Antibody response to different COVID-19 vaccine regimes: a review

Resposta de anticorpos a diferentes regimes vacinais contra a COVID-19: uma revisão

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ABSTRACT
COVID-19 pandemic initiated a race for the development of vaccines. Different technologies have been used to produce them, including inactivated whole-virus, nucleic acid, and adenovirus vector platforms. COVID-19 vaccination was initiated with two doses called "primary vaccination" which can be homologous (the same vaccine used in the first and second dose) or heterologous (different vaccines used in the first and second dose). Waning of vaccine-induced antibodies over time combined with the emerging SARS-CoV-2 variants of concern (VOCs) suggested the importance and necessity of a "booster shot" of the vaccine. The additional dose can be done with the same vaccine used in the primary vaccination (homologous booster) or vaccines can be mix-and-match (heterologous booster). Immune escape of VOCs raises the question of which is the best combination of COVID-19 vaccines. Therefore, this review summarizes the main findings of humoral response to different SARS-CoV-2 vaccination regimens.

Keywords: COVID-19 vaccines, primary vaccination, heterologous, homologous, booster shot.

RESUMO
A pandemia de COVID-19 iniciou uma corrida pelo desenvolvimento de vacinas. Diferentes tecnologias têm sido usadas para produzi-las, incluindo plataformas de vírus inteiro inativados, ácido nucleico e vetor de adenovírus. A vacinação contra a COVID-19 foi iniciada com duas doses denominadas "vacinação primária", que podem ser homólogas (a mesma vacina utilizada na primeira e segunda doses) ou heterólogas (vacinas diferentes utilizadas na primeira e segunda doses). A diminuição dos anticorpos induzidos pela vacina ao longo do tempo, combinados com as variantes emergentes de risco SARS-CoV-2 (COVs), sugerem a importância e a necessidade de uma "dose de reforço" da vacina. A dose adicional pode ser feita com a mesma vacina usada na vacinação primária (reforço homólogo) ou vacinas podem ser misturadas e combinadas (reforço heterólogo). A fuga imunitária de COV levanta a questão de saber qual é a melhor combinação de vacinas contra a COVID-19. Portanto, esta revisão resume os principais achados da resposta humoral aos diferentes esquemas de vacinação contra SARS-CoV-2.

Palavras-chave: vacinas contra a COVID-19, vacinação primária, heteróloga, homóloga, dose de reforço.

1 INTRODUCTION

Officially, COVID-19 pandemic has caused more than 6.8 million deaths since February 2020 (1). However, there is an estimate that the unreported deaths are about 2.7 times higher (2). This health emergency initiated a race for the development of vaccines (3,4). Different technology platforms have been used to produce these vaccines, including nucleic acid, adenovirus vector and inactivated whole-virus, all of them work by exposing the body to portions of the virus (antigens) to provoke an immune response without causing disease (5,6). Until February 2023, the world received more than 13,1 trillion doses of different types of vaccines against COVID-19 (1,7).

Generally, vaccination traditionally known to be effective requires immunization of an individual with two or more doses (8). A prime-boost immunization strategy is defined as immunization with prime and booster doses, when the vaccines used in the first and following doses are the same such regime is called homologous. On the other hand, an immunization regime involving a different vaccine from the primary vaccine is called heterologous, a "mix-and-match" strategy (9,10). Several factors including selection of antigen, type of vector, delivery route, dose, adjuvant, boosting regimen, the order of vector injection can influence the outcome of immunization approaches (11).

Like other coronaviruses, SARS-CoV-2 is a highly transmissible virus, which promotes a rapid emergence of variants of concern (VOCs) (12) and reinfections (13–16). The genome of SARS-CoV-2 encodes four conserved structural proteins, spike (S), envelope (E), membrane (M), and nucleocapsid (N) (17,18). SARS-CoV-2 infects host cells through its S protein or more specifically through its key portion called receptor-binding domain (RBD). The RBD is responsible for binding to cellular receptor angiotensin-converting enzyme 2 (ACE2) in host cells and mediates virus entry (19). When the virus enters the cell, leads to the activation of the immune cells (20). Immune escape has been caused by mutations in the viral protein S, causing breakthrough infections, and leading to reduced effectiveness of vaccines with newly appearing variants (21).

