, through exogamy [36]. In immunology, something similar occurs when natural immunity is combined with immunity generated by vaccines, particularly SARS-CoV-2 infection, resulting in 25- to 100-fold greater antibody responses, driven by memory B cells and CD4+ T cells, with broader cross-protection against virus variants [37]. The above corresponds to the concept of Hybrid Immunity (HyI), which is defined as a robust immune response developed by vaccinated patients who have previously experienced natural infection by the wild pathogen [38]. Current scientific evidence has shown that this scenario favors a greater immune response, with an increase in the production of neutralizing antibodies, compared to individuals vaccinated with a complete immunization schedule (two or three doses) without previous infection [39]. The immunological benefits of HyI have also been considered as a potential alternative.

HyI is the result of the synergy between natural immunity (acquired through contagion) and artificial immunity (acquired through vaccination) [40]. Scientific evidence has shown that the combination of these two forms of immunity enhances the innate and acquired immune response mechanisms, both humoral and cellular, which results in a better form of protection against infectious diseases, as well as minimizing the severity of these [41]. However, HyI is still the subject of research and it is not known for sure how effective it is compared to all-natural or artificial immunity. Therefore, it is an active area of research today.

In the context of the COVID-19 pandemic, HyI has also been considered as an alternative immunization strategy to combat SARS-CoV-2 infection, the emergence of new variants and the maintenance of immunity in prioritized populations. [42]. There are recent studies that suggest that HyI is more effective in preventing SARS-CoV-2 infection than usual forms such as infection or vaccination [43]. For example, Bobrovitz [44] conducted a systematic review and meta-regression to evaluate the magnitude and duration of the protective efficacy of prior SARS-CoV-2 infection and HyI against infection and severe disease caused by the Omicron variant. The results of the study showed that both previous infection alone and previous infection combined with vaccination, conferred rapidly decreasing protection against SARS-CoV-2 infection with the Omicron variant, but high protection and sustained against hospital admission or severe illness related to the same variant. Previous infection was found to provide greater protection against reinfection and more sustained protection against hospital admission or severe disease than vaccination alone. However, individuals with HyI presented the greatest magnitude and duration of protection against all outcomes, highlighting the importance of vaccinating previously infected individuals.

3.1. Evidence of the Advantages of Hybrid Immunity in the Context of Vaccination Against SARS-CoV-2/COVID-19

The study by Reynolds [45], titled "Prior SARS-CoV-2 infection rescues B and T cell responses to variants after first vaccine dose", with the aim of determining whether vaccination with a single dose (Pfizer/BioNTech messenger RNA vaccine BNT162b2), in individuals with and without previous infection (Wuhan-Hu-1 SARS-CoV-2), confers cross-immunity against SARS-CoV-2 variants. It showed that individuals with previous infection, after a single dose of the vaccine, showed a greater cellular response (mediated by T lymphocytes), and a greater humoral response (antibody-secreting memory B lymphocytes) against the SARS-CoV-2 S protein, with effective neutralizing antibodies against the B.1.1.7 and B.1.351 variants; compared to individuals vaccinated with the same dose without preceding infection. Noting that, vaccination with a single dose of BNT162b2 in the context of a previous infection with a heterologous variant substantially increases neutralizing antibody responses against the variants of interest and concern.

Krammer [46], in the PARIS (Protection Associated with Rapid Immunity to SARS-CoV-2) study, showed that pre-existing immunity against SARS-CoV-2 generates a greater antibody response compared to immunologically naïve participants against the new coronavirus. The titers of

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Immunoglobulin G (IgG) type antibodies against the S protein were 25 times higher compared to the control group with a complete vaccination schedule using the mRNA platforms (mRNA: Vaccines BNT162b2 [Pfizer] and mRNA-1273 [Moderna]), respectively. Antibody levels in the group with pre-existing immunity were observed to be significantly elevated 8 days after the 1st vaccination dose. Participants who had no prior immunity failed to achieve the same antibody titers even with the full two-immunization schedule. When comparing the antibody titers in the group with previous immunity, with a complete vaccination schedule (two doses), no statistically significant differences were observed between the 1st dose and the 2nd dose. The researchers conclude that a single dose of vaccine (BNT162b2 [Pfizer] and mRNA-1273 [Moderna]) is sufficient to achieve high titers of IgG antibodies against the S protein of SARS-CoV-2.

