Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

Among adults, what is the clinical and immunologic efficacy and effectiveness and safety of heterologous COVID-19 vaccination compared to standard homologous COVID-19 vaccination in preventing COVID-19 infection?

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RECOMMENDATIONS

We recommend the use of heterologous COVID-19 vaccination for those with serious adverse event to the first dose. *(Very low certainty of evidence; Strong recommendation)*

We suggest the use of heterologous COVID-19 vaccination in the event of the unavailability of the second dose in the recommended schedule. *(Very low certainty of evidence; Weak recommendation)*

Consensus Issues

The panel decided to give a strong recommendation, despite the very low certainty of evidence, on the use of heterologous vaccination among those with serious adverse event to the first dose. This is because of the need to provide the sufficient protection afforded by the second dose, especially for the vulnerable and at-risk populations. The importance of informed consent was emphasized by the panel, particularly on the benefits and harms of the administration of heterologous vaccination versus delayed administration of the second dose in the context of vaccine unavailability.

Key Findings

3 RCTs, 18 observational studies, and 1 case report investigated the use of heterologous vaccination using the following vaccines: BNT162b2, ChAdOx1, mRNA1273, CoronaVac, BBV152, Ad5-nCoV. No study was found using Gam-COVID-Vac, NVX-CoV2373, and BBIBP-CorV as a component of the vaccination regimen.

The overall certainty of evidence for efficacy/effectiveness is very low due to the study design (i.e. observational studies with a lack of control for confounding factors), the use of surrogate outcomes (immunogenicity), missing outcomes, and short follow up. The overall certainty of evidence for safety is low because of the study design (i.e. observational studies), unclear to lack of blinding, and the short follow-up.

Only one retrospective population-based cohort study with ChAdOx1/BNT162b2 or mRNA-1273 as the heterologous regimen showed clinical efficacy against SARS-CoV-2 infection, hospitalization, and death.

Current evidence shows that heterologous primary vaccination is immunogenic and results in acceptable adverse reaction rates. Different combinations and regimen perform differently.

Introduction

Vaccines are one of the key tools to curb the COVID-19 pandemic. However, with the suspension of the use of the ChAdOx1 (AstraZeneca) vaccine in some European countries due to reports of vaccine induced thrombotic thrombocytopenia (VITT) or thrombosis with thrombocytopenia syndrome (TTS), some have recommended to have an mRNA-based vaccine as a second dose.[1,2] Furthermore, with the decreased effectiveness of existing homologous combination vaccines against variants of concern, there is a need to determine if heterologous prime-boost regimens will induce comparable or more robust immune responses.[3-6] Vaccines also cost differently and determining a cost-effective and safe combination is important especially in resource-limited settings. Finally, with the inconsistent and erratic vaccine supplies, a heterologous vaccination may allow programmatic flexibility in the dosing regimen.

Review Methods

In this review, heterologous vaccine was operationally defined as a combination of different types of vaccines originally developed as part of a homologous multiple-dose or single-dose vaccine. The COVID-19 Living OVerview of the Evidence (L·OVE) platform, the COVID-NMA, and www.metaEvidence.org were searched for both randomized and non-randomized studies on adults investigating the efficacy, effectiveness, and safety of a heterologous combination of any COVID-19 vaccine last September 30, 2021. The weekly situational reports published by the World Health Organization (WHO) and relevant reports from major global regulatory agencies including the US Food and Drug Authority (US FDA), the US Center for Disease Control (CDC), the European Medicines Agency (EMA), the United Kingdom Medicines and Healthcare Products Regulatory Agency (UK-MHRA), the WHO, and the Philippine Food and Drug Association (PH FDA) including their reference lists were also reviewed for relevant studies. The search strategies are detailed in Appendix 2.

This review excluded multidose vaccination in which different types of vaccines were specifically developed to be part of the dosing regimen (e.g. Gam-COVID-Vac) and heterologous booster vaccination.

Randomized controlled trials (RCTs) were primarily sought for efficacy outcomes. Studies providing vaccine efficacy against COVID-19 infection of all severity, hospitalization, and deaths were preferred. In the absence of such, observational studies and studies providing immunogenicity results were also considered. Immunogenicity outcomes included geometric mean titers and seropositivity rates of neutralizing antibodies, anti-S, anti-RBD, and IFN-gamma. Geometric mean ratios and differences between seropositivity rates of homologous and heterologous vaccination were computed. The 28-day post-second dose results were used in the review when multiple timings of serologic assessment were done within a study. Both RCTs and observational studies were included for the safety outcomes, namely local and systemic adverse reactions, any adverse event, serious adverse events, and deaths after the second dose.