Concerns over the immune escape of VOCs and waning immunity suggested the importance and necessity of additional doses of COVID-19 vaccines, called booster doses or booster shots (22). In this way, the application of the third or even fourth booster shot was a strategy implemented to combat the COVID-19 pandemic (23,24). The COVID-19 vaccine booster provides a further enhancement or restores protection in fully vaccinated recipients. Boosters can also be homologous or heterologous (25,26). While the immunogenicity of COVID-19 vaccines has been characterized in several well-conducted clinical trials, real-world evidence concerning immune responses against SARS-CoV-2 raised by such vaccines is currently missing. The monitoring of post-vaccination immune response is essential to understand the protection and durability of immunity, evaluate the performance of different vaccination regimens, and clarify the need for further booster doses. Data about the dynamics of antibody response following COVID-19 vaccination are still limited. Therefore, this study aimed to review the literature on antibody response after primary vaccination (Table 1) and after a booster shot (Table 2).

Table 1. Vaccine schedule of primary vaccination and the respective manuscripts evaluated in this review.

	Primary vaccination		
Vaccine schedule	**Technology Platform**	**Name of vaccine (vaccine manufacturer)**	**Reference**
Homologous	Inactivated virus	CoronaVac (Sinovac)	Fonseca et al. (2022); Bayram et al., (2021); Dinc et al., (2022)
		BBIBP-CorV WIBP-CorV (Sinopharm)	Li et al. (2021)
	mRNA	BNT162b2 (Pfizer)	Lustig et al., (2021); Herzberg et al., (2022) and Pozzetto et al., (2021); Chivu-economescu et al., (2022); Brisotto et al. (2021); Shields et al., (2021); Naaber et al., (2021)
		mRNA-1273 (Moderna)	Brisotto et al. (2021)
	Viral vector vaccine	AZD1222/ChAdOx1 (AstraZeneca)	Mishra et al., (2021); Choudhary et al., (2021); Barros-Martins et al., (2021)
Heterologous	Viral Vector plus mRNA	ChAdOx1-S-nCoV-19 and BNT162b2	Pozzetto et al., (2021); Barros-Martins et al., (2021)

Source: created by the author.

Table 2. Vaccine platform technology of primary vaccination and booster dose with the respective manuscripts evaluated in this review.

Platform technology	**Primary vaccination**	**Booster dose homologous or heterologous**	**Reference**
mRNA	BNT162b2	BNT162b2	Skrzat-Klapaczyńska et al. (2022); Agur et al., (2022); Shashar et al., (2022); Hod et al., (2022); Kamar et al. (2021)
		mRNA-1273	Westhoff et al., (2021)
Inactivated virus	BBIBP-CorV	BBIBP-CorV	Cheng et al., (2022)

	CoronaVac	BNT162b2	Silva et al., (2022); Fonseca et al., (2022)
Inactivated virus and mRNA	CoronaVac	CoronaVac or BNT162b2	Yigit et al., (2022); Çağlayan et al., (2022); Low et al., (2022)
		mRNA-1273	Cucunawangsih et al., (2022)
	mRNA or CoronaVac	BNT162b2	Dib et al. (2022)
Inactivated virus, viral vector and mRNA	CoronaVac	CoronaVac, Ad26.COV2-S, BNT162b2 or AZD1222	Costa Clemens et al., (2022)
		CoronaVac, BNT162b2 or AZD1222	Jara et al., (2022)
mRNA and viral vector	BNT162b2 or mRNA-1273	Ad26COVS1	Heinzel et al., (2022

Source: created by the author.