The study carried out by Cavanaugh [47], entitled "Reduced risk of reinfection with SARS-CoV-2 after COVID-19 vaccination—Kentucky, May–June 2021" with the objective of determining the association between vaccination and reinfection with SARS- CoV-2 among people previously infected with SARS-CoV-2 in 2020. They observed that previously infected individuals who were not vaccinated were 2.34 times more likely to be reinfected (OR = 2.34; 95% CI = 1.58-3.47) compared to those who were fully vaccinated; partial vaccination was not significantly associated with reinfection (OR = 1.56; 95% CI = 0.81-3.01). The group of researchers concludes that vaccination against COVID-19 is necessary for all eligible people, regardless of their prior SARS-CoV-2 infection status. The HyI generated helps to reduce cases of reinfection compared to the unvaccinated. These results were reproducible in a cohort study with a population of 325,157 individuals from the United States; the results showed that among vaccinated individuals who received two doses, those with previous infection had greater protection (86,8%; 95% CI). %: 74,5%-93,2%) against SARS-CoV-2 reinfections compared to those who had vaccine immunity without preceding infection [48].

Goel [49], at the Institute of Immunology at the University of Pennsylvania, USA, observed that antibody titers against the S protein and RBD (Receptor Binding Domain) region of SARS-CoV-2 are higher in individuals who had overcome previous infection by the new coronavirus compared to participants who had not had previous infection. The researchers also evaluated the memory B cell response, finding that participants with prior vaccine infection, after being immunized with the BNT162b2 (Pfizer) and mRNA-1273 (Moderna) vaccines, developed a 10-fold memory humoral response. Higher than individuals who had received a complete vaccination schedule without previous infection. Another important aspect in the study was the antibody response against the new variants of concern. The researchers analyzed the humoral response against the D614G strain (dominant strain at the beginning of the study) and the B.1.351 variant, observing that participants who had overcome infection initially by SARS-CoV-2 and subsequently vaccinated, they developed neutralizing antibodies against the ancestral strain and the variant of concern. Unlike patients who had only received a complete immunization schedule, they observed that antibody levels were statistically lower with limited capacity to neutralize the new variant of concern. All these findings support the proposal to take advantage of HyI as a new mass immunization strategy against SARS-CoV-2 [50].

In India, through a follow-up of patients with autoimmune rheumatic diseases, in a cohort of 30 patients with previous SARS-CoV-2 infection and application of a complete vaccination schedule compared to 90 patients who had had COVID-19 in recent years. 6 months, but they had not received any vaccinations. There was 100% seroconversion in the infection plus vaccine group, compared to 90% in the double-dose vaccine group without prior infection ($p<0.0001$); Greater neutralization capacity was also evident (87% patients with at least 30% neutralization) compared to the double-dose vaccine group (60%; $p=0.039$). The neutralization test showed a moderate correlation (Pearson R 0.35; $p<0.001$) with antibody titers. The observed data show that the concept of HyI must be recognized and used in planning vaccination policies against SARS-CoV-2 [51].

In Qatar, Abu-raddad [52] conducted a study in a population that had received a complete two-dose mRNA vaccine schedule and compared the results in those participants with and without prior SARS-CoV-2 infection. The adjusted risk ratio (with 95% CI) for SARS-CoV-2 infections at 120 days

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of follow-up in the group with and without a previous infection was 0.18 (0.15 - 0.21) for those vaccinated with BNT162b2, and 0.35 (0.25 - 0.48) for those vaccinated with mRNA-1273. Serious illnesses were very rare in this study, with no deaths reported from COVID-19.

The study by Schimidt [53], titled "High genetic barrier to escape from human polyclonal SARS-CoV-2 neutralizing antibodies", showed that 20 natural or spontaneous mutations in the S protein of SARS-CoV-2 are sufficient to confer an almost complete resistance to polyclonal neutralizing antibodies generated by convalescent patients and recipients of the mRNA vaccine. However, the researchers identified that in the plasma of individuals who had been infected and subsequently received the mRNA vaccine, they had the ability to neutralize this variant (polymutant) of SARS-CoV-2 with high titers of neutralizing antibodies. This supports the thesis that HyI favors the synthesis of highly diverse antibodies with the capacity to neutralize various variants of SARS-CoV-2.

