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REVIEW

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Emerging heterologous mRNA-based booster strategies within the COVID-19 vaccine landscape

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ABSTRACT

Messenger RNA (mRNA)-based vaccine platforms used for the development of mRNA-1273 and BNT162b2 have provided a robust adaptable approach to offer protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, as variants of concern (VoCs), such as omicron and associated subvariants, emerge, boosting strategies must also adapt to keep pace with the changing landscape. Heterologous vaccination regimens involving the administration of booster vaccines different than the primary vaccination series offer a practical, effective, and safe approach to continue to reduce the global burden of coronavirus disease 2019 (COVID-19). To understand the immunogenicity, effectiveness, and safety of heterologous mRNA-based vaccination strategies, relevant clinical and real-world observational studies were identified and summarized. Overall, heterologous boosting strategies with mRNA-based vaccines that are currently available and those in development will play an important global role in protecting individuals from COVID-19 caused by emerging VoCs.

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Introduction

Strategies for robust protection against COVID-19

Since the onset of the coronavirus disease 2019 (COVID-19) pandemic, the development of safe and effective vaccines to prevent severe COVID-19 disease has been at the forefront of prophylactic strategies.[1–5] Over the course of the pandemic, multiple vaccines based on different scientific platforms have been authorized for primary vaccination schedules globally.[6] With the emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) variants of concern (VoCs), the focus has gradually shifted from primary vaccination approaches to vaccine boosting for those who have already completed the primary series.[7–14]

Evaluating evidence of specific heterologous regimens, combined with considerations, such as those outlined in Table 1, will help guide future COVID-19 boosting approaches. As with heterologous primary series, "mix and match" or heterologous booster strategies, whereby booster vaccines are different than the primary vaccines, could simplify the implementation of mass vaccination programs and supply management within clinics/healthcare centers. These strategies also allow healthcare providers to select the most effective booster combination and schedule for their patients based on the latest evidence and the vaccine(s) available at the time of booster administration. Heterologous boosting strategies not only serve to help mitigate issues with regional vaccine supply and storage but also may expand booster selections based on real-world effectiveness against circulating VoCs and those that may emerge in the future. Together with the heightened need to protect those most vulnerable to severe COVID-19 disease, such as immunocompromised populations and older adults, booster strategies play a key role in global health outcomes. These considerations, combined with the evaluation of available clinical and real-world observational data, serve to aid in the decision-making process of selecting vaccine boosters.[14–33]

Other key considerations for the development of future vaccines against COVID-19 include the ability of a scientific platform to derive safe and highly effective booster strategies and the delivery of a technology that can rapidly be adapted to target future VoCs. As such, the development of the messenger RNA (mRNA)-based vaccine platform provides a robust and adaptable approach against SARS-CoV-2 and VoCs. In this review, we describe the current scientific literature within the context of heterologous vaccine regimens and the associated implications for emerging heterologous mRNA-based booster strategies.

The COVID-19 vaccine landscape

Several COVID-19 vaccines have been developed and evaluated in clinical trials within the United States and Europe, including the mRNA-based vaccines mRNA-1273 (Spikevax™; Moderna, Inc., Cambridge, MA, USA) and BNT162b2 (Comirnaty®; Pfizer Inc, New York, NY, USA; BioNTech Manufacturing GmbH, Mainz, Germany), the adenoviral vector–based vaccines Ad26.COV2.S (Janssen COVID-19 vaccine or JCovden; Johnson & Johnson, New Brunswick, NJ, USA) ChAd-Ox1.S (Vaxzevria™; AstraZeneca, Luton, UK) and the recombinant protein-based adjuvanted vaccine NVX-CoV2373 (Nuvaxovid™; Novavax US, Gaithersburg, MD, USA) (summarized in Table 2).[6, 34–42] Based on demonstrated efficacy in clinical trials, the US Food and Drug Administration (FDA) first granted emergency use authorization (EUA) for mRNA-1273 (2-dose primary

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Table 1. Considerations for COVID-19 boosting strategies[14–17].

Considerations	Description and Importance	Potential Solution(s)
(1) Practicality of mass booster vaccination programs	Simplify implementation to reach maximum accessibility within populations	Administer vaccines that are regionally available[18]
(2) Booster vaccine availability and supply	Regionally supplied vaccines that are available at each clinic/health center	Use heterologous boosting with available vaccines for maximum coverage[19]
(3) Deciding which boosting regimens to administer	Evaluate robust evidence and recommendations that are currently available	Assess data from the latest relevant clinical and real-world studies[20–26]
(4) Effectiveness of booster vaccine regimens	Assess various booster regimens for the highest long-term immune response	Evaluate available immunogenicity and T cell response data over time[27,28]
(5) Safety of booster vaccine regimens	Ensure the reactogenicity of each vaccine to provide safe and tolerable booster regimens	Evaluate long-term benefit-risk profile of vaccine effectiveness against short-term vaccine side effects[29]
(6) Boosting to protect against current COVID-19 VoCs	Using current authorized vaccines to offer booster regimens that are effective and safe against current VoCs	Evaluate the latest real-world boosting data when VoCs are circulating[16]
(7) Boosting to future protect against COVID-19 VoCs	Being able to offer booster regimens that are effective and safe against specific VoCs	Evaluate data from vaccine candidates in clinical development[30]
(8) Boosting to continually protect our most vulnerable populations	Reducing healthcare burden from severe COVID-19 disease among immunocompromised individuals and older adults	Assess the latest clinical data, real-world evidence, and recommendations[31]

COVID-19, coronavirus disease 2019; VoC, variant of concern.

Table 2. A summary of the COVID-19 vaccine landscape as of 21 September 2022.

			FDA[34]			
Vaccine	Trade Name, Manufacturer	Vaccine Type	Authorized for EUA	Full Authorization	EMA Authorized[35]	WHO EUL[6]
mRNA-1273	Spikevax™; Moderna, Inc., Cambridge, MA, USA	mRNA-based, monovalent	2-dose primary, aged ≥6 mo-17 y (per dose, 6 mo-5 y: 25 µg; 6 y-11 y: 50 µg; 12 y-17 y: 100 µg) 3-dose primary, aged ≥6 mo with immunocompromising conditions (per dose, 6 mo-5 y: 25 µg; 6 y-11 y: 50 µg; 12 y-17 y: 100 µg)	2-dose primary, aged ≥18 y (per dose, 100 µg)	2-dose primary, aged ≥6 y (per dose, 6 y-11 y: 50 µg; 12 y: 100 µg) 3-dose primary, aged ≥6 y, with severe immunocompromising conditions (per dose, 6 y-11 y: 50 µg; 12 y: 100 µg) 1-dose booster, aged ≥12 y (per dose, 50 µg)	✓
mRNA-1273.214	Moderna COVID-19 vaccine, bivalent; Spikevax™ bivalent original/omicron; Moderna, Inc., Cambridge, MA, USA	mRNA-based, bivalent	1-dose booster, aged ≥18 y (per dose, 50 µg)		1-dose booster, aged ≥12 y (per dose, 50 µg)	
BNT162b2	Comirnaty®; Pfizer Inc, New York, NY, USA; BioNTech Manufacturing GmbH, Mainz, Germany	mRNA-based, monovalent	2-dose primary, aged 5–11 y (per dose, 10 µg) 3-dose primary, aged ≥6 mo-4 y (per dose, 3 µg) 3-dose primary, aged ≥5 y, with immunocompromising conditions (per dose, 5–11 y: 10 µg; ≥12 y: 30 µg) 1-dose booster, aged 5–11 y (per dose, 10 µg)	2-dose primary series, aged ≥12 y (per dose, 30 µg)	2-dose primary, aged ≥5 y (per dose, 5–11 y: 10 µg; ≥12 y: 30 µg) 3-dose primary, aged ≥5 y, with immunocompromising conditions (per dose, 5–11 y: 10 µg; ≥12 y: 30 µg) 1-dose booster, aged ≥12 y (per dose, 30 µg)	✓
Bivalent BNT162b2 omicron containing vaccine	Pfizer-BioNTech COVID-19 vaccine, bivalent (original and omicron BA.4/BA.5); Pfizer Inc, New York, NY, USA; BioNTech Manufacturing GmbH, Mainz, Germany	mRNA-based, bivalent	1-dose booster, aged ≥12 y (per dose, 30 µg)		1-dose booster, aged ≥12 y (per dose, 30 µg)	
Ad26.COV2.S	Janssen COVID-19 vaccine or JCovden; Johnson & Johnson, New Brunswick, NJ, USA	Adenoviral vector–based	–	1-dose primary, aged ≥18 y (limited use, per dose, ≥8.92 $\log_{10}$ infectious units)* 1-dose booster, aged ≥18 y, (limited use, per dose, ≥8.92 $\log_{10}$ infectious units*	1-dose primary, aged ≥18 y (per dose, ≥8.92 $\log_{10}$ infectious units) 1-dose booster, aged ≥18 y (per dose, ≥8.92 $\log_{10}$ infectious units)	✓
ChAd-Ox1.S	Vaxzevria™; AstraZeneca, Luton, UK	Adenoviral vector–based	–	–	2-dose primary, aged ≥18 y (per dose, 2.5×10^8 infectious units) 1-dose booster, aged ≥18 y (per dose, 2.5×10^8 infectious units)	✓

(*Continued*)

Table 2. (Continued).