2 ANTIBODY RESPONSE TO COVID-19 VACCINES

2.1 PRIMARY VACCINATION

2.1.1 Homologous Regimen

2.1.1.1 Inactivated Virus Vaccines

After two doses, the inactivated virus vaccines against COVID-19 elicited a robust humoral immune response. The second dose increased the seropositivity and the antibody levels in the participants. According to Fonseca et al., (2022) (27), IgG anti-Spike (S) was detectable in 88% of the Healthcare workers (HCWs) 28 days after the first dose (D1) of CoronaVac (Butantan/Sinovac), and in 99.8% of HCWs, 30 days after the second dose (D2). Also, Fonseca et al., (2022) (27) detailed that CoronaVac induced median anti-S IgG levels of 723.4 AU/mL after D1, which increased to 1208 AU/mL after D2. Similarly, Bayram et al., (2021) (28) demonstrated a seropositivity rate of 77.8% and 99.6% in HCWs, after the D1 and D2 with CoronaVac, respectively. Moreover, Dinc et al., (2022) (29) showed a seropositivity rate of 45% in HCWs, two weeks after D1 of CoronaVac, and 99%, 30 days after D2. Finally, Li et al., (2021) (30) reported a seropositivity of 22.58% after D1 and 87.06% after D2 in healthy individuals vaccinated with BBIBP-CorV (Sinopharm), CoronaVac (Butantan/Sinovac), or

WIBP-CorV, virus-inactivated vaccines used in China. Also, Li et al., (2021) (30) found about eight times higher neutralizing antibodies (Nabs) levels after D2 compared to baseline levels. The seroconversion rates regarding Nabs was 9.68% and 78.82% after the D1 and D2, respectively.

2.1.1.2 mRNA Vaccines

Similarly, the studies with mRNA vaccines showed that they were effective in eliciting an antibody response against SARS-CoV-2. Lustig et al., (2021) (31) showed a robust and rapid Nab response after BNT162b2 (Pfizer/BioNTech) administration. The first vaccine dose elicited positive IgG in 88% of HCWs and neutralizing responses in 71.0% of HCWs increasing to 98.4%, and 96.5%, respectively, after D2. In agreement, Herzberg et al., (2022) (32) and Pozzetto et al., (2021) (33) reported a seropositivity rate of 100% in HCWs vaccinated with two doses of BNT162b2. Additionally, Chivu-Economescu et al., (2022) (34) described that all vaccinated HCWs with two doses of BNT162b2 developed anti-S IgG at one week following D2, with exception of one that developed detectable antibodies only six weeks after D2. Furthermore, Brisotto et al., (2021) (35) reported seropositivity of 99.9% in HCWs vaccinated with two doses of BNT162b2 or mRNA-1273 (Moderna). Also, Shields et al., (2021) (36) reported seropositivity of 95% in HCWs, 12 days after a single dose of BNT162b2. Lastly, Naaber et al., (2021) (37), detailed elevated antibodies against Receptor-Binding Domain (RBD) in vaccinated serum samples, with median IgG levels of 1246 AU/mL, after D1 with BNT162b2 that increased significantly to 24534 AU/mL and 12752 AU/mL at one and six weeks after D2, respectively.

A higher humoral immunogenicity of the SARS-CoV-2 mRNA-1273 vaccine compared with the BNT162b2 vaccine has been reported. According to Brisotto et al., (2021) (35) higher levels of antibodies were detected after the mRNA-1273 vaccine compared to BNT162b2 in infection-naïve cases (BNT162b2 median value: 532.55 AU/mL versus mRNA-1273 median value: 736.95 AU/mL), and those with a history of COVID-19 (1072.65 AU/mL and 1813.4 AU/mL, respectively). One justification for the difference in immunogenicity observed could relate to the amount of mRNA used in the respective vaccines, with 30 μg contained in BNT162b2 and 100 μg in mRNA-1273 .