Crotty [54] demonstrated that HyI against SARS-CoV-2 is more powerful than the immune response generated after natural infection. The synergy between both responses is evidenced mainly in the antibody response (humoral) rather than in the T cell response (cellular) after vaccination. Although the enhanced antibody response depends on memory T cells, which is known as a thymodependent humoral response. Other favorable results were found by the group of Stamatatos [55], with the work titled "mRNA vaccination boosts cross-variant neutralizing antibodies elicited by SARS-CoV-2 infection". With the aim of showing the importance of vaccinating both uninfected and previously infected people to obtain cross-neutralizing antibodies. Under the methodology of a clinical trial using sera from recovered patients before and after immunization with messenger RNA vaccines. It resulted in the majority of previously infected subjects benefiting from a single immunization with the Pfizer-BioNTech or Moderna vaccines, as it resulted in a significant increase in serum natural antibody responses against variants matching the vaccine and emerging ones. Additionally, they suggest that the second dose of an mRNA vaccine could be delayed in some people who have previously been infected by SARS-CoV-2. It was also concluded that the application of a single biological, in previously infected patients, generates immunity against reinfection, however, those who obtained the mRNA vaccine such as Pfizer and Moderna probably the waiting time could be longer for the second dose of application.

The Spanish magazine of Public Health report a descriptive and retrospective cohort study in the resident population with a COVID-19 outbreak was the opportunity to study the effect of HyI on transmission, infection progression and viral load. The attack rate was 59%. The clinical spectrum was the same in both sexes. There was a notable protective effect of HyI against transmission (67%). In terms of progression, those with HyI had a lower risk of symptomatic infection. Nasopharyngeal viral load was significantly lower in individuals with HyI and in asymptomatic individuals, supporting the idea of lower transmissibility in this group [56].

Sheng [57] conducted a meta-analysis in which the effectiveness of HyI as a strategic alternative to mitigate reinfection by the dominant Omicron variant was evaluated. It was evident that compared with the natural immunity group, the HyI (booster vaccination) group had the highest level of mitigation in the risk of reinfection (OR = 0.43, 95% CI: 0.34–0.56), followed by the complete vaccination group (OR = 0.58, 95% CI: 0.45–0.74), and lastly the incomplete vaccination group (OR = 0.64, 95% CI: 0.44–0.93). Compared with the complete vaccination-only group, the HyI (complete vaccination) group mitigated the risk of reinfection by 65% (OR = 0.35, 95% CI: 0.27–0.46), and the HyI (booster vaccination) group mitigated the risk of reinfection by an additional 29% (OR = 0.71, 95% CI: 0.61–0.84) compared with the HyI (complete vaccination) group. The effectiveness of HyI (incomplete vaccination) in mitigating the risk of reinfection was 37,8% (95% CI, 28,8–46,8%) within 270–364 days, and decreased to 33,2%% (95% CI, 23,8–42,6%) within 365–639 days; whereas, the effectiveness after complete vaccination was 54,3% (95% CI, 50,8–57,9%) within 270–364 days, and the effectiveness of booster vaccination was 73,4% (95% CI, 68,9–78,0%) within 90–119 days.

Table 3 summarizes the scientific evidence supporting the effectiveness of HyI as an immunization strategy against COVID-19.

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Table 3. Scientific evidence supporting the effectiveness of HyI as an immunization strategy against COVID-19.

Clinical trial	diseases	Vaccine	Objetive
Prior SARS-CoV-2 infection rescues B and T cell responses to variants after first vaccine dose.	Covid19	Pfizer/BioNTech BNT162b2	Investigated if single dose vaccination, with or without prior infection, confers cross protective immunity to variants. We analyzed t and b cell responses after first dose vaccination.
Antibody responses in seropositive persons after a single dose of SARS-CoV-2 mRNA vaccine.	Covid19	BNT162b2 [pfizer] and mRNA-1273 [moderna]	Investigated what is the response would be to the first vaccine dose in persons with previous covid-19.
Duration of severe acute respiratory syndrome coronavirus 2 natural immunity and protection	Covid19	Kim P, et al. Clin Infect Dis. 2022; 75(1):e185-e190. doi: 10.1093/cid/ciab999.	Investigate the effectiveness of previous infection against the delta variant and duration of natural immunity.