Vaccine	Trade Name, Manufacturer	Vaccine Type	FDA[34]		EMA Authorized[35]	WHO EUL[6]
			Authorized for EUA	Full Authorization		
NVX-CoV2373	Nuvaxovid™; Novavax US, Gaithersburg, MD, USA	Recombinant protein-based, adjuvanted	2-dose primary, aged ≥12 y (per dose, 5 µg)	–	2-dose primary, aged ≥12 y (per dose, 5 µg)	✓
COVOVAX™	Serum Institute of India, Novovax formulation, Pune, India	Recombinant protein-based, adjuvanted	–	–	–	✓ 5 µg per dose (2 doses primary)
Ad5-nCoV	Convidesia; CanSinoBio, Tianjin, China	Adenoviral vector–based	–	–	–	✓ 0.5 mL per dose (1 dose primary) †
Sputnik V	Gamaleya; Moscow, Russia	Adenoviral vector–based	–	–	Under rolling review	
BBIBP-CorV	Covilo; Sinopharm, Beijing, China	Inactivated virus whole cell	–	–	–	✓ 4 µg per dose (2 doses primary)
BBV152	Covaxin®; Bharat Biotech, Turakapally, India	Inactivated virus whole cell	–	–	–	✓ 6 µg per dose (2 doses primary)
CoronaVac	Sinovac; Beijing, China	Inactivated virus whole cell	–	–	Under rolling review	600 subunits per dose (2 doses primary)

COVID-19, coronavirus disease 2019; EMA, European Medicines Agency; EUL, emergency use listing; FDA, Food and Drug Administration; mo, months; WHO, World Health Organization; y, years.
*Authorized use of Ad26.COV2.S limited to individuals ≥18 years of age for whom other authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, or who elect to receive Ad26.COV2.S because they would otherwise not receive a COVID-19 vaccine.
†Although not under WHO EUL, vaccine is approved in 74 countries per WHO website. Dosing not stated.

vaccination series) in adults aged ≥18 years and BNT162b2 (2-dose primary vaccination series) in individuals aged ≥16 years in December 2020.[37,43,44] Both mRNA-1273 and BNT162b2 subsequently received full authorization from the FDA for the prevention of COVID-19 in individuals in these age groups.[45,46] The EUA for mRNA-1273 and BNT162b2 has now been extended to children aged ≥6 months.[47] Similarly, the FDA granted an EUA for NVX-CoV2373 (2-dose primary vaccination series, adjuvanted vaccine) in individuals aged ≥12 years and limited EUA of Ad26.COV2.S (1-dose primary vaccination series) in adults ≥18 years for whom other authorized or approved COVID-19 vaccines are not accessible or clinically appropriate or who elect to receive Ad26.COV2.S because they would otherwise not receive a COVID-19 vaccine.[39,48–52] Likewise, mRNA-1273, BNT162b2, Ad26.COV2.S, ChAd-Ox1.S and NVX-CoV2373 have gained authorization for use from the European Medicines Agency (EMA) and in multiple countries worldwide.[35,39,41,53–55]

Widespread COVID-19 vaccination campaigns have facilitated an estimated 12.23 billion administered vaccine doses globally as of mid-July 2022.[18] Overall, 40 COVID-19 vaccines have been authorized worldwide, including those mentioned previously as well as inactivated virus whole-cell vaccines BBIBP-CorV (Covilo; Sinopharm, Beijing, China), BBV152 (Covaxin®; Bharat Biotech, Turakapally, India), and CoronaVac (Sinovac; Beijing, China); the non-replication viral vector Sputnik V (Gamaleya; Moscow, Russia), Ad5-nCoV (Convideia; CanSinoBio, Tianjin, China); and protein subunit-based vaccine COVOVAX™ (Serum Institute of India, Novovax formulation, Pune, India) (summarized in Table 2).[6,15] As of the same date, approximately 67% of the vaccine-eligible population has been fully vaccinated (received the primary vaccination-series) in the United States, among whom the majority received mRNA-based vaccines (38% received mRNA-1273 and 59% received BNT162b2).[56] Globally, vaccines type has varied from country to country, with mRNA-based vaccine doses contributing to a large proportion of all primary and boosters doses.[18]

Considerations for vaccine boosting

Clinical and real-world observational studies suggest that mRNA-based COVID-19 vaccines are highly effective against symptomatic and severe COVID-19.[57–61] However, as the COVID-19 disease landscape continues to evolve, studies indicate a waning of natural and vaccine-elicited immunity over time.[62–64] Additionally, the emergence of SARS-CoV-2 variants, such as B.1.617.2 (delta) and B.1.1.529 (omicron), with subvariants BA.1, BA.2, BA.3, BA.4 and BA.5, has raised concerns of increased transmissibility and evasion of both natural and vaccine-induced immunity.[8–10,13,16,57] Specifically, although the initial real-world observational studies confirmed that a 2-dose mRNA-1273 vaccination schedule is highly effective against SARS-CoV-2 variant infection as well as severe COVID-19 outcomes (i.e., hospitalization and death),[57,62,65] more recent studies indicate that there is a moderate decline in mRNA-based vaccine effectiveness (VE) against infection with the delta variant and the more significant omicron variant and subvariants.[66,67]

As continued protection of populations against severe outcomes from COVID-19 is crucial to help mitigate the healthcare and economic impacts of the disease, booster vaccination lowers the risk of breakthrough disease as a result of SARS-CoV-2 antigenic variation and waning of natural and/or vaccine-

induced immunity.[8–10,13,16,64] Accordingly, stakeholders, including advisory groups, regulatory authorities, and policymakers, have begun to examine the implications of periodic or seasonal booster vaccine administration, with an emphasis on the individuals most at risk of infection (such as the elderly, immunocompromised individuals, and front-line healthcare workers) and those who received their primary dosing earliest in the vaccine rollout.[14,57–64,68–70] It is imperative that the decision of when and which vaccine booster regimen(s) to choose to be made based on clinical evidence.[71–75]

Initial booster studies focused on homologous approaches toward boosting (i.e., the same vaccine is administered for the primary series and booster), and several studies have focused on evaluating the safety and immunogenicity of such booster strategies;[4,71–76] the current knowledge regarding COVID-19 homologous booster strategies is reviewed elsewhere.[77–80] Notably, for mRNA-based COVID-19 vaccines, evidence suggests that homologous booster vaccination after the 2-dose primary series can increase neutralizing antibody titers against wild-type (WT) SARS-CoV-2 and the delta variant compared with titers following the completion of the primary vaccination series.[4] Regarding safety, local and systemic adverse events were similar following dose 2 and the booster dose.[81] Based on such evidence, homologous booster regimens with mRNA-1273 and BNT162b2 have been authorized in the United States and Europe.[35,82,83] Additionally, for adenoviral vector-based vaccines, a second Ad26.COV2.S dose is also authorized as a homologous booster in the United States.[50]

Heterologous primary and booster vaccination regimens

As introduced earlier, a practical strategy to expand COVID-19 vaccine coverage is to consider "mixing and matching" vaccines in a heterologous vaccination schedule.[84,85] More specifically, these heterologous schedules can include regimens of vaccines from different platforms (e.g., Ad26.COV2.S and mRNA-1273) or different vaccines from the same platform (e.g., mRNA-1273 and BNT162b2). If such strategies can elicit tolerability and immunogenicity profiles similar to those of homologous vaccination regimens, they offer several advantages, including potentially optimizing the breadth and longevity of protection against COVID-19 attained with currently available vaccines, providing protection against emerging VoCs with vaccines in development and simplifying the logistics of booster vaccine administration (Table 1). Heterologous vaccination strategies are also being investigated to evaluate immune response across a range of diseases, including Ebola, HIV, malaria, tuberculosis, and influenza.[86,87]

In both the United States and Europe, heterologous boosting with any available COVID-19 vaccine is currently authorized,[17,84] with the decision-making of which booster to receive left to individuals and their healthcare providers. Consequently, additional evidence regarding specific booster regimens following a primary vaccination series is needed to make better decisions regarding the optimal heterologous booster strategies for COVID-19 vaccination. In the United States, an mRNA-based COVID-19 vaccine booster is recommended after completion of any COVID-19 primary vaccination series (mRNA-1273 for individuals aged ≥6 years; BNT162b2 for individuals aged ≥5 years).[88] Additionally, a second mRNA-based COVID-19 vaccine booster is recommended for adults aged ≥50 years and for individuals with certain kinds of immunocompromise (aged ≥18 years with mRNA-1273; aged ≥12 years with BNT162b2).[17,85] Together with the increased importance of protecting those individuals most at risk of developing severe COVID-19 disease and the current global availability of various authorized primary-booster vaccine permutations, guidance on optimal choices should be based on evidence from clinical studies and real-world data that explore heterologous vaccination regimens for both the primary series and booster(s).

To address the need for guidance on optimal vaccine choices, we provide a brief overview of recent studies meeting selection criteria (see Methods for article selection criteria; Table 3) that examined heterologous mRNA-based 2 or 3-dose vaccination schedules of different vaccines, including ≥1 mRNA-based vaccine (mRNA-1273 or BNT162b2), in the context of supporting future booster regimen choices; of note, we discuss data pertaining to the currently authorized COVID-19 primary vaccines in the United States or Europe paired with mRNA-based boosting vaccines.[17,84] No correlate of protection has been established, but since protection against SARS-CoV-2 is likely to be associated with humoral and cellular immune responses,[89–92] we first compared the immunogenicity data of regimens of different mRNA-based vaccines and then summarized vaccine reactogenicity and safety.

Materials and methods

A literature search using PubMed was conducted to capture clinical trials and observational studies of COVID-19 vaccination regimens (Table 3). The search was limited to English language articles published between 1 January 2021 and 29 June 2022, which generated 595 articles. Exclusion criteria were used to remove articles from the list, including articles describing studies with non-mRNA-based vaccines only; real-world observational studies that included data outside of the

Table 3. PubMed literature search criteria and results.

Search terms	• COVID-19 AND vaccine AND booster AND mRNA • Limited to English language articles
Publication period	• 1 January 2021, to 29 June 2022
Search results	• 595 articles selected
Inclusion criteria	• Studies describing heterologous vaccine regimens • Studies describing ≥1 mRNA-based vaccine
Exclusion criteria	• Review articles • Studies of specific populations (such as immunocompromised individuals) • Articles not peer-reviewed* • Studies describing non-mRNA-based vaccines only • Observational studies of small populations (~<100,000 individuals) • Observational studies of data before December 2021
Articles extracted	• 16 articles (15 studies)
Studies identified	• 8 clinical studies • 7 observational studies
Additional studies included†	• 3 clinical studies • 1 observational study

*Except for preprint articles and one study from the Morbidity and Mortality Weekly Report, Centers for Disease Control and Prevention.
†Identified outside the PubMed search from ClinicalTrials.gov, mRNA-based vaccine pipelines, and related searches.