2.1.1.3 Viral Vectored Vaccines

Viral vectored vaccines also induced high seroconversion rates following two doses of vaccine. According to Mishra et al., (2021) (38), just one participant did not achieve seroconversion after D2 of AZD1222 (ChAdOx1), representing a seroconversion rate of 99.2%. The geometric mean titers (GMT) of IgG were 138.01 binding antibody units BAU/mL one month after the D1, 176.48 BAU/mL, and 112.95 BAU/mL one and six months after the D2, respectively. Furthermore, Choudhary et al., (2021) (39) described a seroconversion rate of 81,9% and an antibody median level of 1,299.5 AU/mL, after the D2 of the Covishield vaccine.

2.1.2 Heterologous Regimen

Heterologous regimen can provide better efficacy against VOCs (40) and should be considered in cases of vaccine scarcity, delivery delays, and reports of serious adverse events such as thromboembolism and anaphylaxis (6,41). Barros-Martins et al., (2021) and Munro et al., (2021) (42, 43) claim that the heterologous prime boost improves immunogenicity and expands cellular and humoral immunity against current SARS-CoV-2 variants of concern. According to Pozzetto et al., (2021) (33), heterologous with ChAdOx1-S-nCoV-19 and BNT162b2 (ChAd/BNT) combination displayed better neutralizing activity regardless of the SARS-CoV-2 variant when compared to homologous vaccination with BNT162b2 (BNT/BNT) in a study with HCWs. Similarly, Barros-Martins et al., (2021) (43) described that HCWs vaccinated with ChAd/BNT exhibited significantly higher frequencies of spike-specific CD4+ and CD8+ T cells and high titers of Nab when compared with HCWs with homologous ChAd/ChAd vaccination.

Pozzetto et al., (2021) (33) explained that the ChAdOx1-S-nCoV-19 (Oxford/AstraZeneca) vaccine seems to induce a weaker IgG response but a stronger T cell response when compared to BNT162b2 (Pfizer/BioNTech) vaccine after the priming dose, which could explain the complementarity of both vaccines when used in combination. Furthermore, assessing the number of individuals who received each vaccination regimen and the number of SARS-CoV-2 infections it was identified ten infections of 2,512 individuals (0.40%) and 81 infections of 10,609 individuals (0.76%) in the heterologous and homologous vaccination, respectively. So, individuals vaccinated with BNT–BNT were twice as likely to be infected than those vaccinated with ChAd–BNT (relative risk of 2.03), suggesting that the vaccination regimen was significantly related to the probability of being infected after vaccination (P = 0.0384). In this way, the large-scale controlled trials with all available

permutations of COVID-19 vaccines are important to make the findings applicable in the broader perspective and provide data to practitioners and policymakers globally.

2.2 WANNING OF ANTIBODIES POST-VACCINATION

2.2.1 Inactivated Virus Vaccines

The antibody response in HCWs vaccinated with inactivated virus vaccines decreased significantly over time. Fonseca et al., (2022a) showed that the antibodies declined 61%, 6 months after D2 of CoronaVac (Butantan/Sinovac) (27). Similarly, Choudhary et al., (2021) (39) reported a significant decrease in antibody levels in HCWs vaccinated with BBV-152 (COVAXIN), that started 2 months following D2 and was even more pronounced 6 months after (39). However, Naaber et al., (2021) (37) explain that antibody waning is expected as not all vaccine-induced plasmablasts commit or are maintained as long-lived memory plasma cells.

