Prime-Boost COVID-19 Vaccination against SARS-CoV-2

Subjects: Virology

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The types of these vaccines include two recombinant adenovirus vaccines (ChAdOx1-S and Ad26.COV2-S), one heterologous recombinant adenovirus vaccine (Gam-COVID-Vac), two mRNA vaccines (BNT162b2 and mRNA-1273), two inactivated virus vaccines (BBIBP-CorV and CoronaVac), and one recombinant protein vaccine (NVX-CoV2373).

SARS-CoV-2 COVID-19 heterologous vaccine safety T-cell response

1. Introduction

According to **Table 1**, for full immunization with most vaccines (excluded from Ad26.COV2-S and Gam-COVID-VaC), people need to be inoculated with two doses of the same vaccines (i.e., homologous vaccination, homologous vaccine regimen, or homologous prime-boost schedules) with an interval of 14 days to three months. As of 26 September 2021, only 32.86% of the world was fully immunized with the COVID-19 vaccine [1]. Vaccine shortage delays the schedule for the second dose of homologous vaccination and postpones the achievement of global herd immunity.

Table 1. List of valid vaccines for COVID-19.

Vaccine Name	Developer Country	Manufacturer	Vaccine Type	Storage Temperature/Shelf Life	Number of Doses	Interval between Doses	Vaccine Efficacy/Age (y)	Serious Adverse Event	Reference
ChAdOx1-S (AZD1222)	UK	AstraZeneca, SK Bioscience, and Serum Institute of India	Recombinant adenovirus vector	2–8 °C/6 months	2	Day 28–84	63%/≥18	Cerebral venous sinus thrombosis (CSVT) and other venous thrombosis with thrombocytopenia syndrome	[2][3][4][5]
Ad26.COV2-S	USA and Europe	Janssen Pharmaceutical and Johnson & Johnson	Recombinant adenovirus vector	2–8 °C/4.5 months −20 °C/2 years	1	Day 0	66.9%/≥18	Cerebral venous sinus thrombosis (CSVT) and other venous vthrombosis with	[3][4][5][6]

Vaccine Name	Developer Country	Manufacturer	Vaccine Type	Storage Temperature/Shelf Life	Number of Doses	Interval between Doses	Vaccine Efficacy/Age (y)	Serious Adverse Event	Reference
								thrombocytopenia syndrome	
BNT162b2	USA and Germany	Pfizer and BioNTech	mRNA	−70 °C/6 months	2	Day 21	92%/≥16	Anaphylaxis and myocarditis	[3][5][7][8]
mRNA-1273	USA and Europe	Moderna Biotech	mRNA	2–8 °C/1 month −20 °C/6 months	2	Day 28	94.1%/≥18	Myocarditis, anaphylaxis, and other serious allergic reactions	[3][5][8][9] [10]
BBIBP-CorV (BIBP vaccine or Sinopharm COVID-19 vaccine)	China	Beijing Institute of Biological Products and Sinopharm	Inactivated virus	2–8 °C/2 years	2	Day 14	78.1%/18–59	No adverse reports **	[3][5]
CoronaVac	China	Sinovac	Inactivated virus	2–8 °C/2 years	2	Day 14	50.7%/18–59 51.1%/ ≥60	No adverse reports **	[3][5][11] [12]
NVX-CoV2373	USA	Novavax	Recombinant protein	2–8 °C/not reported	2	Day 21	89.7%/≥18 *	Myocarditis	[13]
Gam-COVID-Vac (Sputnik V)	Russia	Gamaleya Research Institute of Epidemiology and Microbiology	Heterologous recombinant adenovirus vector	2–8 °C for dry form or −18.5 °C for liquid form/not reported	1st dose rAd5; 2nd dose rAd6	Day 21	91.6%/≥18	No adverse reports **	[14][15]

* The vaccine efficacy was based on combination of vaccination with one or two dose. ** Accorded to WHO website.

women [17][18][19]. Those uncommon serious adverse events may trigger the decline of COVID-19 vaccination, including those people who had received the first dose of ChAdOx1-S. These events have enhance the forming of vaccine hesitancy, which is a behavior of a delayed acceptance or refusal of vaccination despite the vaccination services which are available [16][20]. Subsequently, vaccine hesitancy may become one of the key factors to delay the completion of global herd immunity.