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against the delta variant: a retrospective cohort study.			
Distinct antibody and memory B cell responses in SARS-CoV-2 naïve and recovered individuals following mRNA vaccination.	Covid19	BNT162b2 (pfizer) and mRNA-1273 (moderna)	Investigate the response of antibody and antigen-specific memory b cells over time.
Hybrid Immunity Versus Vaccine-Induced Immunity Against SARS-CoV-2 in Patients With Autoimmune Rheumatic Diseases.	Covid19	ChAdOx1 vaccine	Investigate the immune response in hybrid immunity for the planning vaccination policies.
Association of prior SARS-CoV-2 infection with risk of breakthrough infection	Covid19	BNT162b2 (pfizer-biontech) and mRNA-1273 (moderna)	To assess protection from sars-cov-2 breakthrough infection after mRNA vaccination among persons

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following mRNA vaccination in Qatar.			with vs without prior sars-cov-2 infection.
High genetic barrier to SARS-CoV-2 polyclonal neutralizing antibody escape.	Covid19	mRNA vaccine	Study of the polyclonal neutralizing antibody.
Hybrid immunity to SARS-CoV-2 in kidney transplant recipients and hemodialysis patients.	Covid19	BNT162b2 mRNA	Study what kind of Immunity develops people with natural immunity who are subsequently vaccinated.
mRNA vaccination boosts cross-variant neutralizing antibodies elicited by SARS-CoV-2 infection.	Covid19	Pfizer-biontech o moderna	Examine if sera from patients prior to, and following immunizations with existing mRNA vaccines could neutralize the wuhan-hu-1 and b.1.351 variants.
COVID-19 outbreak in a home in correctly	Covid19	Comirnaty	Study the effect of hybrid immunity on transmission,

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vaccinated elderly people. Influence of hybrid immunity on viral load, risk of infection and risk of disease progression.			infection progression and viral load on this covid-19 outbreak.

4. Conclusion

SARS-CoV-2 infection and its triggering pathology COVID-19 remain a priority public health problem worldwide. Two years after the end of the COVID-19 pandemic, SARS-CoV-2 remains one of the most worrying pathogens with high pandemic potential [58]. Although epidemiological rates of mortality and morbidity have declined significantly, vaccination against SARS-CoV-2 is the most important health tool to maintain disease control and provide long-term immunity. New immunization strategies, HI and HyI, have been shown to be effective and safe in different clinical settings globally. The immunological mechanisms underlying the observed benefits are not yet fully understood, so this is an active area of research at the basic and clinical science level. In the public health context, the consolidation of these immunization strategies provide a favourable environment for community health. This new knowledge serves as a basis for responding to future health emergencies associated with immuno-preventable diseases.

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References

1. Excler J-L: Saville M, Privor-Dumm L, et al. Factors, enablers and challenges for COVID- 19 vaccine development. BMJ Glob Health 2023;8:e011879.doi:10.1136/ bmjgh-2023-011879).
2. Shattock AJ, Johnson HC, Sim SY, Carter A, Lambach P, Hutubessy RCW, et al. Contribution of vaccination to improved survival and health: modelling 50 years of the Expanded Programme on Immunization. Lancet. 2024 May 25; 403(10441):2307-2316. doi: 10.1016/S0140-6736(24)00850-X. Epub 2024 May 2. PMID: 38705159; PMCID: PMC11140691).
3. Hogan AB, Wu SL, Toor J, Olivera Mesa D, Doohan P, Watson OJ, et al. Long-term vaccination strategies to mitigate the impact of SARS-CoV-2 transmission: A modelling study. PLoS Med. 2023 Nov 28; 20(11):e1004195. doi: 10.1371/journal.pmed.1004195. PMID: 38016000; PMCID: PMC10715640).
4. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020 Apr; 5(4):536-544. doi: 10.1038/s41564-020-0695-z. Epub 2020 Mar 2. PMID: 32123347; PMCID: PMC7095448.