2.2.2 mRNA Vaccines

Likewise, a substantial decay in IgG titles between four and six months following D2 of mRNA vaccines was described by most studies. Brisotto et al., (2021) (35) mentioned an antibody decay from 559.8 AU/mL to 92.7 AU/mL at one and four months after a full schedule of BNT162b2 or mRNA-1273 vaccination. De La Monte et al., (2021) (44) showed that the post-peak IgG2-S levels declined progressively, and within 6 months reached the mean level measured one month after the first vaccine dose mRNA-1273. Khoury et al., (2021) (45) reported that the antibody titer reached the climate after one month of the D2 of BNT162b2 vaccine and declined rapidly thereafter: the median antibody levels were 895; 22, 266; 9,682; 2,554 and 1,401 AU/mL at the day of the second dose, and then once a month for consecutive four months, respectively. In other words, four months after vaccination, the mean antibody level was 6% of the peak levels. However, Chivu-Economescu et al., (2022) (34) highlighted that antibody titers do not necessarily translate to immunity. They showed that the capacity of neutralizing activity was maintained in HCWs with low IgG levels. Also, cellular immune responses were present in vaccinated participants with declining antibody levels or low neutralizing activity. Thus, the waning of antibodies was not related to reduced protection against symptomatic or asymptomatic disease.

2.2.3 Viral Vectored Vaccines

A substantial decline in antibody levels also was reported in viral vector vaccines. Mishra et al., (2021) (38) announced a substantial waning in IgG titer, six months after D2 of

the AZD1222 (ChAdOx1) vaccine. The GMT of IgG was 176.48 BAU/mL, one month after D2, and 112.95 BAU/mL, six months after D2. Seven participants showed seroreversion and 11 had breakthrough infections. Similarly, Choudhary et al., (2021) (39) reported a significant 2-fold decrease in antibody titer in 6 months follow-up among the AZD1222 (Covishield) recipients, however without cases of seroreversion. Likewise, Gonzalez et al., (2022) (46) showed that IgG levels declined over a period of 6 months after the vaccination with Sputnik V (Gam-COVID-Vac), but all the samples analyzed remained seropositive. The mean of IgG anti-spike antibodies for the group that was seronegative (naive) at baseline declined from 732 IU/mL at 42 days after D2 to 196.9 and 64 IU/mL by 120 and 180 days, respectively, after D2. IgG level waning was also observed in participants who were seropositive (due to prior infection) at baseline. For this group, the GMT of antibodies declined from 9,429, after D2 to 5,193 and 2,719 at 42 and 120 days, respectively after the vaccination. Although the total amount of IgG anti-spike decreases more than 10-fold over a period of 6 months after Sputnik V (RDIF) vaccination, they claimed that the neutralizing capacity in naive individuals showed only a 2-fold reduction, suggesting that declining antibody titers are not indicative of declining protection.

2.3 COVID-19 BOOSTER DOSE

A booster shot had shown excellent strengthening of the immune system. In HCWs, the administration of BNT162B2 booster injection in previous CoronaVac recipients enhanced the antibody response. According to Silva et al., (2022), the IgM (0.16 for 0.54 Index) and IgG (195.9 for 42.106 AU/mL) anti-Spikes were stimulated mainly 30 days after the third dose. In turn, Fonseca et al., (2022b) (47) related that BNT162B2 booster after two doses of CoronaVac increased the median levels of IgG anti-S antibodies 200.2 AU/mL (230 days after the second dose) to 41.371 AU/mL (15 days after the third dose). Likewise, Cucunawangsih et al., (2022) (49) related that administering the booster with mRNA-1273 in vaccinated with two doses of CoronaVac led to a strong immune boost in all HCWs, with a significant increase in the median of anti-S IgG antibodies after the third dose (41.7 U/mL to 28 394 U/mL). Additionally, Skrzat-Klapaczyńska et al., (2022) observed an increase in the number of HWCs previously vaccinated with the BNT162b2 vaccine exhibiting the maximum detection value of anti-S IgG (> 433 BAU/mL) after a booster dose of the same vaccine, with titers comparable to individuals SARS-CoV-2 infected in pre-vaccine period (50). Further, Cheng et al., (2022) (52) reported that the neutralizing titers induced by the first two doses of BBIBP-CorV in healthy adults reached a peak at 2 months and declined to 33.89% at 6 months. Following the booster dose with the same

vaccine, IgA, IgG, and neutralizing antibodies increase with a neutralizing titer 13.2 times higher than before the booster .