The status of vaccine shortage and vaccine hesitancy can affect the timing of global herd immunity. The use of heterologous vaccines may be beneficial for earlier reduction of the COVID-19 pandemic. Since the vaccine shortage and vaccine hesitancy slow the rate of herd immunity, the current vaccine regimen has been switched to heterologous vaccination from homologous vaccination [21][22]. Several studies have been reported for the safety and immunogenicity of heterologous ChAdOx1-S and mRNA vaccination (heterologous combing with first dose/second dose of ChAdOx1-S/mRNA and mRNA vaccine/ChAdOx1-S) [23][24][25][26][27][28][29][30][31]. However, the implication of heterologous ChAdOx1-S and mRNA vaccination against COVID-19 is still unclear. The safety and immunogenicity for each vaccine regmien are crtical factors to combat COVID-19. Hence, we conduct a systematic review to summarize the current findings on the safety and immuno-genicity of this heterologous vaccination and elucidate their implications against COVID-19.

2. Safety and Immunogenicity

The safety of heterologous ChAdOx1-S and mRNA vaccination was reported in five clinical studies [25][26][27][28][29][30] and one prospective study [32]. Two clinical studies had separately enrolled the participants for heterologous ChAdOx1-S/BNT162b2 vaccination from Spain (n = 451) [27] and Germany (n = 26) [28]. Two clinical studies utilized

the same participants from the UK to separately evaluate the vaccine safety within seven and 28 days after the boost (*n* = 110) [24][29]. Another one was estimated the vaccine effectiveness (VE) of heterologous vaccine (ChAdOx1 with mRNA vaccine as the second dose) from Denmark [30]. The interval for heterologous vaccination of ChAdOx1-S/BNT162b2 was 8–12 weeks for the study in Spain [27], eight weeks for that in Germany [28], four weeks for that in the United Kingdom [25][29], and 82 days in Denmark [30]. For the prospective study, the individuals were screened who received the ChAdOx1-S/BNT162b2 with the 10–12-week vaccine interval (*n* = 104). Although the intervals were dissimilar, these studies all reported no serious adverse events regarding heterologous ChAdOx1-S/BNT162b2 vaccination after one [32], seven [26][27], 28 days [29], or more than one day [28].

The two clinical studies from the United Kingdom also enrolled the participants for heterologous BNT162b2/ChAdOx1-S vaccination with the four-week interval. All participants with heterologous BNT162b2/ChAdOx1-S vaccination did not present vaccine-related serious adverse events within seven [26] and 28 days [29] after boost (*n* = 114). The occurrence of serious adverse events was not related to the vaccination order of BNT162b2 and ChAdOx1-S.

A clinical study in Sweden further reported no serious adverse events in the participants with the heterologous ChAdOx1-S/mRNA-1273 vaccination on day 7 to day 10 after the boost [26]. This was also found in the individuals with heterologous ChAdOx1-S/mRNA-1273 or ChAdOx1-S/BNT162b2 vaccination within seven days after the boost (*n* = 96). Regardless of interventions or intervals of heterologous ChAdOx1-S and mRNA vaccination, there were no serious adverse events regarding this heterologous vaccine regimen. However, the serious adverse events are still listed in the safety concerns of ChAdOx1-S and mRNA vaccine as very rare, which have been only observed in one per 100,000 to 250,000 ChAdOx1-S vaccinated people [33] and 2.5 to 24 per 10,000,000 mRNA vaccinated people [6][7][8]. Current studies in the safety of heterologous ChAdOx1-S and mRNA vaccination were based only on small populations. More clinical studies are needed to evaluate the safety of heterologous vaccination.