 doi:10.20944/preprints202506.1872.v1

5. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020; 323(13):1239-42.
6. Ferdinands JM, Rao S, Dixon BE, Mitchell PK, DeSilva MB, Irving SA, et al. Waning 2-dose and 3-dose effectiveness of mRNA vaccines against COVID-19-associated emergency department and urgent care encounters and hospitalizations among adults during periods of Delta and Omicron variant predominance — VISION Network, 10 states, August 2021–January 2022. *MMWR Morb Mortal Wkly Rep*. 2022; 71(7):255-63.
7. Chemaitelly H, Ayoub HH, AlMukdad S, Coyle P, Tang P, Yassine HM, et al. Duration of mRNA vaccine protection against SARS-CoV-2 Omicron BA.1 and BA.2 subvariants in Qatar. *Nat Commun*. 2022; 13(1):3082.
8. Di Fusco M, Lin J, Vaghela S, Lingohr-Smith M, Nguyen JL, Scassellati Sforzolini T, Judy J, Cane A, Moran MM. COVID-19 vaccine effectiveness among immunocompromised populations: a targeted literature review of real-world studies. Expert Rev Vaccines. 2022 Apr; 21(4):435-451. doi: 10.1080/14760584.2022.2035222. Epub 2022 Feb 3. PMID: 35112973; PMCID: PMC8862165.
9. Bayani F, Hashkavaei NS, Arjmand S, Rezaei S, Uskoković V, Alijanianzadeh M, Uversky VN, Ranaei Siadat SO, Mozaffari-Jovin S, Sefidbakht Y. An overview of the vaccine platforms to combat COVID-19 with a focus on the subunit vaccines. Prog Biophys Mol Biol. 2023 Mar; 178:32-49. doi: 10.1016/j.pbiomolbio.2023.02.004. Epub 2023 Feb 18. PMID: 36801471; PMCID: PMC9938630.
10. Konje JC, Al Beloushi M, Ahmed B. Immunisation against COVID-19 in Pregnancy and of Women Planning Pregnancy. Viruses. 2023 Feb 24; 15(3):621. doi: 10.3390/v15030621. PMID: 36992330; PMCID: PMC10059008.
11. Atmar RL, Lyke KE, Deming ME, Jackson LA, Branche AR, Sahly HM, et al. Homologous and Heterologous Covid-19 Booster Vaccinations. N Engl J Med. 2022; 386(11):1046–57. https://doi.org/10.1056/NEJMoa2116414 PMID: 35081293
12. World Health Organization. Interim recommendations for heterologousCOVID-19 vaccine schedules. [cited 2022 Feb 7]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE- recommendation-heterologous-schedules.
13. Agrawal B. Heterologous Immunity: Role in Natural and Vaccine-Induced Resistance to Infections. Front. Immunol. 2019;10:2631.doi: 10.3389/fimmu.2019.02631
14. Singh S, Yanow SK, Agrawal B. Editorial: Heterologous Immunity: Implications and Applications in Vaccines and Immunotherapies. Front. Immunol. 2020; 11:1408.doi: 10.3389/fimmu.2020.01408.
15. Monath TP, Levenbook I, Soike K, Zhang ZX, Ratterree M, Draper K, BarrettAD, Nichols R, Weltzin R, Arroyo J, Guirakhoo F. Chimeric yellow fever virus 17D- Japanese encephalitis virus vaccine: dose-response effectiveness and extended safety testing in rhesus monkeys. J Virol. 2000 Feb; 74(4):1742-51. doi: 10.1128/jvi.74.4.1742-1751.2000.
16. Katzelnick LC, Gresh L, Halloran ME, Mercado JC, Kuan G, Gordon A, et al. Antibody-dependent enhancement of severe dengue disease in humans. Science. (2017) 358:929–32. doi: 10.1126/science.aan6836.
17. Sablerolles RSG, Rietdijk WJR, Goorhuis A, Postma DF, Visser LG, Geers D,et al. Immunogenicity and Reactogenicity of Vaccine Boosters after Ad26.COV2.S Priming. N Engl J Med. 2022; 386 (10):951–63. https://doi.org/10.1056/NEJMoa2116747
18. Stuart ASV, Shaw RH, Liu X, Greenland M, Aley PK, Andrews NJ, et al. Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): a single-blind, randomised, phase 2, non-inferiority trial. Lancet. 2021; 399(10319):36–49. https://doi.org/10.1016/S0140-6736(21)02718.
19. Munro APS, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet. 2021; 398(10318):2258–76. https://doi.org/10.1016/S0140-6736(21)02717-3
20. WHO. Evidence to recommendations for COVID-19 vaccines: evidence framework: a framework to inform the assessment of evidence and formulation of subsequent COVID-19 vaccine recommendations, 10