Hemodialysis and transplant patients also have benefited from a booster shot. Agur et al., (2022) (53) showed an improvement in the seropositivity rate of the hemodialysis patients (HDP) patients who received 3 doses of BNT162b2 vaccine, from 78% (62/80) before the booster dose of the up to 96% (77/80) after the booster. The IgG levels increased significantly following the booster from a median level of 153 AU/mL [IQR 56–409] to 15,529 AU/mL [IQR 5,634–39,314]. Additionally, about 88% (70/80) became "high responders" (>1,000 AU/mL), and of these, 79% (63/80) mounted a "robust response" (>4,160 AU/mL). Shashar et al., (2022) (54) also observed high seropositivity after the BNT162b2 vaccine booster in HDP previously vaccinated with two doses of the same vaccine, in which 65/66 patients (98.5%) developed a positive antibody response (472,7 ± 749,5 AU/mL to 16336,8 ± 15397,3 AU/mL) compared to a sustained decrease in the control group that did not receive the booster (mean 695,7 ± 642,7 AU/mL to 383,6 ± 298,6 AU/mL).

The same behavior of improvement in seropositivity and antibody serum levels could be observed after the homologous booster in transplant patients. Hod et al., (2022) showed an increase both IgG and neutralizing antibodies (Nabs) after D3 of BNT162b2 vaccine. Response rate raised from 32.3% (32/99) before the D3 to 85.9% (85/99) post-D3 with a significant increase in geometric mean titers (GMTs) for IgG and Nabs (0.79 vs. 3.08 and 17.46 vs. 362.2 respective) (55). Of the 32 recipients with a positive humoral response prior to D3, 31 (96.9%) remained positive after D3, with a significant increase in GMTs for IgG and Nabs. Sixty-seven patients (67.7%) had a blunted antibody response before the D3; among these, 54 (80.6%) exhibited a positive antibody response following the booster dose, with a significant increase in GMTs for IgG and Nabs (55). Additionally, showed that the end-stage renal disease (ESRD) secondary to diabetic nephropathy (DN), age and renal allograft function were independent predictors for antibody response in renal transplant recipients (RTR). They also showed that 70.1% of RTR reported adverse reactions (AEs) and systemic AEs were more frequent in recipients with a positive humoral response as opposed to non-responders (45.2% versus 15.4% respectively) (55). Similarly, Kamar et al., (2021) evaluated solid-organ transplant recipients of three doses of the BNT162b2 vaccine, the response rate increased from 40% before the third dose to 68% four weeks after the homologous booster, despite only 44% of seronegative patients seroconverted following the booster. In another study, ten RTRs who failed to respond to a second dose of the BNT162b2 vaccine received a booster of the mRNA-1273 vaccine, which induced humoral and cellular responses in 60% and 90% of the patients, respectively

(56). Based on this data, we can suggest that a third booster dose is crucial for transplant recipients to achieve a higher degree of protection from COVID-19 infection.

2.4 HETEROLOGOUS VERSUS HOMOLOGOUS COVID-19 BOOSTER VACCINATION

Previous studies had reported that heterologous vaccination induced a better immune response than homologous protocols. The study by Yigit et al., (2022) (58) evaluated IgG antibody titers and seroconversion rates in HCWs after two doses of CoronaVac and a booster with CoronaVac or BNT162b2. They found that antibody titers in the heterologous boost group were higher than the homologous boost group (Median of 12,860 vs 1361,11 BAU, respectively). Similarly, Çağlayan et al., (2022) (59) measured the anti-RBD IgG antibody levels in HCWs who had completed two doses of CoronaVac, two months after the third dose of CoronaVac or BNT162b2. The antibody level increased 104.8-fold (median: 17 609.4 vs. 168 AU/mL) and 8.7-fold (median: 1237.9 vs. 141.4 AU/mL) in the participants who received BNT162b2 and CoronaVac, respectively.