December 2021 to June 2022 time period (to capture the latest circulating VoCs); small participant populations for observational studies (~<100,000 individuals, to capture a large-enough real environment); and articles that were not peer-reviewed. If a study evaluated both an mRNA vaccine and a non-mRNA vaccine as a booster, it was included. Exceptions were made to the selection criteria if a study was not yet peer-reviewed but otherwise met the inclusion criteria laid out in Table 3. Using these criteria, 16 articles that identified 15 studies (two articles described the same study) were selected for inclusion in this review, including eight articles describing clinical trials and seven reporting observational studies. Further three clinical studies (that matched the inclusion criteria) and one observational study were identified outside of the PubMed search based on knowledge of mRNA-based vaccines in development, pipelines, and related articles.

Briefly, the 11 clinical studies include 1) the National Institute of Health Division of Microbiology and Infectious Diseases (NIH DMID) study in the United States evaluating heterologous booster regimens with mRNA-1273, BNT162b2, or Ad26.COV2.S;[26,32] 2) the COV-BOOST study in the United Kingdom assessing heterologous boost combinations with BNT162b2 or ChAd-Ox1.S;[21] 3) a COV-BOOST extension study;[93] 4) the Com-COV2 study in the United Kingdom assessing heterologous primary vaccination series with mRNA-1273, BNT162b2, ChAd-Ox1.S or NVX-CoV2373;[20] 5) the ARNCOMBI study in France comparing heterologous primary vaccination series with two doses of different vaccines to homologous dosing with mRNA-1273 and BNT162b2;[94] 6) the SWITCH trial in the Netherlands evaluating Ad26.COV2.S as a primary vaccine with Ad26.COV2.S, mRNA-1273, or BNT162b2 as the second dose;[95] 7) the HKSH study in Hong Kong assessing boosting with CoronaVac or BNT162b2;[96] 8) the PRIBIVAC trial in Singapore evaluating heterologous or homologous boosting with mRNA-1273 or BNT162b2;[97] and 9–11) three studies investigating VoC targeting monovalent or bivalent vaccines.[98,99] The study details are shown in Table 4. In addition, eight observational real-world studies assessing outcomes following heterologous regimens with mRNA-1273 or BNT162b2 were also selected (Table 5).[23,25,100–104] Studies were conducted in adults ≥18 years of age.

Summary of results

Immunogenicity of heterologous primary regimens

Heterologous 2-dose primary regimens have been identified as a valid tool to expand COVID-19 vaccination recommendations and may provide useful information about the ability to mix and match booster doses. As such, the Com-COV2 study showed that a heterologous primary vaccination series with a first dose of ChAd-Ox1.S or BNT162b2 followed by a second dose of mRNA-1273 was non-inferior to the homologous 2-dose primary schedule with ChAd-Ox1.S or BNT162b2.[20] At 28 days following the second dose, anti-spike immunoglobulin G (IgG) was highest for ChAd-Ox1.S/mRNA-1273 or BNT162b2/mRNA-1273 heterologous combinations compared with homologous primary combinations.[20] Notably, among the currently authorized vaccines assessed, the ChAd-Ox1.S/mRNA-1273 schedule showed the highest cellular response (Figure 1a).[20] Similar to the Com-COV2 study, results from the recent ARNCOMBI study found that heterologous BTN162b2/mRNA-1273 was non-inferior to homologous BNT162b2 or mRNA-1273 vaccine regimens (Figure 1b).[94] Results from the SWITCH trial in individuals who received Ad26.COV2.S as their primary vaccine dose showed that S-specific antibody binding was the highest among individuals who received mRNA-1273 as dose 2 followed by BNT162b2 as dose 2 (Figure 1c) and a post hoc analysis also found that mRNA-1273 as dose 2 induced higher antibody binding compared with BNT162b2 as dose 2.[95]

Immunogenicity of heterologous booster regimens

Humoral and cellular immunogenicity data from heterologous booster studies are important in determining the best protective strategies against COVID-19 disease. Data from the phase 1/2 NIH DMID trial showed that at 29 days following boost, anti-spike IgG was highest in individuals boosted with mRNA-1273 (i.e. received mRNA-1273 for dose 3 after either a primary vaccination series of mRNA-1273, BNT192b2, or Ad26.COV2.S) when compared with other homologous or heterologous 3-dose regimens (Figure 1d).[26,32] Likewise, pseudovirus antibody neutralization was highest following boosting with mRNA-1273 (for both homologous and heterologous regimen) compared with the other regimens evaluated (Figure 1d).[26] Evaluation of cellular immune response found that all three vaccines used for the primary vaccination series (mRNA-1273, BNT192b2, or Ad26.COV2.S) induced CD4+ T-cell responses, and similar to the kinetics of natural infection, persisted in the majority of individuals for up to 6 months.[26] Comparatively, a more durable CD8+ T-cell response was shown in participants who received a primary regimen of Ad26.COV2.S or mRNA vaccine with Ad26.COV2.S as a heterologous booster.[26]

In the COV-BOOST study, anti-spike IgG levels were highest 28 days following boost among participants who received a heterologous boost with mRNA-1273 after a primary 2-dose series of ChAd-Ox1.S or BNT162b2 compared with a homologous booster vaccination (Figure 1e).[21] Notably, all vaccines given as the booster dose in this study induced substantial cellular immune responses in participants primed with two doses of ChAd-Ox1.S.[21] The mRNA vaccines and Ad26.COV2.S also showed increased T-cell responses when administered after a 2-dose primary vaccination series of ChAd-Ox1.S or BNT162b2, with ChAd-Ox1.S followed by an mRNA-1273 heterologous booster evoking the strongest T-cell response.[21] Further data from a sub-trial extension arm of COV-BOOST showed that administration of a fourth-dose of an mRNA-based vaccine to substantially increase both humoral and cellular immunity for approximately 7 months following the third-dose. Anti-spike IgG levels at Day 14 following the fourth dose were higher than those at Day 28 after the third dose for both the BNT162b2 and mRNA-1273 homologous and heterologous schedules.[93]

Table 4. Recent clinical trials evaluating heterologous vaccine regimens (2, 3, or 4 doses)*.