 doi:10.20944/preprints202506.1872.v1

December 2020. Ginebra: Organización Mundial de la Salud; 2020 (https://www.who.int/publications/i/item/WHO-2019-nCoVSAGE-Framework- Evidence-2020-1, consultado el 27 de mayo de 2021).

21. WHO. Background document on the mRNA vaccine BNT162b2 (Pfizer- BioNTech) against COVID-19: background document to the WHO interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under emergency use listing, 14 January 2021. Ginebra: Organización Mundial de la Salud; 2021 (https://www.who.int/publications/i/item/background-document-on- mRNA-vaccine-bnt162b2-(pfizer-biontech)-against- covid-19.
22. Guidance for the development of evidence-based vaccination recommendations; 2020 https://www.who.int/immunization/sage/Guidelines_development_recommendation s.pdf.
23. WHO. Annexes to the recommendations for use of the Moderna mRNA-1273 vaccine against COVID-19. (https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-mRNA-1273-GRADE-ETR-annexes, accessed 19 November 2021).
24. Skowronski DM, Setayeshgar S, Febriani Y, Ouakki M, Zou M, Talbot D et al. Two-dose SARS-CoV-2 vaccine effectiveness with mixed schedules and extended dosing intervals: test-negative design studies from British Columbia and Quebec, Canada. medRxiv. 2021:2021.10.26.21265397. doi: 10.1101/2021.10.26.21265397.
25. Organization. WH. Interim statement on decision-making considerations for the use of variant updated COVID-19 vaccines. 2022 (https://www.who.int/news/item/17-06-2022-interim-statement-on-decision-making- considerations-for-the-use-of-variant-updated-covid-19-vaccines.
26. Belik M, Jalkanen P, Lundberg R, Reinholm A, Laine L, Väisänen E, et al. Comparative analysis of COVID-19 vaccine responses and third booster dose- induced neutralizing antibodies against Delta and Omicron variants. Nat Commun 2022; 13:2476. https://doi.org/10.1038/s41467-022-30162-5
27. Pozzetto B, Legros V, Djebali S, Barateau V, Guibert N, Villard M, et al. Immunogenicity and efficacy of heterologous ChAdOx1–BNT162b2 vaccination. Nature 2021; 600:701–706 (2021). https://doi.org/10.1038/s41586-021-04120-y
28. SAGE updates COVID-19 vaccination guidance. https://www.who.int/news/item/28-03-2023-sage-updates-covid-19-vaccination- guidance
29. Highlights from the Meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization 20-22 March 2023. https://www.who.int/news/item/28-03- 2023-sage-updates-covid-19-vaccination-guidance
30. Kumwichar P, Poonsiri C, Botwright S, Sirichumroonwit N, Loharjun B, Thawillarp S, et al. Durability of the Effectiveness of Heterologous COVID-19 Vaccine Regimens in Thailand: Retrospective Cohort Study Using National Registration Data JMIR Public Health Surveill 2024;10:e48255 URL: https://publichealth.jmir.org/2024/1/e48255 doi: 10.2196/48255 PMID: 38441923).
31. Nithichanon A, Kamuthachad L, Salao K, Phoksawat W, Kamsom C, Wongratanacheewin S, et al. A two-arm analysis of the immune response to heterologous boosting of inactivated SARS-CoV-2 vaccines. Sci Rep. 2023 Oct 31; 13(1):18762. doi: 10.1038/s41598-023-46053-8. PMID: 37907584; PMCID: PMC10618206).
32. Wagenhäuser I, Almanzar G, Förg FB, Stein A, Eiter I, Reusch J, et al. Heterologous and homologous COVID-19 mRNA vaccination schemes for induction of basic immunity show similar immunogenicity regarding long-term spike-specific cellular immunity in healthcare workers. Vaccine. 2024 Aug 30; 42(21):126132. doi: 10.1016/j.vaccine.2024.07.033. Epub 2024 Jul 20. PMID: 39034219).
33. Pardo I, Maezato AM, Callado GY, Gutfreund MC, Hsieh MK, Lin V, et al. Effectiveness of heterologous and homologous COVID-19 vaccination among immunocompromised individuals: a systematic literature review and meta-analysis. Antimicrob Steward Healthc Epidemiol. 2024 Sep 26; 4(1):e152. doi: 10.1017/ash.2024.369. PMID: 39346662; PMCID: PMC11427957).
34. Resolución 1866 de 2021, Ministerio de Salud y Protección Social, República de Colombia. https://vlex.com.co/vid/resolucion-numero-001866-2021-878621762
35. Esquema de inmunización heteróloga y homologa recomendada por el Ministerio de Salud y Protección Social. https://www.minsalud.gov.co/salud/publica/Vacunacion/paginas/vacunacion-covid-19.aspx