Results

Characteristics of studies

As of September 17, 2021, a total of 21 studies composed of 3 RCTs and 18 observational studies were included in this review. Of these studies, 13 used ChAdOx1/BNT162b2, two used BNT162b2/ChAdOx1[7,8], two used ChAdOx1/mRNA1273[9,24], one used ChAdOx1/BBV152[10], one used mRNA-1273/BNT162b2[27], one used CoronaVac/ ChAdOx1[11], and one used CoronaVac/Ad5-nCoV.[12] Three studies used a

ChAdOx1/BNT162b2 or mRNA-1273.[13-15] No study was found on the use of Gam-COVID-Vac, NVX-CoV2373, or BBIBP-CorV in the regimen.

Eight of the studies were on healthcare workers, two on immunocompromised populations, and the rest were on the general population. Three were RCTs, one of which compared heterologous ChAdOx1/BNT162b2 vaccination with a single dose ChAdOx1/observation[16], one was a four-arm trial comparing ChAdOx1/BNT162b2, BNT162b2/ChAdOx1, ChAdOx1/ChAdOx1, and BNT162b2/BNT162b2 regimens[7], and one compared CoronaVac/Ad5 with the homologous CoronaVac vaccination.[12] The rest were observational cohort studies. Only one study reported clinical effectiveness.[15] Nine studies provided information on the safety of heterologous vaccination. Majority reported on reactogenicity within the first seven days. Six studies reported heterologous vaccination against the variants of concern.

In general, heterologous vaccinations had longer dosing intervals (8 to 12 weeks), regardless of the regimen. On the other hand, most of the homologous vaccinations had dosing intervals of 21 to 28 days, except for the ChAdOx1/ChAdOx1 regimen which had dosing intervals ranging from 4 to 12 weeks across the studies.

The characteristics of included studies are detailed in Appendix 5.

Risk of bias assessment

Two of the three randomized controlled trials were assessed to have low risk of bias.[12,16] Although one of these was open label, the domains for blinding were assessed to be low risk given the objective outcomes.[16] The third RCT was assessed to have serious risk of bias due to missing data and non-blinding of clinical assessors.[7] All the observational studies were assessed to have serious risk of bias due to the non-randomized nature of the study design, with majority further downgraded to very serious risk due to non-blinding, missing outcomes, and lack of control for confounding factors, and short follow up. The detailed risk of bias assessment is presented in Appendix 4.

Clinical efficacy and effectiveness

ChAdOx1/BNT162b2 or mRNA-1273

One retrospective population-based cohort study from Denmark reported the vaccine effectiveness rate of the ChAdOx1/mRNA-based vaccination regimen against any COVID-19 infection at 66% (95% CI 59-72) within 13 days of the second dose and at 88% (95% CI 83-92) after 14 days of a ChAdOx1/mRNA-based vaccination regimen. Vaccine effectiveness against all-cause hospitalization was 43% (95% CI 36-49) within 13 days and 50% (95% CI 45-55) after 14 days. The adjusted VE against COVID-19-related hospitalization after 14 days of vaccination was at 93% (95% CI 80-98). No deaths were reported after vaccination.[15]

Immunogenicity

Across the studies, heterologous primary vaccination resulted in higher humoral and cellular immune response compared with homologous vaccination.

ChAdOx1/BNT162b2 or mRNA-1273

One prospective cohort looked at immunocompetent individuals receiving ChAdOx as a first dose followed by either BNT162b2 or mRNA-1273 as the second dose. The immunocompetent controls from this study were used in another matched cohort study of solid organ transplant recipients. Both studies mirrored the response of the ChaAdOx1/BNT162b2 regimen described above, with

at least similar to higher immunogenicity seen in the heterologous vaccination compared to the homologous regimen.[13,14]

ChAdOx1/BNT162b2

One randomized placebo-controlled trial demonstrated significantly higher antibody titers as well as cellular responses 14 days after ChAdOx1/BNT162b2 vaccination.[16] Another RCT compared the outcomes after ChAdOx1/BNT162b2 vaccination with the homologous vaccinations of either vaccine and with the reverse sequence (BNT162b2/ChAdOx1). It showed no significant difference in the antibody seropositivity rates across the groups. However, significantly higher antibody titers (>2-fold rise or GMR > 2.0) after ChAdOx1/BNT162b2 than homologous ChAdOx1 vaccination or the BNT162b2/ChAdOx1 combination. Similar levels of antibody titers were seen with the homologous BNT162b2 vaccination.[7]

The above findings were also seen in the observational studies which had the same vaccination regimen in the patient cohorts investigated.[13,14,17-22] Differences in seropositivity rates across the vaccination regimen were not significant with differences of 10%.