The immunogenicity of heterologous ChAdOx1-S and mRNA vaccination is important for COVID-19 protection. Current studies have evaluated the immunogenicity of heterologous ChAdOx1-S and mRNA vaccination via detecting the level of SARS-CoV-2-specific IgG, the ability of neutralization antibody against wild type or variant SARS-CoV-2 or Spike-specific T-cell immune response (**Table 2**). These five studies reported the levels of SARS-CoV-2-specific IgG between homologous and heterologous vaccine groups [25][28][29][30][31][32]. Four of those studies independently showed that the level of SARS-CoV-2-Spike-specific IgG was significantly higher (in people who received ChAdOx1-S, then the boost of BNT162b2 or mRNA-1273) than that in people having homologous ChAdOx1-S/ChAdOx1-S vaccination regardless of the inoculating intervals [25][29][30][31][32][33]. Moreover, this IgG level of the heterologous vaccination groups was similar to or higher than that of the homologous vaccination with BNT162b2/BNT162b2 [28][29][32] or mRNA 1273/mRNA 1273 [31]. A similar observation was found on the level of SARS-CoV-2- receptor-binding domain-specific IgG [25][32]. One clinical study further showed that the heterologous ChAdOx1-S/BNT162b2 vaccination could induce a higher level of SARS-CoV-2-Spike-specific IgG in comparison to the heterologous BNT162b2/ChAdOx1-S vaccination [29].

Table 2. Studies of heterologous ChAdOx1-S with mRNA vaccination.

Reference	Country	Design	Interval between Doses	Intervention (1st/2nd Dose)	Results
Johan N. et al., 2021 [25]	Sweden	An open, multicenter phase IV study	9–12 weeks	Homologous vaccine group: ChAdOx1-S/ChAdOx1-S (*n* = 37, 28- to 62-year-old) Heterologous vaccine group: ChAdOx1-S/mRNA-1273 (*n* = 51, 23- to 59-year-old)	S-specific and RBD-specific IgG geometric mean titers At the day of the 2nd dose inoculation, the similar titer of S-specific and RBD-specific IgG between two groups • At D7 to D10 after 2nd dose inoculation, S-specific and RBD-specific IgG titers in the ChAdOx1-S/mRNA-1273 were separately 115-fold and 125-fold of that on the day of the 2nd dose inoculation, and that was 5-fold in the ChAdOx1-S/ChAdOx1-S • At D30 after 2nd dose inoculation, S-specific and RBD-specific IgG titers in two groups were the same with that on D7 to D10 time point. Neutralization antibody against wild type SARS-CoV-2 • At the day of 2nd dose inoculation, the titer of ID_{50} was similar between two groups

Reference	Country	Design	Interval between Doses	Intervention (1st/2nd Dose)	Results
					• At D7 to D10 after 2nd dose inoculation, the titer of ID_{50} in the ChAdOx1-S/mRNA-1273 was 20-fold of that on the day of 2nd dose inoculation and it was 2-fold in the ChAdOx1-S/ChAdOx1-S • At D30 after 2nd dose inoculation, the titer of ID_{50} in two groups was 1.6 to 1.7-fold of that on D7 to D10 time point, but it was not significant Neutralization antibody against B.1.351, Beta variant SARS-CoV-2 • At the D7 to D10 after 2nd dose inoculation, the ChAdOx1-S/mRNA-1273 had induced the antibodies that could neutralize the B.1.351, Beta variant SARS-CoV-2, but the ChAdOx1-S/ChAdOx1-S could not induce potent antibodies against this variant Adverse events (on the D7 to D10 after 2nd dose inoculation) • No serious adverse events were reported

Reference	Country	Design	Interval between Doses	Intervention (1st/2nd Dose)	Results
					in two groups • The incidence of systemic adverse events such as fever, headache, chills and injection site pain, was frequently found in the ChAdOx1-S/mRNA-1273 than that in the ChAdOx1-S/ChAdOx1-S • The grade of adverse events was not statistically significant different between two groups
Robert, H.S. et al., 2021 [23][24][26]	UK	A single-blind, randomized, multicenter phase II study	4 weeks	Homologous vaccine group (50- to 69-year-old): ChAdOx1-S/ChAdOx1-S (*n* = 115); BNT162b2/BNT162b2 (*n* = 110) Heterologous vaccine group (50- to 69-year-old): ChAdOx1-S/BNT162b2 (n = 110); BNT162b2/ChAdOx1-S (*n* = 114)	Adverse events • No serious adverse events reported in all groups within 7 days after inoculation • The systemic adverse events were more frequently found in the heterologous vaccine groups than that in their homologous vaccine groups within 2 days after inoculation
Alberto, M.B. et al., 2021 [24][27]	Spain	An open-label, randomized, controlled	8–12 weeks	Without homologous vaccine group, only 1 dose of ChAdOx1-S (*n* = 226, 18- to 60-	S-specific and RBD-specific IgG geometric mean titers