 doi:10.20944/preprints202506.1872.v1

36. Birchler JA, Yao H, and Chudalayandi S. Unraveling the genetic basis of hybrid vigor. PNAS 2006; 103(35):12957–12958.
37. Prendecki M., Clarke C., Brown J., Cox A., Gleeson S., Guckian M., et al. Effect of previous SARS-CoV-2 infection on humoral and Tcell responses to single- dose BNT162b2 vaccine. The Lancet 2021; 397:1178-1181.
38. Mazzoni A, Di Lauria N, Maggi L, Salvati L, Vanni A, Capone M, et al. First- dose mRNA vaccination is sufficient to reactivate immunological memory to SARS- CoV-2 in subjects who have recovered from COVID-19. J Clin Invest. 2021; 131(12):e149150. doi: 10.1172/JCI149150. PMID: 33939647; PMCID: PMC8203460.
39. Saadat S, Tehrani Z.R, Logue J, Newman M, Frieman M.B, Harris A.D, et al. Single Dose Vaccination in Healthcare Workers Previously Infected with SARS-CoV- 2. medRxiv, 2021; 2021.2001.2030.21250843.
40. Hall V, Foulkes S, Insalata F, et al. Protection against SARS-CoV-2 after Covid-19 Vaccination and Previous Infection. N Engl J Med 2022; 386(13): 1207-20.
41. Tenforde MW, Link-Gelles R, Patel MM. Long-term Protection Associated With COVID-19 Vaccination and Prior Infection. JAMA 2022; 328(14): 1402-4.
42. Shrestha NK, Shrestha P, Burke PC, Nowacki AS, Terpeluk P, Gordon SM. Coronavirus Disease 2019 (COVID-19) Vaccine Boosting in Previously Infected or Vaccinated Individuals. Clin Infect Dis 2022.
43. Richardson SI, Madzorera VS, Spencer H, et al. SARS-CoV-2 Omicron triggers cross-reactive neutralization and Fc effector functions in previously vaccinated, but not unvaccinated, individuals. Cell Host Microbe 2022; 30(6): 880-6 e4.
44. Bobrovitz N, Ware H, Ma X, Li Z, Hosseini R, Cao C, et al. Protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against the omicron variant and severe disease: a systematic review and meta-regression. Lancet Infect Dis 2023; 23: 556–67. https://doi.org/10.1016/S1473-3099 (22)00801- 5
45. Reynolds CJ, Pade C, Gibbons JM, Butler DK, Otter AD, Menacho K, et al. Prior SARS-CoV-2 infection rescues B and T cell responses to variants after first vaccine dose. Science. 2021; 372(6549):1418–23. doi: 10.1126/science.abh1282.
46. Krammer F, Srivastava K, Alshammary H, Amoako AA, Awawda MH, Beach KF, et al. Antibody Responses in Seropositive Persons after a Single Dose of SARS- CoV-2 mRNA Vaccine. N Engl J Med. 2021; 384(14):1372-1374. doi: 10.1056/NEJMc2101667.
47. Cavanaugh AM, Spicer KB, Thoroughman D, Glick C, Winter K. Reduced Risk of Reinfection with SARS-CoV-2 After COVID-19 Vaccination - Kentucky, May-June 2021. MMWR Morb Mortal Wkly Rep. 2021 Aug 13; 70(32):1081-1083. doi: 10.15585/mmwr.mm7032e1.
48. Kim P, Gordon SM, Sheehan MM, Rothberg MB. Duration of Severe Acute Respiratory Syndrome Coronavirus 2 Natural Immunity and Protection Against the Delta Variant: A Retrospective Cohort Study. Clin Infect Dis. 2022; 75(1):e185-e190. doi: 10.1093/cid/ciab999.
49. Goel RR, Apostolidis SA, Painter MM, Mathew D, Pattekar A, Kuthuru O, et al. Distinct antibody and memory B cell responses in SARS-CoV-2 naïve and recovered individuals after mRNA vaccination. Sci. Immunol. 2021; 6:1-13. 10.1126/sciimmunol.abi6950.
50. Shrestha NK, Burke PC, Nowacki AS, Terpeluk P, Gordon SM. Necessity of Coronavirus Disease 2019 (COVID-19) Vaccination in Persons Who Have Already Had COVID-19. Clin Infect Dis. 2022; 75(1):e662-e671. doi: 10.1093/cid/ciac022.
51. Shenoy P, Ahmed S, Paul A, Cherian S, Umesh R, Shenoy V, et al. Hybrid immunity versus vaccine-induced immunity against SARS-CoV-2 in patients with autoimmune rheumatic diseases. Lancet Rheumatol. 2022 ;(2):e80-e82. doi: 10.1016/S2665-9913(21)00356-8.
52. Abu-Raddad LJ, Chemaitelly H, Ayoub HH, Yassine HM, Benslimane FM, Al Khatib HA, et al. Association of Prior SARS-CoV-2 Infection With Risk of Breakthrough Infection Following mRNA Vaccination in Qatar. JAMA. 2021; 326(19):1930-1939. doi: 10.1001/jama.2021.19623.
53. Schmidt F, Weisblum Y, Rutkowska M, Poston D, DaSilva J, Zhang F, et al. High genetic barrier to SARS-CoV-2 polyclonal neutralizing antibody escape. Nature. 2021; 600(7889):512-516. doi: 10.1038/s41586-021-04005-0.