ChAdOx1/mRNA 1273

One report from an ongoing clinical study assessed 51 healthcare workers who received mRNA-1273 9 to 12 weeks after a first dose of ChAdOx1, and compared their immunologic response to 37 healthcare workers who chose a homologous ChAdOx1 second dose. Those who received mRNA-1273 as a second dose showed a greater increase in neutralization titer at 7-10 days post boost, which was sustained at 30 days. Moreover, heterologous vaccination induced neutralizing antibodies against the Beta variant whereas homologous ChAdOx1 did not.[9]

Another study compared the post-boost anti-S and anti-RBD antibody titers among vaccinees who received either a heterologous ChAdOx1/mRNA-1273 or ChAdOx1/BNT162b2, or a homologous ChAdOx1 or BNT162b2 regimen. Heterologous vaccination was found to result in higher antibody titers.[17]

BNT162b2/ChAdOx1

In the randomized controlled study that used BNT162b2/ChAdOx1 in one of its arms, such combination demonstrated higher and equivalent seropositivity rates and geometric mean titers compared to homologous ChAdOx1 and homologous BNT162b2, respectively. However, in terms of T cell responses, results showed higher GMT's for the heterologous combinations, but with lower seropositivity for the BNT162b2/ChAdOx1 combination, compared to both homologous combinations and the ChAdOx1/BNT162b2 combination.[7] The observational study which compared BNT162b2/ChAdOx1 to homologous vaccination of either component consistently showed the same results with higher immunologic responses with the heterologous vaccination.[17]

ChAdOx1/BBV152

One prospective study compared the heterologous ChAdOx1/BBV152 vaccination with homologous vaccination with either of the two components. It showed higher titers after heterologous vaccination than both homologous preparations. It also showed higher titers against variants of concern compared to either homologous vaccination.[10]

mRNA-1273/BNT162b2

One prospective study compared heterologous mRNA-1273/BNT162b2 vaccination with homologous vaccination with either of the two components. It showed no difference in the IgG levels among all groups.[23]

CoronaVac/ChAdOx1

One retrospective study used CoronaVac in combination with ChAdOx1. The ChAdOx1/CoronaVac regimen resulted in higher humoral titers compared to both homologous vaccinations. However, the CoronaVac/ChAdOx1 regimen showed equivalent anti-S IgG titers with the homologous ChAdOx1 regimen, but still with higher titers compared with the homologous CoronaVac vaccination.[11]

CoronaVac/Ad5-nCoV

One randomized controlled trial compared CoronaVac/Ad5 vaccination with homologous CoronaVac vaccination.[12] It showed higher humoral titers, and higher humoral and cellular seropositivity rates after heterologous vaccination. Adverse event rates, both local and systemic reactogenicity, was significantly higher after heterologous compared to homologous vaccination. No severe adverse events were recorded in both groups in this trial.

Effectiveness against Variants of Concern

Six observational studies reported on the immunogenicity responses to heterologous vaccination in relation to the variants of concern (Alpha, Beta and Delta). Five studies used ChAdOx1/BNT162b2 [9,21,22,24,25] and one used CoronaVac/ChAdOx1.[10] All studies consistently demonstrated significantly higher humoral titers and seropositivity rates after heterologous vaccinations compared to homologous vaccination. No study was identified on heterologous vaccination against the Gamma variant.

Safety

While generally well-tolerated with mostly mild to moderate adverse reactions, heterologous vaccination was consistently shown to have higher (but not statistically significant) local and systemic reactogenicity rates when compared with homologous vaccination, regardless of the combination.[9,10,13,16,19,22,26,27] The most commonly reported events with higher rates included pain at injection site, fever, headache, myalgia, and fatigue. Only two studies reported severe adverse reactions, which included headache and myalgia. No long-term safety information is available at this time.