Likewise, Costa Clemens et al., (2022) (60) compared heterologous versus homologous boosters in previous recipients of two doses of CoronaVac. The third heterologous dose was of either a recombinant adenoviral vectored vaccine (Ad26.COV2-S, Janssen), an mRNA vaccine (BNT162b2, Pfizer–BioNTech), or a recombinant adenoviral-vectored ChAdOx1 nCoV-19 vaccine (AZD1222, AstraZeneca). This study demonstrated that all groups had a substantial rise in antibody concentrations, 28 days after the booster shot. However, all heterologous regimens had anti-Spike IgG levels superior to that induced by the homologous boost with CoronaVac, with a geometric fold-rise of 77 (95% CI 67–88) for Ad26.COV2-S, 152 (134–173) for BNT162b2, 90 (95% CI 77–104) for ChAdOx1 nCoV-19, and 12 (11–14) for CoronaVac. Additionally, all participants in the three heterologous booster groups had neutralization titers that were above the lower limit of detection 28 days after vaccination compared with 38 (83%) of 46 responders (95% CI 68·6–92·2) in the homologous CoronaVac group. Thus, the study showed that heterologous booster induced a more robust immune response than homologous boosting (60).

Corroborating these findings, Jara et al., (2022) evaluated the effectiveness of the homologous and heterologous boosters in preventing COVID-19 cases, hospitalizations, intensive care unit (ICU) admissions, and deaths. They analyzed individuals who received a primary immunization schedule (two doses) with CoronaVac and a heterologous booster dose with AZD1222, BNT162b2, or homologous booster with CoronaVac. The results suggested high effectiveness with homologous (CoronaVac) and heterologous (BNT162b2 or AZD1222)

booster schedules in preventing COVID-19 and related outcomes (61). Nonetheless, they showed that protection is significantly greater for individuals receiving a heterologous vaccine booster compared to a homologous booster with CoronaVac (61). Similarly, Low et al., (2022) (62) compared the odds of symptomatic SARS-CoV-2 infection between individuals who received the primary series CoronaVac plus a BNT162b2, individuals who received 3 doses of CoronaVac, and individuals who received 3 doses of BNT162b2. Receipt of heterologous booster (primary series of CoronaVac plus a BNT162b2 booster) was associated with lower odds of SARS-CoV-2 infection (OR, 0.17 [95% CI, 0.17-0.18]) compared with homologous booster (3 doses of CoronaVac) or 3 doses of BNT162b2 (OR, 0.01 [95% CI, 0.00-0.01]).

The differences between immunogenicity induced by homologous and heterologous vaccine regimens were also evaluated in transplant patients. The study by Heinzel et al., 2022 (63) evaluated seroconversion after a third dose of homologous (BNT162b2 or mRNA-1273) or heterologous (Ad26COVS1) vaccine in kidney transplant recipients who had received two doses of mRNA vaccine and did not develop antibodies against the viral Spike protein. Three months after vaccination with the third dose, the seroconversion rate was 50% among individuals who had received heterologous vaccination and 45% among those who received homologous vaccination, with no statistically significant difference. However, when they compared the antibody levels, the heterologous group reached significantly higher antibody levels (>141 and > 264 BAU/ml) than the homologous group (> 141 BAU/mL: 4 vs. 15%, p = 0.009 and > 264 BAU/mL: 1 vs 10%, p = 0.018 for homologous vs the heterologous group, respectively).

On the other hand, Dib et al., (2022) (64) evaluated solid-organ transplant (SOT) recipients vaccinated with two doses of CoronaVac or BNT162b2 followed by an additional dose of BNT162b2, 21 weeks after primary vaccination. The anti-SARS-CoV-2 total IgG antibodies seropositivity (82.3% vs 65.4%, *p* = 0.035) and NAb positivity (77.4% vs 55.1%, p = 0.007) were higher for the homologous versus the heterologous group. It is worth mentioning that this was the first study that compared the response to a homologous versus heterologous vaccine booster that included inactivated vaccines in SOT recipients. In this review, we summarize the results of different vaccination schedules against COVID-19 in the increase of antibody titers and observed a faster increase in antibody levels in individuals who received heterologous vaccination schedules (Figure 1).