Clinical Trial	Location	No. of Doses	Dose 1	Dose 2	Dose 3/4	Population, n mITT (PP)	Mean Interval to Last Dose, Weeks (SD)	Variants Included	Reference
Com-COV2	United	2	ChAd-Ox1.S[a]	ChAd-Ox1.S[a]	–	171 (164)	9.4 (0.96)	WT, delta, beta	Stuart ASV et al.[20] *The Lancet*. https://doi.org/10.1016/S0140–6736/21/02718-5
Single-blinded non-inferiority	Kingdom		ChAd-Ox1.S[a]	NVX-CoV2373[e]	–	167 (160)	9.5 (1.01)		
randomized trial			ChAd-Ox1.S[a]	mRNA-1273[c]	–	167 (162)	9.5 (0.95)		
			BNT162b2[b]	mRNA-1273[c]	–	164 (154)	9.5 (0.95)		
			BNT162b2[b]	BNT162b2[b]	–	167 (163)	9.5 (0.98)		
			BNT162b2[b]	NVX-CoV2373[e]	–	172 (166)	9.6 (0.96)		
ARNCOMBI	France	2	mRNA-1273[c]	mRNA-1273[c]	–	99 (97)	4-7[z]	WT, delta, alpha,	Janssen et al.[94]
Open-label non-inferiority			BNT162b2[b]	mRNA-1273[c]	–	100 (96)		beta	*EClinicalMedicine*
randomized trial			BNT162b2[b]	BNT162b2[b]	–	97 (94)			DOI: 10.1016/s1473–3099(22)00271-7
			mRNA-1273[c]	BNT162b2[b]	–	103 (103)			
SWITCH single-blind randomized	Netherlands	2	Ad26.COV2.S[f]	None	–	114 (105)	13.4 (12.3–14.0)[s]	NS	Saberolles et al.[95] *NEJM*
trial			Ad26.COV2.S[f]	Ad26.COV2.S[f]	–	116 (106)			DOI: 10.1056/NEJMoa211674
			Ad26.COV2.S[f]	mRNA-1273[c]	–	116 (112)			
			Ad26.COV2.S[f]	BNT162b2[b]	–	115 (111)			
NIH DMID	United	2/3	Ad26.COV2.S[f]	mRNA-1273[c]	–	53	13.7 (1.0)	WT, delta, beta	Atmar et al.[26]
Phase 1/2 open-label trial	States		mRNA-1273[c]	mRNA-1273[c]	mRNA-1273[c]	51	16.4 (1.9)		*NEJM*
			BNT162b2[b]	BNT162b2[b]	mRNA-1273[c]	50	16.8 (2.2)		DOI: 10.1056/NEJMoa2116414
			Ad26.COV2.S[f]	Ad26.COV2.S[f]	–	50	17.7 (2.0)		
			/mRNA-1273[c]	mRNA-1273[c]	Ad26.COV2.S[f]	49	19.3 (4.2)		
			BNT162b2[b]	BNT162b2[b]	Ad26.COV2.S[f]	51	20.6 (5.8)		
			Ad26.COV2.S[f]	BNT162b2[b]	–	53	19.9 (2.5)		
			mRNA-1273[c]	mRNA-1273[c]	BNT162b2[b]	51	22.9 (4.6)		
			BNT162b2[b]	BNT162b2[b]	BNT162b2[b]	50	24.1 (5.2)		
COV-BOOST phase 2 randomized	United	3	ChAd-Ox1.S[a]	ChAd-Ox1.S[a]	ChAd-Ox1.S[a]	100	9.9 (8.7–10.9)[s]	WT, delta, beta	Munro et al.[21]
trial	Kingdom		BNT162b2[b]	BNT162b2[b]	ChAd-Ox1.S[a]	98	4.9 (3.0–9.3)[s]		*The Lancet* https://doi.org/10.1016/
			ChAd-Ox1.S[a]	ChAd-Ox1.S[a]	Ad26.COV2.S[f]	101	10.6 (9.7–11.0)[s]		S0140–6736/21/02717-3
			BNT162b2[b]	BNT162b2[b]	Ad26.COV2.S[f]	89	8.9 (3.6–10.6)[s]		
			ChAd-Ox1.S[e]	ChAd-Ox1.S[a]	mRNA-1273[c]	98	10.0 (9.0–11.0)[s]		
			BNT162b2[b]	BNT162b2[b]	mRNA-1273[c]	92	9.4 (3.3–10.9)[s]		
			ChAd-Ox1.S[a]	ChAd-Ox1.S[a]	BNT162b2-half[g]	105	10.6 (9.4–11.0)[s]		
			BNT162b2[b]	BNT162b2[b]	BNT162b2-half[g]	94	8.6 (3.2–10.7)[s]		
			ChAd-Ox1.S[a]	ChAd-Ox1.S[a]	BNT162b2[b]	95	10.4 (9.4–11.0)[s]		
			BNT162b2[b]	BNT162b2[b]	BNT162b2[b]	96	9.3 (4.0–10.6)[s]		
			ChAd-Ox1.S[a]	ChAd-Ox1.S[a]	NVX-CoV2373[e]	96	9.7 (8.6–10.6)[s]		
			BNT162b2[f]	BNT162b2[f]	NVX-CoV2373[e]	103	6.0 (3.3–9.4)[s]		
			ChAd-Ox1.S[a]	ChAd-Ox1.S[a]	NVX-CoV2373-half[h]	97	10.0 (9.0–11.0)[s]		
			BNT162b2[b]	BNT162b2[b]	NVX-CoV2373-half[h]	99	8.0 (4.0–10.0)[s]		
COV-BOOST sub-trial extension	United	4	ChAd-Ox1.S[a]	ChAd-Ox1.S[a]	BNT162b2[b]/	44	29.1 (29.0–30.0)[z]	omicron	Munro et al.[93]
	Kingdom				BNT162b2[b]				*Lancet Infect Dis*
			ChAd-Ox1.S[a]	ChAd-Ox1.S[a]	BNT162b2[b]/mRNA-1273[d]	44	29.4 (29.1–30.3)[z]		DOI: 10.1016/S1473–3099(22)00271-7
			BNT162b2[b]	BNT162b2[b]	BNT162b2[b]/	39	29.7 (29.1–30.6)[z]		
					BNT162b2[b]				
			BNT162b2[f]	BNT162b2[f]	BNT162b2/	39	30.7 (29.5–31.1)[z]		
					BNT162b2[f]				
Bivalent vaccine open label	United	3	mRNA-1273[c]	mRNA-1273[c]	mRNA-1273[d]	171 (170)	31.3 (28.4–33.0)[s]	WT, beta, delta,	Chalkias et al.[98] *Preprint* https://doi.org/
phase 2/3 trial	States		mRNA-1273[c]	mRNA-1273[c]	mRNA-1273.211[j]	300 (300)	37.7 (35.1–39.4)[s]	omicron	10.21203/rs.3.rs-1555201/v1
			mRNA-1273[c]	mRNA-1273[c]	mRNA-1273.211[i]	596 (595)	42.0 (40.9–43.3)[s]		
Bivalent vaccine randomized,	United	3	mRNA-1273[c]	mRNA-1273[c]	mRNA-1273[d]	3924	TBC	WT, omicron	NCT05249829
observer blind, phase 2/3 trial	States		mRNA-1273[c]	mRNA-1273[c]	mRNA-1273.214[k]	(estimated)		(BA.4, BA.5)	
			mRNA-1273[c]	mRNA-1273[c]	mRNA-1273.214[k]				

(*Continued*)

Table 4. (Continued).

Clinical Trial	Location	No. of Doses	Dose 1	Dose 2	Dose 3/4	Population, n mITT (PP)	Mean Interval to Last Dose, Weeks (SD)	Variants Included	Reference
HKSH open label study	Hong Kong	3	CoronaVac[l]	CoronaVac[l]	CoronaVac[l]	83	28.9 (13.4–31.7)[t]	WT, delta, omicron	Lai et al.[96] *Vaccines* DOI: 10.3390/vaccines10040556
			BBIBP-CorV[m]	BBIBP-CorV[m]	CoronaVac[l]	15	30.4 (29.3–37.9)[t]		
			CoronaVac[l]	CoronaVac[l]	BNT162b2[b]	115	28.9 (13.4–31.7)[t]		
			BBIBP-CorV[m]	BBIBP-CorV[m]	BNT162b2[b]	21	30.4 (29.3–37.9)[t]		
Monovalent/bivalent phase 1 trial	United States	3	mRNA-1273[n]	mRNA-1273[n]	mRNA-1273c	48	42.0 (4.3)	WT, alpha, beta, delta	Anderson et al.[99] *Res Sq Preprint* DOI: 10.21203/rs.3.rs -1,222,037/v1
			mRNA-1273[n]	mRNA-1273[n]	mRNA-1273.351[p]	25	45.9 (3.6)		
			mRNA-1273[n]	mRNA-1273[n]	mRNA-1273[q] and mRNA-1273.351[r]	23	45.6 (3.7)		
PRIBIVAC subject blind, randomized-controlled trial	Singapore	3	BNT162b2[b]	BNT162b2[b]	BNT162b2[b]	50	38.8 (27.1–42.4)	WT, alpha, beta, delta, omicron	Poh et al.[97] *Clin Inf Dis* DOI: 10.1093/cid/ciac345
			BNT162b2[b]	BNT162b2[b]	mRNA-1273[c]	48	33.1 (27.0–42.1)		

*Table includes vaccines authorized in the United States or Europe, or by WHO.
[a]2.5×10^8 Inf.U ChAd-Ox1.S per dose; [b]30 µg BNT162b2 per dose; [c]100 µg mRNA-1273 per dose; [d]50 µg mRNA-1273 per dose; [e]5 µg of SARS-CoV recombinant spike protein adjuvanted with 50 µg of Matrix-M; [f]5×10^{10} vp Ad26.COV.2 per dose; [g]15 µg BNT162b2 per dose; [h]2.5 µg of SARS-CoV recombinant spike protein adjuvanted with 25 µg of Matrix-M; [i]100 µg, mRNA-1273.211; [j]50 µg, mRNA-1273.211; [k]50 µg, mRNA-1273.214; [l]600 SU per dose; [m]4 µg per dose; [n]25, 50, 100, or 250 µg mRNA-1273 per dose; [p]50 µg mRNA-1273.351 per dose; [q]25 µg mRNA-1273 per dose; [r]50 µg mRNA-1273.351 per dose; [s]median interval to booster, weeks (Q1-Q3); [t]range to booster, weeks.
HKSH, Hong Kong Sanatorium and Hospital; Inf.U, infectious units; mITT, modified intention-to-treat; mRNA, messenger RNA; NIH DMID, National Institutes of Health Division of Microbiology and Infectious Diseases; NS, not stated; PP, per protocol; Q, quartile; SARS-CoV, severe acute respiratory syndrome coronavirus; SD, standard deviation; SU, subunits; vp, viral particles; WHO, World Health Organization; WT, wild-type.

Table 5. Recent real-world observational studies evaluating heterologous vaccine regimens (2 or 3 doses)*.