The summary of findings are in Appendix 3.

Ongoing Studies

Search of *clinicaltrials.gov* registry last October 2, 2021 yielded 19 trials on heterologous COVID-19 vaccination with the earliest trial completion on October 2021.

Recommendations from Other Groups

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
World Health Organization (WHO) as of August 10, 2021	For COVID-19 vaccines with a 2-dose primary series schedule, the same vaccine product should be used for both doses. If different COVID-19 vaccine products are inadvertently administered in the two doses, no additional doses of either vaccine are recommended. At present, mix and match schedules constitute off-label use of respective vaccines and as such should only be used if benefits outweigh the risks such as in situations of interrupted vaccine supply.[28]
Australian Technical Advisory Group on Immunization (ATAGI) as of September 23, 2021	Recommends use of heterologous vaccination for special circumstances such as serious vaccine-attributable adverse events after the first dose, precautionary conditions for which the use of BNT162b2 (Cominarty) or mRNA-1273 (Spikevax) are recommended instead of ChAdOx1 (AstraZeneca), and in those given an incomplete course of a COVID-19 vaccine brand not available in Australia.[29]
US Centers for Disease Control – Advisory Committee on Immunization (ACIP), UK-Joint Committee on Vaccination and Immunization (UK-JCVI), and European Medicines Agency (EMA)	No specific recommendation on heterologous primary vaccination

Research Gaps

The following are the identified knowledge and information gaps regarding heterologous primary vaccination:

1. Clinical efficacy and effectiveness of heterologous vaccination compared with homologous vaccination
    a. short-term and long-term outcomes
    b. in special populations (children, immunocompromised persons, the elderly, pregnant and lactating women)
    c. against variants of concern
2. Comparative efficacy and effectiveness of the different heterologous vaccination regimens
3. Duration of protection of heterologous vaccination, including comparison across the possible different regimens
4. Long-term safety of heterologous vaccination
5. Comparative safety of the different heterologous vaccination regimens

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Appendix 1. Evidence to Decision

Table 1. Summary of Initial Judgements Prior to Panel Discussion (N = 10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No (1)	Yes (9)					
Benefits	Large (2)	Moderate (5)	Small (2)	Uncertain (1)			• ChAdOx1/mRNA-based paradigm showed prevention of SARS-CoV-2 infection 66% (95% CI 59-72) at 0-13 days follow-up; 88% (95% CI 83-92) at 14 days follow-up; no reported hospitalization and deaths. • Immunologic profiles showed similar to increased titers for varying combinations.
Harm	Large (1)	Small (5)	Uncertain (4)				• Varies per combination used, from similar to higher local and systemic reactogenicity.
Certainty of evidence	High	Moderate (4)	Low (4)	Very low (2)			• Very low to moderate
Balance of effects	Favors intervention (6)	Does not favor vaccine	Uncertain (4)				
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (6)	Possibly no important uncertainty or variability (1)	No important uncertainty or variability			• WHO Recommendation: Mix and match schedules constitute off-label use and that benefits should outweigh risks such as in situations of interrupted vaccine supply. • ATAGI Recommendation: Heterologous vaccination be used conditionally.
Resources required	Uncertain (4)	Large cost (2)	Moderate cost (4)	Negligible cost or savings	Moderate savings	Large savings	• Varies per vaccine combination used
Certainty of evidence of resources required	No included studies (9)	Very low (1)	Low	Moderate	High		

Cost effectiveness	No included studies (9)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention (1)			
Equity	Uncertain (4)	Reduced (1)	Probably no impact	Increased (5)			• Addresses issues of limitation and unpredictability of supplies, programmatic flexibility in dosing regimen, and special needs of immunocompromised patients and other selected populations. • Addresses wide disparity in vaccine coverage: 85.1% fully-vaccinated senior citizens in NCR; only 28.3% in BARMM.
Acceptability	Uncertain (5)	No	Yes (5)				• No Philippine guidelines yet
Feasibility	Uncertain (5)	No	Yes (5)				