Reference	Country	Design	Interval between Doses	Intervention (1st/2nd Dose)	Results
		multicenter phase II study		year-old): Heterologous vaccine group (18- to 60-year-old): ChAdOx1-S/BNT162b2 (*n* = 451)	• At the day of 2nd dose inoculation, the similar titer of S-specific and RBD-specific IgG between two groups • The titer of S-specific and RBD-specific IgG in the 1st dose of ChAdOx1-S on the day of 2nd dose inoculation, which was similar to that on D7 and D14 after inoculation • At D7 and D14 after 2nd dose inoculation, both S-specific and RBD-specific IgG titers in the ChAdOx1-S/BNT162b2 were significantly higher than that in the 1st dose of ChAdOx1-S Neutralization antibody against pseudovirus-SARS-CoV-2 • At the day of 2nd dose inoculation, PVNT50 was similar between two groups • At D14 after 2nd dose inoculation, PVNT50 in the ChAdOx1-S/BNT162b2 were 45-

Reference	Country	Design	Interval between Doses	Intervention (1st/2nd Dose)	Results
					fold of that in the 1st dose of ChAdOx1-S S-specific T cell immune response • At the day of 2nd dose inoculation, production of IFN-γ was similar between two groups • At the D14 after 2nd dose inoculation, production of IFN-γ in the ChAdOx1-S/BNT162b2 was significantly higher than in the 1st dose of ChAdOx1-S Adverse events • No serious adverse events were reported in heterologous vaccine group • Incidence of systematic adverse events were more than others in ChAdOx1-S/BNT162b2 within D7 after 2nd dose of inoculation • There was no data regarding the difference in the incidence of adverse

Reference	Country	Design	Interval between Doses	Intervention (1st/2nd Dose)	Results
					events between the two group
Tina S. et al., 2021 [31]	Germany	Observation study	9–12 weeks: ChAdOx1-S/ChAdOx1-S; ChAdOx1-S/BNT162b2 or mRNA-1273 3–6 weeks: BNT162b2/BNT162b2 or mRNA-1273/mRNA-1273	Homologous vaccine group: ChAdOx1-S/ChAdOx1-S (*n* = 55, 36- to 61-year-old); BNT162b2/BNT162b2 or mRNA-1273/mRNA-1273 (*n* = 62, 29- to 52-year-old) Heterologous vaccine group: ChAdOx1-S/BNT162b2 or mRNA-1273 (*n* = 96, 30- to 59-year-old)	S-specific IgG geometric mean titers: • At the D14 after 2nd dose inoculation, the titer of S-specific IgG was similar between ChAdOx1-S/BNT162b2 or mRNA-1273 and 2 dose of BNT162b2 or mRNA-1273, that was significantly higher than that in the ChAdOx1-S/ChAdOx1-S Neutralization antibody against SARS-CoV-2 by surrogate virus neutralization test • At the D14 after 2nd dose inoculation, the percentage inhibition of neutralization antibody was similar between ChAdOx1-S/BNT162b2 or mRNA-1273 and 2nd dose of BNT162b2 or mRNA-1273, that was significantly higher than that in the ChAdOx1-S/ChAdOx1-S S-specific T cell immune response:

Reference	Country	Design	Interval between Doses	Intervention (1st/2nd Dose)	Results
					• At the D14 after 2nd dose inoculation, percentage of CD69+ IFN-γ+ CD4+ T cells was similar between ChAdOx1-S/BNT162b2 or mRNA-1273 and 2nd dose of BNT162b2 or mRNA-1273, that was significantly higher than that in the ChAdOx1-S/ChAdOx1-S • The percentage of CD69+ IFN-γ+ CD8+ T cells was significantly higher than that in both ChAdOx1-S/ChAdOx1-S and 2nd dose of BNT162b2 or mRNA-1273 Adverse events (within D7 after 2nd inoculation): • No serious adverse events were reported in heterologous vaccine group • The incidence of adverse events in the ChAdOx1-S/BNT162b2 or mRNA-1273 was similar to that in the 2