Clinical Study	Location	No. of Doses	Dose 1	Dose 2	Dose 3	Population, n	Mean Interval to Last Dose, Weeks (range)	Variants Included (n, cases)	Reference
Nationwide cohort study	Sweden	2	ChAd-Ox1.S[a]	ChAd-Ox1.S[a]	-	430,100	ns	delta (ns)	Nordstrom[100]
			ChAd-Ox1.S[a]	mRNA-1273[b]	-	16,402			
			ChAd-Ox1.S[a]	BNT162b2[c]	-	94,569			
Retrospective test-negative case-controlled study	United States	2	mRNA-1273[b]	mRNA-1273[b]	-	11,383	ns	delta (3062), omicron (4414)	Accorsi[101]
			BNT162b2[c]	BNT162b2[c]	-	19,839		delta (1948), omicron (2520)	
			mRNA-1273[b]	BNT162b2[c]	-	26		delta (4), omicron (7)	
			BNT162b2[c]	mRNA-1273[b]	-	23		delta (6), omicron (4)	
		3	mRNA-1273[b]	mRNA-1273[b]	mRNA-1273[b]	7577	30.4 (26.1–47.8)	delta (172), omicron (732)	
			BNT162b2[c]	BNT162b2[c]	mRNA-1273[b]	953		delta (26), omicron (114)	
			BNT162b2[c]	BNT162b2[c]	BNT162b2[c]	12,476		delta (464), omicron (1494)	
			mRNA-1273[b]	mRNA-1273[b]	BNT162b2[c]	687		delta (17), omicron (99)	
			mRNA-1273[b] or BNT162b[c]	mRNA-1273[b] or BNT162b2[c]	mRNA-1273[b] or BNT162b2[c]	14		delta (1), omicron (3)	
Test-negative case-controlled study	England	2	ChAd-Ox1.S[a]	ChAd-Ox1.S[a]	-	134,225	ns	delta (ns)	Andrews *Nat Med*[102]
			BNT162b2[c]	BNT162b2[c]	-	38,645			
		3	ChAd-Ox1.S[a]	ChAd-Ox1.S[a]	mRNA-1273[b] or BNT162b2[c]	88,973			
			BNT162b2[c]	BNT162b2[c]	mRNA-1273[b] or BNT162b2[c]	132,434			
Test-negative case-controlled study	England	3	ChAd-Ox1.S[a]	ChAd-Ox1.S[a]	ChAd-Ox1.S[a], mRNA-1273[b] or BNT162b2[c]	651,426	ns	delta (21,551), omicron (213,245)	Andrews *NEJM*[23]
			mRNA-1273[b]	mRNA-1273[b]	mRNA-1273[b] or BNT162b2[c]	21,754		delta (245), omicron (8882)	
			BNT162b2[c]	BNT162b2[c]	mRNA-1273[b] or BNT162b2[c]	528,477		delta (10,437), omicron (169,574)	
VISION Network multivariate analysis	United States	2	Ad26.COV2.S[d]	Ad26.COV2.S[d]	-	467[f]	ns (1.0–17.1)	omicron (ns)	Natarajan[24]
			Ad26.COV2.S[d]	mRNA vaccine	-	1271[f]			
		3	mRNA vaccine	mRNA vaccine	-	22,010[f]			
Nationwide prospective FONASA study	Chile	3	CoronaVac[e]	CoronaVac[e]	-	2,889,319	ns (21.6–26.4)	alpha, beta, gamma, delta (ns)	Jara[25]
					CoronaVac[e]	186,946			
					BNT162b2[c]	2,019,260			
					ChAd-Ox1.S[a]	1,921,340			
Nationwide cohort study	Spain	2/3	ChAd-Ox1.S[a]	ChAd-Ox1.S[a]	mRNA-1273[b]	337,686	ns (13.0–≥25.7)	omicron (ns)	Monge[103]
			Ad26.COV2.S[d]	mRNA-1273[b]	-	109,876			
			mRNA-1273[b]	mRNA-1273[b]	mRNA-1273[b]	645,640			
			BNT162b2[c]	BNT162b2[c]	mRNA-1273[b]	3,475,122			
			ChAd-Ox1.S[a]	ChAd-Ox1.S[a]	BNT162b2[c]	136,700			
			Ad26.COV2.S[d]	BNT162b2[c]	-	28,540			
			mRNA-1273[b]	mRNA-1273[b]	BNT162b2[c]	86,406			
			BNT162b2[c]	BNT162b2[c]	BNT162b2[c]	1,402,348			
Cohort study	Germany	2	ChAd-Ox1.S[a]	ChAd-Ox1.S[a]	-	5	ns	alpha, beta, gamma (ns)	Fabricus[104]
			ChAd-Ox1.S[a]	mRNA-1273[b]	-	10			
			ChAd-Ox1.S[a]	BNT162b2[c]	-	26			
			mRNA-1273[b]	mRNA-1273[b]	-	13			
			BNT162b2[c]	BNT162b2[c]	-	61	4		

*Table includes vaccines authorized in the United States or Europe, or by WHO.
[a]2.5×10^8 Inf.U ChAd-Ox1.S per dose; [b]100 µg mRNA-1273 per dose; [c]30 µg BNT162b2 per dose; [d]5×10^{10} vp Ad26.COV.2 per dose; [e]600 SU per dose; [f]number of emergency department/urgent care visits from individuals evaluated from VISION Network data.
Inf.U, infectious units; mRNA, messenger RNA; ns, not stated; SU, subunits; vp, viral particles; WHO, World Health Organization.

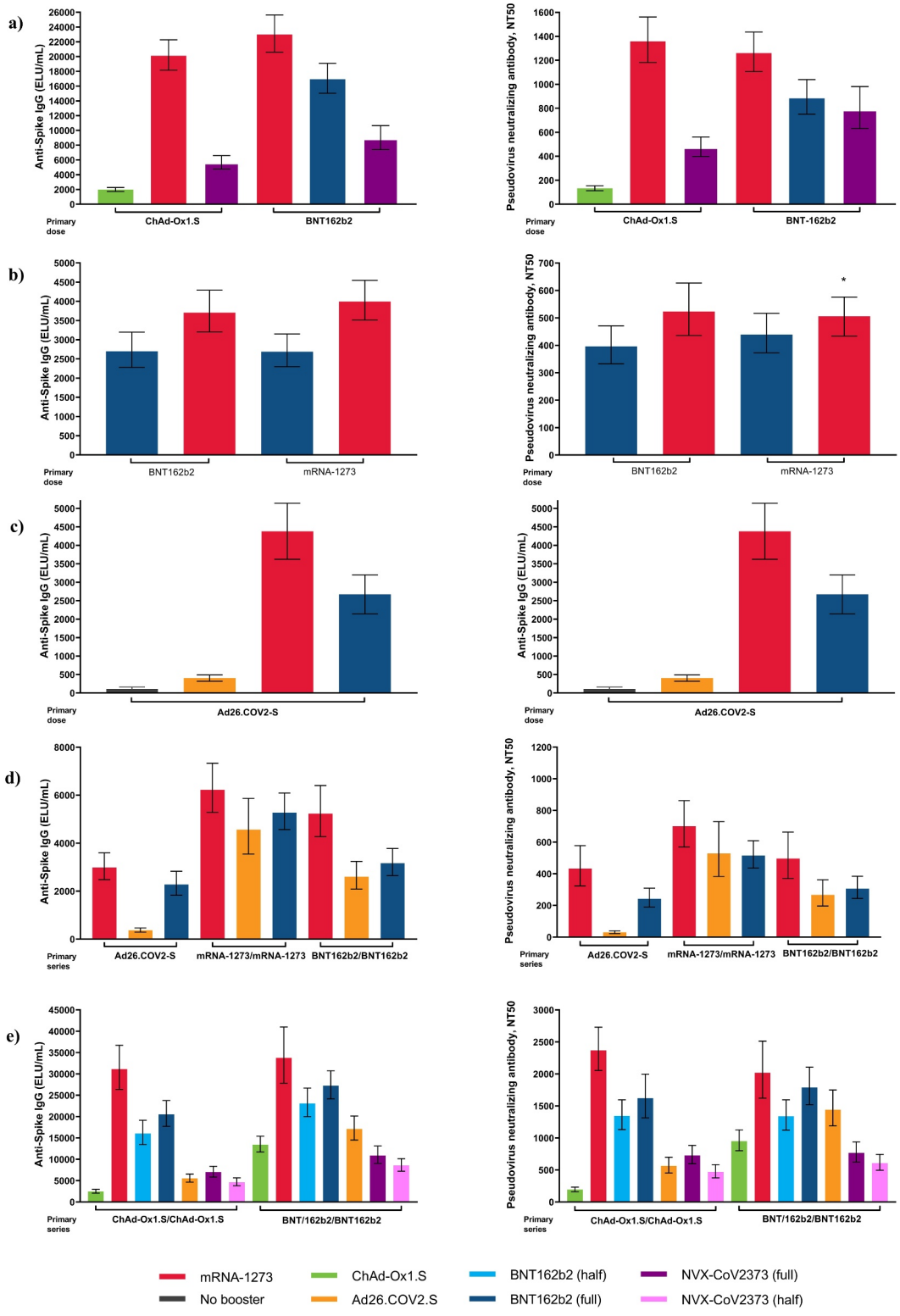

Figure 1. Immunogenicity outcomes by priming vaccine series and booster from five COVID-19 clinical trials including prime-boosting 2-dose regimens in: a) Com-COV2, b) ARNCOMBI, and c) SWITCH; and prime boosting 3-dose regimens in: d) NIH DMID and e) COV-BOOST. Response to booster is shown as bars. a) Com-COV2 trial with ChAd-Ox1.S (2.5 x 10^8 Inf.U), mRNA-1273 (100 µg), or BNT162b2 (30 µg) as the second dose administered 8 to 12 weeks after primary vaccination. Anti-spike IgG GMC at Day 28 following boost (left) and neutralizing antibody GMT at Day 28 following boost (right).[20] b) ARNCOMBI trial with mRNA-1273 (100 µg), or BNT162b2 (30 µg) as the second dose administered 4 to 7 weeks after primary vaccination. Anti-spike IgG GMC at Day 28 following boost (left) and neutralizing antibody titer GMT at Day 28 following boost (right). *Error bar is estimated from the reproduced figure (as data points not stated).[94] c) SWITCH trial with Ad26.COV2.S (≥8.92 × 10^{10} vp), mRNA-1273 (100 µg), or BNT162b2 (30 µg) as the second dose administered 12 to 14 weeks after primary vaccination. S1-specific anti-spike IgG GMT at Day 28 post boost (left), neutralizing antibody titer GMT at Day 28 following boost (right).[95] d) NIH DMID trial with Ad26.COV2.S (5 × 10^{10} vp), BNT162b2 (30 µg), mRNA-1273 (100 µg) for primary and booster vaccines; boosters administered ≥11 weeks after primary vaccination series. Anti-spike IgG GMT at Day 29 following boost (left), and neutralizing antibody GMT at Day 29 post boost (right).[26] e) COV-BOOST trial with ChAd-Ox1.S (2.5 x 10^8 Inf.U), Ad26.COV2.S (5 x 10^{10} vp), mRNA-1273 (100 µg), BNT162b2 (30 µg) or BNT162b2 half (15 µg) boosters administered 11 to 15 weeks after primary vaccination series. Anti-spike IgG GMC at Day 28 following booster (left), neutralizing antibody titer GMT at Day 28 post boost (right).[21] COVID-19, coronavirus disease 2019; D0, day 0; D2, dose 2; D28, day 28; GM, geometric mean; GMC, geometric mean concentration; GMT, geometric mean titer; IgG, immunoglobulin G; N_{50}, 50% neutralizing antibody titer; vp, viral particles.