 doi:10.20944/preprints202506.1872.v1

54. Crotty S. Hybrid Immunity. COVID-19 vaccine responses provide insights into how the immune system perceives threats. Science 2021; 372:1392-1393.
55. Stamatatos L, Czartoski J, Wan YH, Homad LJ, Rubin V, Glantz H, et al. mRNA vaccination boosts cross-variant neutralizing antibodies elicited by SARS- CoV-2 infection. Science. 2021; 372(6549):1413–8. doi: 10.1126/science.abg9175. Epub ahead of print.
56. Gascó-Laborda JC, Gil-Fortuño M, Ortiz-Rambla J, Meseguer Ferrer N, Pérez-Olaso Ó, Lluch-Bacas L, et al. COVID-19 outbreak in a properly vaccinated nursing home. Influence of hybrid immunity on viral load, risk of infection and risk of disease progression [Brote de la COVID-19 en una residencia en ancianos correctamente vacunados. Influencia de la inmunidad híbrida en la carga viral, el riesgo de infección y el riesgo de progresión de la enfermedad]. Rev Esp Salud Publica. 2024 May 24; 98:e202405036. Spanish. PMID: 38785412.
57. Ref. Zheng H, Wu S, Chen W, Cai S, Zhan M, Chen C, Lin J, Xie Z, Ou J and Ye W (2024) Meta-analysis of hybrid immunity to mitigate the risk of Omicron variant reinfection. Front. Public Health 12:1457266. doi: 10.3389/fpubh.2024.1457266).
58. Salmanton-García J, Wipfler P, Leckler J, Nauclér P, Mallon PW, Bruijning-Verhagen PCJL. Et al. Predicting the next pandemic: VACCELERATE ranking of the WorldHealth Organization's Blueprint forAction toPreventEpidemics. Travel Med Infect Dis. 2024; 57:102676. doi: 10.1016/j.tmaid.2023.102676.