Appendix 2. Search Strategy

The COVID-19 Living OVerview of the Evidence (L·OVE) platform, the COVID-NMA, and www.metaEvidence.org were searched for both randomized and non-randomized studies on adults investigating the efficacy, effectiveness, and safety of a heterologous COVID-19 vaccine. For the COVID-19 L·OVE platform, the search was by PICO with the following filters in order: "prevention or treatment", “public health”, "vaccination", and “SARS-CoV-2 vaccines”. Only systematic reviews and primary studies were included with the latter's yield further filtered to include all study designs but only those reporting data; the reference lists of systematic reviews were examined for eligible studies. For the COVID-NMA, the living evidence synthesis of RCTs related to vaccines was examined. For the database of www.metaEvidence.org, the search filters were the following: “vaccines”,”COVID-19 prophylaxis”, “all patients”, “all studies (RCT and observational)”. The reference lists of the weekly situational (epidemiological) reports published by the World Health Organization (WHO), and the VIEW-Hub Resource Library COVID-19 Vaccine Effectiveness Reports were searched for relevant studies. The WHO COVID-19 literature on coronavirus disease database was also searched using “heterologous” as a search term. Relevant reports from major global regulatory agencies including the US Food and Drug Authority (US FDA), the US Center for Disease Control (CDC), the European Medicines Agency (EMA), the United Kingdom Medicines and Healthcare Products Regulatory Agency (UK-MHRA), the WHO, and the Philippine Food and Drug Association (PH FDA) including their reference lists were also reviewed for relevant studies.

Appendix 3. Summary of Findings

	N	Risk of Bias	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
ChAdOx1/mRNA-based vaccine								
Prevention of COVID-19 infection	1 Obs	Serious (observational, uncontrolled confounders)	Not serious	Not assessed	Not serious	Not assessed	VE at 0-13d: 66% (95% CI 59-72) VE at ≥14d: 88% (95% CI 83-92)	Low
Prevention of severe infection / hospitalization / death	1 Obs	Serious (observational, uncontrolled confounders)	Not serious	Not assessed	Not serious	Not assessed	No death or hospitalization	Low
Immunogenicity	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Reactogenicity	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Adverse events	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
ChAdOx1/mRNA-1273								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity	2 Obs	Serious (observational, uncontrolled confounders)	Serious (surrogate outcomes)	Not serious	Not serious	Not serious	Similar to significant rise in antibody titers	Very low

Reactogenicity	1 Obs	Serious (observational, short follow-up)	Not serious	Not serious	Not serious	Not serious	Higher reactogenicity	na
Adverse events	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
ChAdOx1/BNT162b2								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity	3 Obs	Very serious (observational, uncontrolled confounders, missing outcomes)	Serious (surrogate outcomes)	Not serious	Not serious	Not serious	Increased titers more vs. homologous ChAdOx1 than homologous BNT162b2 Anti-spike IgG: 0.92 to 175-fold Anti-RBD: 77.7 to 175-fold NAb: 0.9 to 62.95-fold IFN-γ: 2.3 to 4.25-fold	Very low
Reactogenicity	2 RCT, 4 Obs	Serious (observational, short follow-up)	Not serious	Not serious	Not serious	Not serious	Similar to higher reactogenicity than homologous regimen	Low
Adverse events	2 RCT, 2 Obs	Serious (observational, short follow-up)	Not serious	Not serious	Not serious	Not serious	Mixed reports of lower, similar, or higher adverse events than the homologous regimen	Low
Serious adverse events / Death	2 RCT	Serious (short follow-up)	Not serious	Not serious	Not serious	Not serious	No vaccine-related severe adverse events reported	Moderate

	N	**Risk of Bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Others**	**Effect**	**Certainty**
ChAdOx1/mRNA vaccine or vector vaccine/mRNA vaccine								

Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity	2 Obs	Serious (observational, uncontrolled confounders)	Serious (surrogate outcomes)	Not serious	Not serious	Not serious	Similar to significant rise in antibody titers	Very low
Reactogenicity	1 Obs	Serious (observational, short follow-up)	Not serious	Not serious	Not serious	Not serious	More reactogenic than homologous regimen	Low
Adverse events	1 Obs	Serious (observational, short follow-up)	Not serious	Not serious	Not serious	Not serious	Similar adverse events	Low
Serious adverse events / Death	1 Obs	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
BNT162b2/ChAdOx1								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na