Overall, the clinical studies discussed here provide evidence to suggest that heterologous primary and booster regimens typically produce immune responses that are similar to or better than homologous schedules.[20,21,32] Additionally, the studies suggest that a vaccination regimen including mRNA-based COVID-19 vaccines, notably mRNA-1273, may provide optimal immune responses against SARS-CoV-2 compared with other heterologous primary or booster vaccine regimens and that combined with an adenoviral vector-based vaccine primary regimen yields a more durable cellular immune response.[26]

Heterologous boosting against emerging variants of concern

As SARS-CoV-2 VoCs continue to emerge within the COVID-19 landscape, vaccination strategies must be able to rapidly target them. Indeed, results from current clinical and real-world observational studies suggest that a heterologous boost regimen may serve as an effective approach.[21,100,104,105]

Currently, the majority of the published heterologous vaccine clinical trial data is from general populations of healthy adults. As more data are gathered, regimens may also later be tailored against specific circulating VoCs and specific populations most at risk of COVID-19 infection. Interim results from the randomized PRIBIVAC study evaluating homologous and heterologous boosting with mRNA-based vaccines found heterologous boosting with mRNA-1273 induced stronger neutralization capacity compared with homologous BNT162b2 against VoCs (including omicron) among older individuals aged ≥60 years (84% and 73%, p = .0073, respectively).[97]

As the SARS-CoV-2 virus continues to evolve, booster vaccines are needed to provide protection against emerging VoCs. Results from the COV-BOOST clinical study found that heterologous boosting with mRNA vaccines generated humoral and cellular immune responses against VoCs strains comparable to those of the WT strains.[21] A ChAd-Ox1.S/ChAd-Ox1.S primary vaccination series plus an mRNA-1273 booster regimen had a similar neutralization capacity against the delta strain as against the WT (50% neutralizing antibody titer [N_{50}] WT strain, geometric mean titer [GMR]: 26.98; 95% confidence interval [CI], 21.88–33.26 vs N_{50} delta, GMR: 27.17; 95% CI, 20.81–35.47).[21] Comparatively, for a ChAd-Ox1.S/ChAd-Ox1.S primary vaccination series plus BNT162b2 booster, neutralization antibody titers against the delta strain trended lower compared with WT strains (N_{50} WT, GMR: 21.58; 95% CI, 16.93–27.51 vs N_{50} delta, GMR: 14.43; 95% CI, 10.97–18.98).[21] Cellular immune responses associated with both of these mRNA vaccines were similar for the beta and delta strains compared with WT strains, with the strongest response against the delta strain observed among individuals who received vaccinations of ChAd-Ox1.S/ChAd-Ox1.S plus an mRNA-1273 booster.[21]

Similarly, an observational study in Germany in adults assessing BNT162b2, mRNA-1273, and ChAd-Ox1.S heterologous primary and booster combinations in both COVID-19–naive and – convalescent individuals showed that humoral and cellular responses develop significantly faster with mRNA vaccines compared with ChAd-Ox1.S.[104] Additionally, the study demonstrated that compared with ChAd-Ox1.S, mRNA vaccines produce higher neutralizing antibody titers against SARS-CoV-2 VoCs, including the alpha, beta, and gamma variants.[104] The highest neutralization capacity against VoCs was induced by the heterologous ChAd-Ox1.S/mRNA-1273 regimen (87% for alpha, 85% for beta, and 71% for gamma), followed by ChAd-Ox1.S/BNT162b2 (82% for alpha, 70% for beta, and 55% for gamma).[104]

Studies have also investigated the effectiveness of heterologous booster schedules against SARS-CoV-2 variants (Table 5). A large retrospective nationwide Swedish cohort study in adults assessed both heterologous boosting (a ChAd-Ox1.S primary vaccination series followed by BNT162b2 or a ChAd-Ox1.S primary vaccination series followed by mRNA-1273) and homologous boosting with ChAd-Ox1.S after ChAd-Ox1.S priming with a single dose.[100] In this study, heterologous ChAd-Ox1.S/mRNA-1273 and ChAd-Ox1.S/BNT162b2 vaccinations were associated with 79% and 67% VE against symptomatic COVID-19, respectively, including against disease caused by the delta variant, the dominant variant during the study period.[100] When examining all heterologous schedules combined, VE against symptomatic COVID-19 was significantly higher (68%, 95% CI, 61–74; $p < .001$) compared with the homologous ChAd-Ox1.S/ChAd-Ox1.S schedule (50%, 95% CI, 41–58; $p < .001$).[100]

Real-world observational studies have provided snapshots of current vaccination strategies during times when the delta and omicron variants were dominant (Table 5). Results from the nationwide prospective FONASA study in Chile (during delta variant dominance) in which the primary regimen comprised 2-dose CoronaVac, indicated that heterologous boosting with BNT162b2 or ChAd-Ox1.S had superior VE across all clinical outcomes evaluated (symptomatic COVID-19, hospitalization, and admission to an intensive care unit) compared with homologous CoronaVac vaccination (three doses).[25] Data from a test-negative study in England found that boosting with mRNA-based vaccines offered protection against the delta variant, with respect to mild and severe COVID-19 disease; however, protection against symptomatic disease waned after 10 weeks.[102] Another test-negative study found that after a primary vaccination with either ChAd-Ox1.S or BNT162b2, boosting with either BNT162b2 or mRNA-1273 provided a substantial increase in protection against symptomatic disease, which again waned over a 5-to 9-week period; VE was substantially lower against omicron compared with the delta variant.[23]

The increased immune evasion and hyper-transmissibility of omicron and the reported waning of VE following boosting further highlights the need to stay up-to-date with optimizing vaccination strategies.[66,106] Indeed, mRNA-based vaccine boosters have been shown to be more protective compared with receiving only a primary mRNA-based vaccine series, especially noting the significantly higher difference in terms of 3- versus 2-dose protection against the omicron variant.[101,107,108] During omicron dominance, the VISION network study in the United States compared boosting with Ad26.COV2.S and mRNA-based vaccines with respect to VE against emergency department and urgent care visits. The study found

that VE was highest with mRNA-based vaccine boosting (79% for an Ad26.COV2.S/mRNA-based vaccine regimen, 83% for a 3-dose mRNA-based vaccine regimen, and 54% for a homologous Ad26.COV2.S/Ad26.COV2.S regimen).[24] Similarly, VE against hospitalization was highest with mRNA-based vaccine boosting (78% for an Ad26.COV2.S single dose primary vaccination series followed by an mRNA-based booster, 90% for a 3-dose mRNA-based vaccine regimen, and 67% for an Ad26.COV2.S/Ad26.COV2.S regimen).[24] Another study based on data collected during omicron dominance indicated that the VE of mRNA-based vaccine boosting (mRNA-1273 or BNT162b2) was moderately effective in preventing infection (51%); the highest VE against infection with an mRNA-based booster (dose 3) was observed in individuals primed with 2-dose ChAd-Ox1.S (59%) and 2-dose mRNA-1273 (55%), followed by 2-dose BNT162b2 (50%) and Ad26.COV2.S (48%).[103]

Overall, these real-world observational studies, in conjunction with the clinical data, suggest that mRNA-based heterologous boosting strategies may be successful against emerging variants. While most available data were collected during the dominant circulation of the delta, omicron, and subvariants BA.1 and BA.2, 2 doses of an mRNA-based vaccine regimen followed by a booster have also shown evidence of cross-neutralization against the BA.4/5 variant and omicron subvariant BA.2.12.1.[109] This suggests incremental clinical protection gains may still be obtained with the current boosting strategies. Additional data relating to the most recent omicron subvariants, BA.4/5, and future variants, will further inform such recommendations.[101,108,110,111]

Safety and reactogenicity of heterologous vaccine regimens

In addition to being able to elicit a strong immunogenic response, heterologous booster vaccination regimens also need to demonstrate an acceptable safety profile that is comparable to that of the primary vaccination series. Although the studies summarized here were not powered to detect reactogenicity differences and were limited in size, overall results showed that adverse events were short-lived. Among the studies reviewed, results from the phase 1/2 NIH DMID study demonstrated that both homologous and heterologous booster vaccinations combinations were well-tolerated and that reactogenicity events such as injection site pain, malaise, headache, and myalgia within a 7-day period following booster administration were similar to those reported for the primary vaccination series (Figures 2 and 3).[26,32] Among the many booster permutations evaluated in the COV-BOOST study, three vaccines showed high reactogenicity, which included mRNA-1273 after a ChAd-Ox1.S or BNT162b2 2-dose primary vaccination series and ChAd-Ox1.S or Ad26.COV2.S after a BNT162b2 2-dose primary vaccination series.[21] Although not powered to compare regimens, mRNA-1273 appeared more reactogenic in terms of reported pain and redness at the injection site and fatigue compared with BNT162b2 within the 7-day period following booster administeration.[21] Participants who received an mRNA-based vaccine or Ad26.COV2.S after two doses of ChAd-Ox1.S demonstrated more frequent systemic and local adverse events within the 7-day period post-vaccination compared with individuals receiving other vaccine combinations.[21] Overall, serious adverse events were infrequent and were largely similar between vaccine and control groups.[21] A sub-trial extension arm of COV-BOOST conducted during the time period in which omicron was a dominant strain found that a second booster (dose 4 of the regimen) of BNT162b2 (30 μg) or mRNA-1273 (50 μg) was well tolerated, with short-lived reactogenicity events similar to the primary vaccination series (dose 2) and the first booster (dose 3), including pain, malaise, headache, myalgia, and fatigue experienced within the 7-day period following the booster dose.[93]

In Com-COV2, heterologous dose 2 with mRNA-1273 showed increased systemic reactogenicity compared with the homologous primary vaccination series within the 7-day period following dose 2, including feeling feverish (although with no increase in temperature); having chills, muscle aches, and general malaise; and reporting headache (Figures 2 and 3).[20] Additionally, results suggest increased reactogenicity for the heterologous over the homologous mRNA primary vaccination series vaccine schedule (BNT162b2/mRNA-1273 vs BNT162b2/BNT162b2). However, this effect may be due to the mixing of different mRNA-based vaccines or due to the higher dosage of mRNA-1273.[20] In all, mRNA-based heterologous regimens produced transient local and systemic adverse events, with acceptable tolerability profiles, especially in the context of the benefits associated with higher immunogenicity and T-cell response.[20] In the ARNCOMBI study, although dose 2 with mRNA-1273 was associated with a higher rate of local and systemic adverse events (pain at the injections site, headache, myalgia, and joint pain) compared with dose 2 with BNT162b2 ($p < .0001$), overall, all homologous and heterologous primary vaccination regimens were well tolerated.[94]

The safety and reactogenic profiles of mRNA-based boosters paired with various primary regimens administered worldwide have also been investigated. In the HKSH study, a 2-dose BBIBP-CorV or a 2-dose CoronaVac primary vaccination series, followed by a BNT162b2 booster, was reported to be safe, with adverse events similar to those reported for other heterologous mRNA-based vaccine regimens.[96]

Although not described within publications from this search, rare cases of myocarditis and pericarditis have been reported after the administration of mRNA-1273 or BNT-162b2.[112,113] In particular, rates of myocarditis in mRNA-1273 vaccine recipients were not higher than expected for the general population, with the exception of males aged 18–24 years.