Figure 1. Antibody response to different vaccination schedules against COVID-19. Green line represents the behavior of antibody titers in the heterologous vaccination schedule. Red line represents the behavior of antibody titers in the homologous vaccination schedule. On the left, primary and booster vaccination schedules are illustrated.
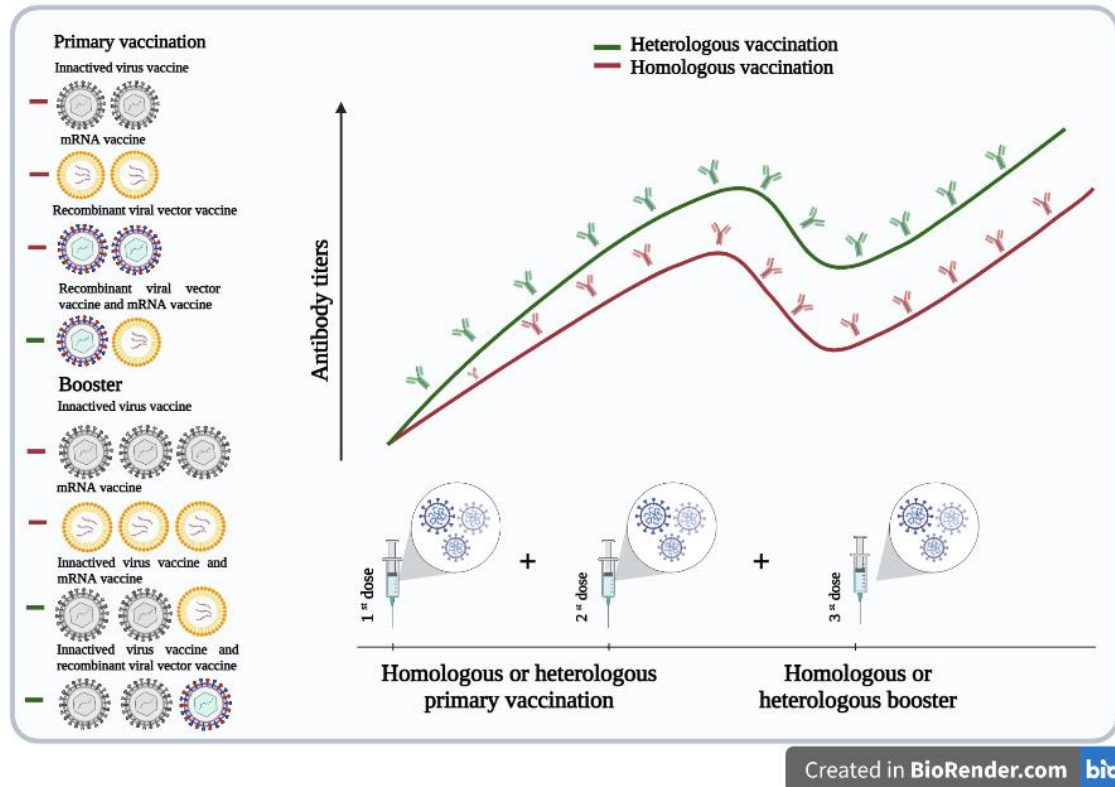
Source: BioRender.com

3 CONCLUSION

In this review, we had real-world evidence that regardless of the COVID-19 vaccine platforms used (inactivated whole-virus, nucleic acid, or viral vector), a robust SARS-CoV-2 antibody response was induced after two doses of vaccine. One dose of any vaccine already elicited an antibody response, although the second dose increased the seropositivity rate and the IgG levels. Heterologous primary vaccine schedules improved the antibody levels and their neutralizing capacity, although, the studies are scarce and did not include the inactivated vaccines. The antibody levels declined progressively after the second dose in all vaccines evaluated. An additional dose of vaccine (booster) increased the antibody levels, mainly if a different vaccine of the primary vaccination was used.

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