Immunogenicity	1 RCT	Serious (lack of blinding of assessors)	Serious (surrogate outcomes)	Not serious	Not serious	Not serious	Similar to minimal rise in antibody titers vs. homologous BNT162b2 Significant rise in antibody titers vs. homologous ChAdOx1	Low
Reactogenicity	1 RCT, 1 obs	Serious (lack of blinding of assessors, observational, short follow-up)	Not serious	Not serious	Not serious	Not serious	Higher reactogenicity than homologous regimen	Moderate
Adverse events	1 RCT	Serious (lack of blinding of assessors, short follow-up)	Not serious	Not serious	Not serious	Not serious	No significant difference	Moderate
Serious adverse events / Death	1 RCT 1 obs	Serious (lack of blinding of assessors, observational short follow-up)	Not serious	Not serious	Not serious	Not serious	None related to vaccination	Moderate
ChAdOx1/BBV152								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity	1 Obs	Very serious (observational, uncontrolled confounders, missing outcomes)	Serious (surrogate outcomes)	Not serious	Not serious	Not serious	Minimal rise in antibody titers	Very low

Reactogenicity	1 Obs	Serious (observational, short follow-up)	Not serious	Not serious	Not serious	Not serious	Similar to homologous regimen	Low
Adverse events	1 Obs	Serious (observational, short follow-up)	Not serious	Not serious	Not serious	Not serious	Similar to homologous regimen	Low
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
mRNA-1273/BNT162b2								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity	1 Obs	Very serious (observational, uncontrolled confounders, missing outcomes)	Serious (surrogate outcomes)	Not serious	Not serious	Not serious	No difference in antibody titers	Very low
Reactogenicity	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Adverse events	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na

	N	Risk of Bias	Indirectness	Inconsistency	Imprecision	Others	Effect	Certainty
CoronaVac/ChAdOx1								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity	1 Obs	Very serious (observational, uncontrolled confounders, missing outcomes)	Serious (surrogate outcomes)	Not serious	Not serious	Not serious	Significant rise in antibody titers vs. homologous CoronoVac Similar rise in antibody titers vs. homologous ChAdOx1	Very low
Reactogenicity	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Adverse events	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Serious adverse events / Death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
CoronaVac/Ad5								
Prevention of COVID-19 infection	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Prevention of severe infection / hospitalization / death	0	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	na	na
Immunogenicity	1 RCT	Not serious	Serious (surrogate outcomes)	Not serious	Not serious	Not serious	Significant rise in antibody titers vs. homologous CoronaVac	Low
Reactogenicity	1 RCT	Serious (short follow-up)	Not serious	Not serious	Not serious	Not serious	Higher local reactogenicity, similar systemic reactogenicity	Moderate

Adverse events	1 RCT	Serious (short follow-up)	Not serious	Not serious	Not serious	Not serious	Low incidence in both groups	Moderate
Serious adverse events / Death	1 RCT	Serious (short follow-up)	Not serious	Not serious	Not serious	Not serious	None reported	Moderate

Appendix 4. Risk of Bias Assessment

STUDY ID	STUDY DESIGN	RANDOMIZATION	ALLOCATION CONCEALMENT	BLINDING OF PARTICIPANTS	BLINDING OF INVESTIGATORS	BLINDING OF ASSESSORS	MISSING OUTCOMES / FOLLOW UP	SELECTIVE REPORTING	ASSESSMENT OF CONFOUNDING FACTORS												OVERALL for CONTROL OF COUNFOUNDERS	OVERALL RISK
									AGE			EXPOSURE RISK			COMORBIDITIES			VARIANT PREVALENCE				
									A	B	C	A	B	C	A	B	C	A	B	C		
Barros-Martin	Retrospective Cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	Y	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Behrens	Retrospective Cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	Y	NA	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Benning	Prospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	Y	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Borobia	RCT (Ph2)	LOW	LOW	LOW	LOW	LOW	LOW	LOW	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NOT SERIOUS
Dimeglio	Prospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	Y	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Gram	Retrospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	Y	Y	U	Y	Y	U	Y	Y	U	Y	LOW	SERIOUS
GroB	Single cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Hammerschmidt	Prospective cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	Y	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Hillus	Prospective cohort	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	Y	N	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Kant	Prospective cohort	HIGH	HIGH	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	Y	N	N	N	U	N	Y	Y	NA	N	U	N	HIGH	VERY SERIOUS
Li J	RCT	LOW	LOW	LOW	LOW	LOW	LOW	LOW	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NOT SERIOUS
Liu / Shaw	RCT	LOW	LOW	LOW	LOW	HIGH	HIGH	LOW	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	SERIOUS
Normark	Prospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	N	N	N	U	N	Y	N	N	N	U	N	HIGH	VERY SERIOUS
Powell	Retrospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	HIGH	UNCLEAR	Y	N	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Rose	Retrospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	N	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Schmidt	Prospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	N	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Schmidt2	Retrospective cohort	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Tenbusch	Retrospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	N	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Vallee	Retrospective cohort	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	Y	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS
Vinh	Prospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	U	N	N	U	N	Y	U	N	N	U	N	HIGH	VERY SERIOUS
Yorsaeng	Prospective cohort	HIGH	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	Y	N	N	N	U	N	N	U	N	N	U	N	HIGH	VERY SERIOUS