Reference	Country	Design	Interval between Doses	Intervention (1st/2nd Dose)	Results
					doses of BNT162b2 or mRNA-1273, but more than that in the 2 doses of ChAdOx1-S • The incidence of adverse events in the ChAdOx1-S/BNT162b2 was similar to that in the ChAdOx1-S prime
Rüdiger G. et al., 2021 [28]	Germany	Clinical study	8 weeks	Homologous vaccine group: BNT162b2/BNT162b2 (*n* = NR, 25-to 55-year-old) Heterologous vaccine group: ChAdOx1-S/BNT162-b2 (*n* = 26, 25- to 46-year-old)	S-specific IgG titer: • At the D14–19 after 2nd dose inoculation, this titer in the ChAdOx1-S/BNT162b2 were separately significantly higher than that at the day of 2nd dose inoculation and that in the 2 doses of BNT162b2 at D13–15 after 2nd dose inoculation Neutralization antibody against pseudovirus-wild type-SARS-CoV-2 • At the D14–19 after 2nd dose inoculation, the PVNT50 in the ChAdOx1-S/BNT162b2 were separately significantly higher than that at the day of 2nd dose inoculation and that in

Reference	Country	Design	Interval between Doses	Intervention (1st/2nd Dose)	Results
					the 2 doses of BNT162b2 at D13–15 after 2nd dose inoculation Neutralization antibody against pseudovirus-variant-SARS-CoV-2 • PVNT50 against alpha- and beta-SARS-CoV-2 in in the ChAdOx1-S/BNT162b2 at D14–19 after 2nd dose inoculation, was separately higher than that in the 2 doses of BNT162b2 at D13–15 after 2nd dose inoculation, but the PVNT50 against delta-SARS-CoV was similar between two groups S-specific T cell immune response: • A significantly high percentage of S-specific IFN-γ+CD4 or CD8 T cells the ChAdOx1-S/BNT162b2 at the D6–11 and D14–19 after 2nd dose inoculation in comparison to that at D2 before 1st dose inoculation

Reference	Country	Design	Interval between Doses	Intervention (1st/2nd Dose)	Results
					• There was no data regarding the difference on S-specific T cell immune response between two groups Adverse events (lasting than D1 after boost): • No serious adverse events were reported in heterologous vaccine group • There is no data regarding the difference in the incidence of adverse events between the two groups
Xin Xue L. et. al., 2021 [29]	UK	A single blinded, randomized, multicenter, phase II, non-inferiority study	4 weeks	Homologous vaccine group (50- to 69-year-old): ChAdOx1-S/ChAdOx1-S (*n* = 112); BNT162b2/BNT162b2 (*n* = 110) Heterologous vaccine group (50- to 69-year-old): ChAdOx1-S/BNT162b2 (*n* = 110); BNT162b2/ChAdOx1-S (*n* = 114)	S-specific IgG geometric mean titers: • At D28 after 2nd dose inoculation, there was a similar titer between the ChAdOx1-S/BNT162b2 and BNT162b2/BNT162b2, but that in ChAdOx1-S/BNT162b2 were significantly higher than that in ChAdOx1-S/ChAdOx1-S and BNT162b2/ChAdOx1-S Neutralization antibody against pseudovirus-wild type-SARS-CoV-2:

Reference	Country	Design	Interval between Doses	Intervention (1st/2nd Dose)	Results
					• At D28 after 2nd dose inoculation, there was a similar $PVNT_{50}$ between the ChAdOx1-S/BNT162b2 and BNT162b2/BNT162b2, but that in ChAdOx1-S/BNT162b2 were significantly higher than that in ChAdOx1-S/ChAdOx1-S and BNT162b2/ChAdOx1-S S-specific T cell immune response: • At D28 after 2nd dose inoculation, the number of IFN-γ+T cell per 10^6 PBMC in ChAdOx1-S/BNT162b2 was more than that in ChAdOx1-S/BNT162b2, BNT162b2/BNT162b2 and BNT162b2/ChAdOx1-S Adverse events: • Within D28 after 2nd dose inoculation, the incidence of systemic adverse events was increased in heterologous vaccine group as compared to