Emerging mRNA-based vaccine boosters in development

As described previously, heterologous boosting with mRNA-based boosters elicits strong immune responses to WT SARS-CoV-2 infection and provided additional protection against VoCs such as omicron and its variants. To further counter emerging VoCs, booster vaccines targeting a specific variant and/or variants may provide better coverage and help equip healthcare professionals to prevent future outbreaks and avoid the associated impact on healthcare systems. The mRNA-based vaccine platform as a technology also offers

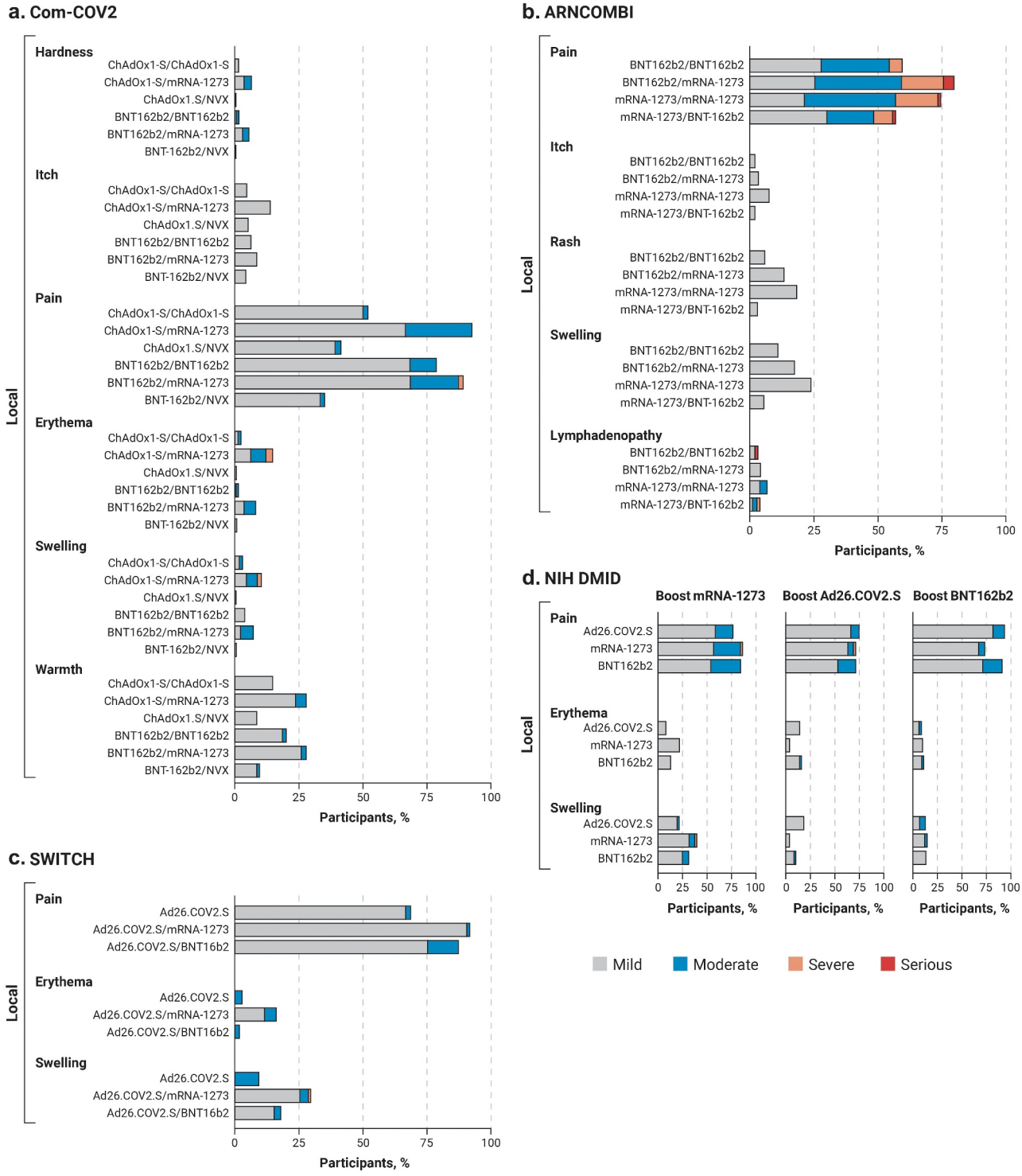

Figure 2. Solicited local reactions within 0 to 7 days of injection in four clinical trials evaluating heterologous vaccine regimens. a) Com-COV2, b) ARNCOMBI, c) SWITCH, and d) NIH DMID. a) Com-COV2 study with dose 2 of ChAd-Ox1.S (2.5×10^8 Inf.U), mRNA-1273 (100 µg), or BNT162b2 (30 µg) administered approximately 8 to 12 weeks after primary vaccination;[20] b) ARNCOMBI study with dose 2 of mRNA-1273 (100 µg), or BNT162b2 (30 µg) administered 4 to 7 weeks after primary vaccination;[94] c) SWITCH study with dose 3 of Ad26.COV2.S (≥8.92×10^{10} vp), mRNA-1273 (100 µg), or BNT162b2 (30 µg) administered after primary vaccination;[95] and d) NIH DMID study with dose 3 of Ad26.COV2.S (5×10^{10} vps), mRNA-1273 (100 µg), or BNT162b2 (30 µg) administered ≥11 weeks after primary vaccination series.[21] mRNA, messenger RNA; NIH DMID, National Institutes of Health Division of Microbiology and Infectious Diseases; vp, viral particle.

a fast, efficient, and flexible solution to adapt to the COVID-19 variant landscape as it evolves. Clinical evaluation of a multivalent COVID-19 mRNA-based booster platform is currently underway, with bivalent booster candidates that include mRNA-1273.211, mRNA-1273.214, mRNA-1273.351, Pfizer-BioNTech's omicron-adaptive vaccine, and mRNA-based vaccines containing the BA.4/BA.5 variant.[30,99,114,115]

mRNA-1273.211 contains equal amounts of two spike protein sequences from WT SARS-CoV-2 and the beta variant (the beta variant shares key antibody escape mutations as omicron); mRNA-1273.214 contains equal amounts of two