Reference	Country	Design	Interval between Doses	Intervention (1st/2nd Dose)	Results
					their homologous vaccine group, but no significant difference between those vaccine schedules • Within D28 after 2nd dose inoculation, there were four serious adverse events across all groups, but not related to vaccine immunization
David H. et al., 2021 [32]	Germany	Prospective study	3 weeks: BNT162b2/BNT162b2 10–12 weeks: ChAdOx1-S/ChAdOx1-S, ChAdOx1-S/BNT162b2	Homologous vaccine group: ChAdOx1-S/ChAdOx1-S (*n* = 38, 33- to 59-year-old); BNT162b2/BNT162b2 (*n* = 174, 29- to 43-year-old) Heterologous vaccine group: ChAdOx1-S/BNT162-b2 (*n* = 104, 29- to 51-year-old)	S1-specific and RBD-specific IgG signal-to cutoff- ratio: • At D21–28 after 2nd dose inoculation, the ratio of S1-specific IgG in the ChAdOx1-S/BNT162b2 was more than that in all homologous vaccine groups, but no significant difference • At D21–28 after 2nd dose inoculation, the ratio of RBD-specific IgG in ChAdOx1-S/BNT162b2 was similar to that in BNT162b2/BNT162b2 and slightly more than that in the ChAdOx1-S/ChAdOx1-S Index of S1-specific IgG avidity:

Reference	Country	Design	Interval between Doses	Intervention (1st/2nd Dose)	Results
[25][28][29][31]	50	[31]	[28][29]	[25]	[29]	[25][28][32]	[25][28][32]	[29]	[29][31][32]	[33]	• At D21–28 after 2nd dose inoculation, the index of S1-specific IgG avidity in the ChAdOx1-S/BNT162b2 was significantly higher than that in all homologous vaccine groups Neutralization antibody against pseudovirus-variant-SARS-CoV-2 • At D21–28 after 2nd dose inoculation, $PVNT_{50}$ against alpha- and beta- SARS-CoV-2 in the ChAdOx1-S/BNT162b2 was significantly higher than that in all homologous vaccine groups S1-specific T cell immune response: • At the D21–28 after 2nd inoculation, the production of IFN-γ in the ChAdOx1-S/BNT162b2 was significantly higher than that in in all homologous vaccine groups Adverse events (within 24 h after 2nd dose inoculation):

1. Our World in Data. Coronavirus (COVID-19) Vaccinations. Available online: https://ourworldindata.org/covid-vaccinations?country=OWID_WRL (accessed on 27 September 2021).

Reference	Country	Design	Interval between Doses	Intervention (1st/2nd Dose)	Results
					• No serious adverse events were reported across all groups • The incidence of systemic adverse event in the ChAdOx1-S/BNT162b2 was slightly more than in ChAdOx1-S/ChAdOx1-S and less than that in BNT162b2/BNT162b2 and ChAdOx1-S prime
Gram M.A. et al. [30]	Denmark	Clinical study	82 days	Heterologous vaccine group: ChAdOx1-S/BNT162b2 (*n* = 88,050) ChAdOx1-S/mRNA-1273 (*n* = 44,501) Median age of 45 and 46 years at the first and second dose	• A reduction in the risk of SARS-CoV-2 infection when combining the ChAdOx1 and an mRNA vaccine. • The vaccine effectiveness (VE) against SARS-CoV-2 infection when combining the ChAdOx1 and an mRNA vaccine was 88%. • The VE of ChAdOx1/mRNA is similar to the two doses of the BNT162b2 mRNA vaccine.

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Reference	Country	Design	Interval between Doses	Intervention (1st/2nd Dose)	Results
					• No COVID-19 related hospitalizations were observed after the second dose. • No COVID-19 related deaths were observed after neither the first dose ChAdOx1 nor the ChAdOx1/mRNA vaccine schedule.

S, spike protein; RBD, receptor-binding domain; ID_{50}, 50% inhibitory dilution; $PVNT_{50}$, 50% of pseudovirus neutralization titer; NR, not reported; S1, S1 domain of spike protein.