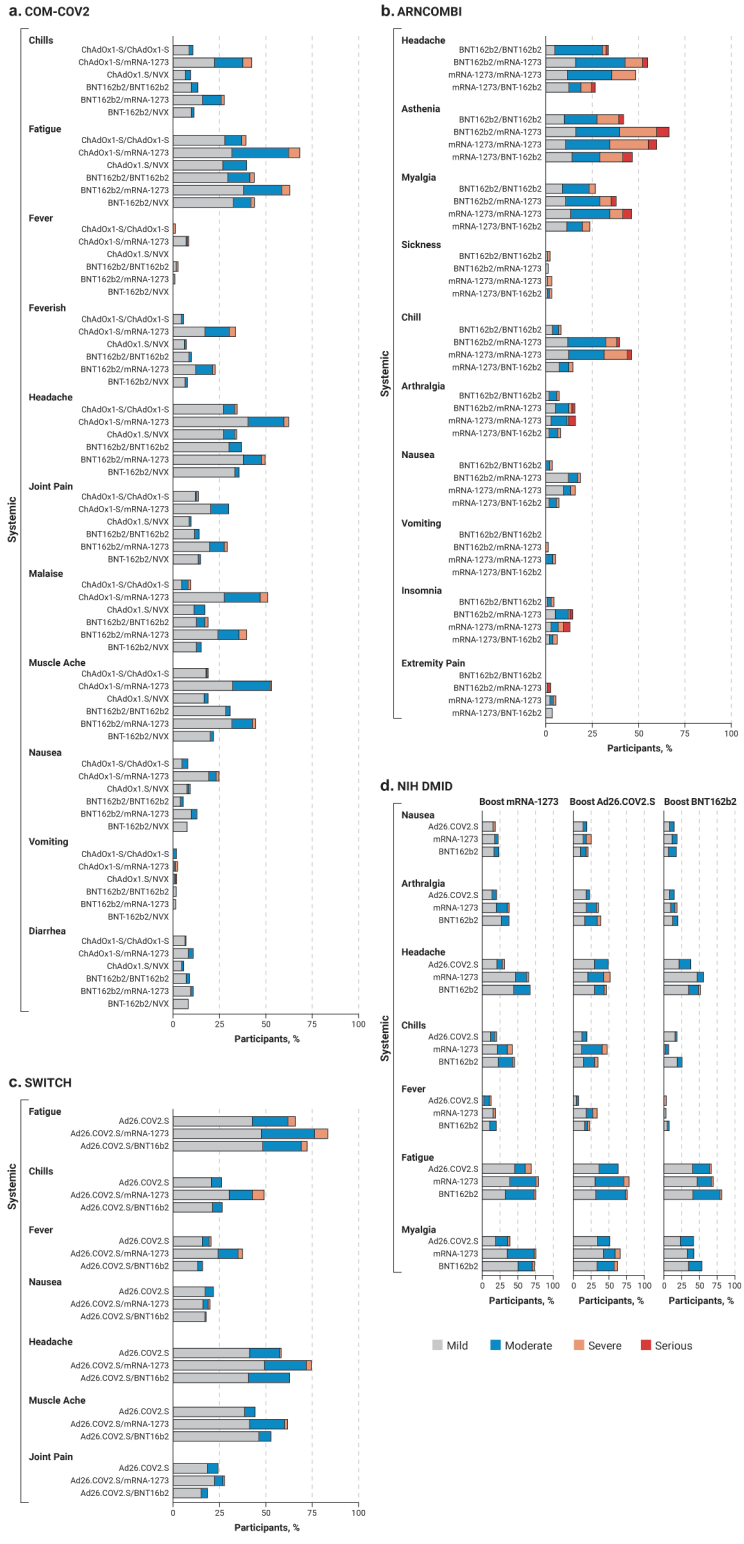

Figure 3. Solicited systemic reactions within 0 to 7 days of injection in four clinical trials evaluating heterologous vaccine regimens. a) Com-COV2, b) ARNCOMBI, c) SWITCH, and d) NIH DMID. Vaccine dosing regimens are as described per Figure 2. a) Com-COV2 study: approximately 8 to 12 weeks after the primary vaccination, dose 2 of either ChAd-Ox1.S (2.5×10^8 Inf.U), mRNA-1273 (100 µg), or BNT162b2 (30 µg) was administered;[20] b) ARNCOMBI study: approximately 4 to 7 weeks after the primary vaccination dose 2 of mRNA-1273 (100 µg) or BNT162b2 (30 µg) was administered;[94] c) SWITCH study: after the primary vaccination series, dose 3 of Ad26.COV2.S (≥8.92×10^{10} vp), mRNA-1273 (100 µg), or BNT162b2 (30 µg) was administered;[95] and d) NIH DMID study: ≥11 weeks after primary vaccination series dose 3 of either wAd26.COV2.S (5×10^{10} vps), mRNA-1273 (100 µg), or BNT162b2 (30 µg) was administered.[21] mRNA, messenger RNA; NIH DMID, National Institutes of Health Division of Microbiology and Infectious Diseases; vp, viral particle.

spike protein sequences from WT SARS-CoV-2 infection, including omicron. Interim results from a phase 2/3 study of mRNA-1273.211 (NCT04927065; Table 4) in adults have demonstrated increased neutralizing antibody titers with mRNA-1273.211 as a booster (dose 3) against the beta, delta, and omicron variants 4 weeks after administration compared with an mRNA-1273 booster.[98] This superior immunogenicity continued for beta and omicron variants 6

months following booster administration. In addition, the safety and tolerability profile were consistent with the authorized 50 µg mRNA-1273 booster.[98] Another phase 2/3 study evaluating the mRNA-1273.214 booster vaccine in adults (dose 3) is underway, with full results expected in late 2022 (NCT05249829; Table 4). Preliminary results (1 month following booster dose) showed that mRNA-1273.214 administered as a heterologous booster (dose 3) exhibited a 5.4-fold increase in neutralizing antibody response (95% CI, 5.0–5.9) against omicron BA.4/BA.5 above baseline in all individuals regardless of prior SAR-2 COV-2 infection, and a 6.3-fold increase (95% CI, 5.7–6.9) in the subset of seronegative individuals.[115] The mRNA-1273.214 booster was generally well tolerated, and the reactogenicity and safety profiles were consistent with that of homologous boosting with mRNA-1273.[115] Pfizer-BioNTech's omicron adaptive vaccines are also being evaluated as heterologous boosters (dose 3 or 4) in a phase 2/3 trial in individuals ≥56 years of age (Table 4).[114] Interim results showed that these vaccines candidates (monovalent and bivalent) elicited substantially higher responses against the omicron BA.1 subvariant compared with homologous boosting with BNT1626b and that both vaccines were generally well tolerated.[114]

With the greater protection that mRNA-based vaccines strategies may offer against emerging VoCs, increasing accessibility will aid in optimizing global coverage. Supply of any vaccine can greatly depend on available storage facilities, and for future mRNA-based vaccines, improving ease of storage will further enhance vaccine options at the practical level. Currently, mRNA-1273 and BNT1626b must be stored at low temperatures (−50°C to −15°C; −90°C to −60°C, respectively) over a long period of time, although both can be stored undiluted in the refrigerator for up to 1 month.[37,116] To enhance the storage supply, the refrigerator stable (2°C to 5°C) mRNA-based vaccine mRNA-1283 has been developed and is currently being evaluated as a next-generation mRNA-based vaccine in clinical trials (NCT04813796 and NCT05137236).[33,117]

Discussion

As various heterologous booster permutations continue to evolve, it remains important to assess the immunogenicity of these vaccination regimens; these data can then inform national vaccination recommendations. Available studies show that heterologous mRNA-based boosting, specifically with mRNA-1273, induces stronger humoral and cellular immune responses compared with homologous or heterologous boosts with BNT162b2 or ChAd-Ox1.S.[20,21,94] Currently, there is no agreed upon correlate of protection against SARS-CoV-2, although cellular and humoral responses are commonly used. Results from real-world studies also demonstrate that an mRNA-1273 or BNT162b2 heterologous booster following primary ChAd-Ox1.S vaccination provides strong protection against symptomatic COVID-19.[93,100,104] Additionally, for certain VoCs, heterologous ChAd-Ox1.S-Ox1/mRNA-1273 and ChAd-Ox1.S/BNT162b2 vaccination schedules have shown strong neutralization capacity.[21,100,104] Although a higher immunogenic response to mRNA-1273 may evoke greater protection, it may also be associated with more reactogenicity.[118] However, local and systemic adverse events are transient in nature (with a 7-day window following injection), and the safety and tolerability profile is generally acceptable, especially in the context of mRNA-1273, providing immune responses that ultimately help prevent serious outcomes associated with severe COVID-19 disease.

Currently, there are limited data investigating heterologous boosting against asymptomatic SARS-CoV-2 infection. During the emergence of omicron, a higher rate of asymptomatic infection was reported compared with during delta dominance (~23–26% and 8%, respectively), with results from a few studies that assessed booster vaccination, reporting that a higher proportion of individuals presented with asymptomatic infection and non-severe disease compared with individuals who were unvaccinated or received a primary vaccination series only.[119,120] As populations are exposed to different circulating VoCs over time and receive various primary vaccination regimens, future heterologous mRNA-based boosting strategies might also assess the impact of asymptomatic infection in addition to symptomatic infection.

To help keep pace with the evolving COVID-19 pandemic, heterologous primary and booster vaccine strategies can offer safe and improved prophylactic options compared with homologous vaccine schedules in terms of both immunogenicity and reactogenicity.[121] Clinical and real-world evidence to date supports heterologous vaccination schedules among both COVID-19-convalescent and -naive populations, although the optimal booster combination and interval after completing the primary vaccination series are still being examined.[20,21,32,100,104,122] In addition, the seasonal timing of a booster dose, use in children and adolescents, concomitant use with other routine vaccines, and ability to combat the emergence of current and future VoCs should also be further considered.

With 40 COVID-19 vaccines approved by the World Health Organization (WHO) and more likely to be approved in the future, considerations of heterologous boosters after region-specific primary vaccination regimens can simplify future booster strategies.[15] The current evidence strongly supports the administration of one booster (>1 booster dose for immunocompromised or older adults) to significantly reduce the risk of severe COVID-19 disease especially with the emergence of VoCs such as omicron.[23,24,101,102] As of mid-July 2022, boosters have been administered to only 53%, 11%, and 1.2% of individuals (who have already received a primary COVID-19 vaccine regimen) in high-income, low- to middle-income and low-income countries, respectively.[123] Indeed, there remains a huge proportion of these populations who would benefit from the administration of a booster, and with various primary regimens supplied around the globe, heterologous boosting strategies can support the practicalities of supply and superior effectiveness within an acceptable safety profile to include protection against current and future VoCs.

The studies summarized in this review suggest that heterologous boosting with mRNA-based vaccines shows superior vaccine effectiveness, which may complement the various primary regimens already administered globally. Several studies have suggested that the addition of mRNA-1273 to vaccine regimens results in higher immunogenicity and observed protection even to "non-vaccine-matched" VoCs. In addition, the

administration of an adenoviral vector-based vaccine within a heterologous mRNA-based vaccine regimen appears to increase overall CD8+ T-cell response. In a practical context, such "mix and match" strategies can serve to simplify the implementation of mass vaccination programs, which will continue to evolve as VoCs emerge across the COVID-19 landscape. A limitation of currently published studies is the absence of long-term data to assess the association between waning antibody response and overall vaccine protection.

Conclusions

Heterologous vaccine booster strategies following a primary vaccine series facilitate a safe, effective, and pragmatic approach toward preventing severe outcomes from COVID-19. In particular, flexible mRNA-based vaccine platforms provide the advantage of rapidly designing new vaccines against emerging SARS-CoV-2 variants that can be promptly deployed to mitigate COVID-19. It is also crucial to consider the primary regimens already admin-istered or still to be administered worldwide to determine how heterologous priming and boosting regimens may be optimized within this framework. Data from future clinical and real-world observational studies across the globe will further strengthen decisive COVID-19 booster vaccination strategies.

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Disclosure statement

RD, PB, and JMM are employees of Moderna, Inc., and hold stock/stock options. BJK is a consultant for Moderna, Inc., RNH was an employee of Moderna, Inc., at the time of writing the manuscript and held stock/stock options at the company.

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Data availability statement

The data summarized in this review are from published articles and are publicly available.

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