16. Gallè, F.; Sabella, E.; Roma, P.; De Giglio, O.; Caggiano, G.; Tafuri, S.; Da Molin, G.; Ferracuti, S.; Montagna, M.; Liguori, G.; et al. Knowledge and Acceptance of COVID-19 Vaccination among Undergraduate Students from Central and Southern Italy. Vaccines 2021, 9, 638.
17. MacDonald, N.E.; SAGE Working Group on Vaccine Hesitancy. Vaccine hesitancy: Definition, scope and determinants. Vaccine 2015, 33, 4161–4164.
18. Greinacher, A.; Thiele, T.; Warkentin, T.E.; Weisser, K.; Kyrle, P.A.; Eichinger, S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N. Engl. J. Med. 2021, 384, 2092–2101.
19. Schultz, N.H.; Sørvoll, I.H.; Michelsen, A.E.; Munthe, L.A.; Lund-Johansen, F.; Ahlen, M.T.; Wiedmann, M.; Aomodt, A.H.; Skottor, T.H.; Tjonnfjord, G.E.; et al. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. N. Engl. J. Med. 2021, 384, 2124–2130.
20. Pottegård, A.; Lund, L.C.; Karlstad, Ø.; Dahl, J.; Andersen, M.; Hallas, J.; Hviid, A. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: Population based cohort study. BMJ 2021, 373, n1114.
21. European Centre for Disease Prevention and Control. Overview of EU/EEA Country Recommendations on COVID-19 Vaccination with Vaxzevria, and a Scoping Review of Evidence to Guide Decision-Making. Available online: https://www.ecdc.europa (accessed on 21 August 2021).
22. Government of Canada. Archived 12: NACI Rapid Response: Interchangeability of Authorized COVID-19 Vaccines. Available online: https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci.html (accessed on 19 August 2021).
23. Ledford, H. Could mixing COVID vaccines boost immune response? Nature 2021, 590, 375–376.

24. Callaway, E. Mix-and-match COVID vaccines trigger potent immune response. Nature 2021, 593, 491.
25. Normark, J.; Vikström, L.; Gwon, Y.-D.; Persson, I.-L.; Edin, A.; Björsell, T.; Dernstedt, A.; Christ, W.; Tevell, S.; Evander, M.; et al. Heterologous ChAdOx1 nCoV-19 and mRNA-1273 Vaccination. N. Engl. J. Med. 2021, 385, 1049–1051.
26. Shaw, R.H.; Stuart, A.; Greenland, M.; Liu, X.; Van-Tam, J.S.N.; Snape, M.D. Heterologous prime-boost COVID-19 vaccination: Initial reactogenicity data. Lancet 2021, 397, 2043–2046.
27. Borobia, A.M.; Carcas, A.J.; Pérez-Olmeda, M.; Castaño, L.; Bertran, M.J.; García-Pérez, J.; Campins, M.; Portolés, A.; González-Pérez, M.; Morales, M.T.G.; et al. Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants (CombiVacS): A multicentre, open-label, randomised, controlled, phase 2 trial. Lancet 2021, 398, 121–130.
28. Gross, R.; Zanoni, M.; Seidel, A.; Conzelmann, C.; Gilg, A.; Krnavek, D.; Mueller, J.A. Heterologous ChAdOx1 nCoV-19 and BNT162b2 prime-boost vaccination elicits potent neutralizing antibody responses and T-cell reactivity. medRxiv 2021.
29. Liu, X.; Shaw, R.H.; Stuart, A.S.V.; Greenland, M.; Aley, P.K.; Andrews, N.J.; Cameron, J.C.; Charlton, S.; Clutterbuck, E.A.; Collins, A.M.; et al. Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): A single-blind, randomised, non-inferiority trial. Lancet 2021, 398, 856–869.
30. Gram, M.A.; Emborg, H.D.; Moustsen-Helms, I.R.; Nielsen, J.; Sørensen, A.K.B.; Valentiner-Branth, P.; Nielsen, K. Vaccine effectiveness when combining the ChAdOx1 vaccine as the first dose with an mRNA COVID-19 vaccine as the second dose. medRxiv 2021.
31. Shimabukuro, T. Allergic reactions including anaphylaxis after receipt of the first dose of Moderna COVID-19 vaccine—United States, December 21, 2020–January 10, 2021. Am. J. Transplant. 2021, 21, 1326–1331.
32. Hillus, D.; Schwarz, T.; Tober-Lau, P.; Hastor, H.; Thibeault, C.; Kasper, S.; COVIM/EICOV Study Group. Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx1 nCoV-19 and BNT162b2: A prospective cohort study. Lancet Respir Med. 2021, in press.
33. Rizk, J.G.; Gupta, A.; Sardar, P.; Henry, B.M.; Lewin, J.C.; Lippi, G.; Lavie, C.J. Clinical Characteristics and Pharmacological Management of COVID-19 Vaccine-Induced Immune Thrombotic Thrombocytopenia with Cerebral Venous Sinus Thrombosis: A Review. JAMA Cardiol. 2021, in press.