LOW	UNCLEAR	HIGH	NOT APPLICABLE

Y	YES	N	NO	U	UNCLEAR	NA	NOT APPLICABLE

Appendix 5. Characteristics of Studies

ChAdOx1/BNT162b2									
Study author (country)	**Type of study (date)**	**Study design**	**Population**	**Heterologous regimen (dosing interval)**	**Homologous regimen/comparator (dosing interval)**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Borobia (Spain)	Full publication (July 2021)	RCT (Ph2)	Healthy, 18-60yo, received prim ChAdOx1 8-12 weeks prior to screening N = 676 Excluded clinically significant acute illness, T' at least 38'C, COVID-19 disease; pregnancy 2 withdrawals in vaccine group, 1 in control 7 exclusions from vaccine and 3 in control	ChAdOx1/BNT162b2 (8-12 weeks) (n = 441) 2 withdrew consent, 7excluded 1 lost to follow up	no second dose or ChAdOx (i.e. maintain observation) (n = 222) 1 withdrew consent 3 excluded	14 d after V2	Anti-spike IgG(GMT) ***3684.87 vs 101.2*** ***GMR : 37 fold increase*** () anti-RBD* GMT (pseudovirusneutralization) ***7756.63 vs 99.84*** ***GMR = 77.69 (59.57 -101.32)*** NAb† (% neutralizing capacity) ***100% vs 100%*** (GMT) ***1905.69 vs 41.81*** ***GMR : 45 time increase*** IFN-γ cytokine production against SARS-CoV-2 spike peptide‡ (GMT) ***521.22 vs 122.67***	Very low	Open label Randomization list centrally generated by SAS, balanced wirhtdrawals and exclusions

Liu (UK)	Preprint/correspondence (July 2021)	RCT (Ph2)	Adults > 50 y.o, with no or well-controlled, mild-moderate comorbidities (N=463) Excluded Previous lab-confirmed SARS-CoV-2 infection, history of anaphylaxis, history of allergy fo a vaccine ingredient, pregnancy, breastfeeding, intent to conceive, current use of anticoagulants	ChAdOx1/BNT162b2 28-day interval (n = 90) (n= 24, immuno) BNT162b2/ChAdOx1 28-day interval (n = 90) (n = 25, immuno)	ChAdOx1/ChAdOx1, 28-day interval (n = 90) (n = 25, immuno) BNT162b2/BNT162b2 28-day interval (n = 93) (n = 26, immuno)	28 d after V2	ELISA) Anti-spike IgG* - *see tables* Anti-spike binding IgG† (IFN-γ ELISpot) Cellular responses IFN-γ Pseudotype virus neutralization assay (PNA)) NAb	Low	Participant-blind non-inferiority trial, IWRS clinical assessors unmasked only a sample of population with immunologic studies
GroB (Germany)	Preprint (July 2021)	Single cohort, self-controlled	Received ChAdOx1 as first dose (n = 26)	ChAdOx1/BNT162b2 56 days (n = 26)	(no comparison) boost compared to prime	6-11 d after V2 14-19 d after V2	% positivity IgG % positivity IgA Anti-spike-IgM titer Anti-spike-IgG titer (Surrogate virus neutralization test (sVNT) % positivity Anti spike RBD (Vesicular stomatits virus- based pseudovirus) IgG% ***6-11 days post boost : 100%*** ***14-19 days post : 100%*** ***IgA%*** ***6-11 days post boost : 92%*** ***14-19 days post : 100%*** Nab (B.1.1.7 ***2 fold lower potency for Beta (vs Alpha)***	Very low	

Rose (Germany)	Preprint (July 2021)	Prospective cohort	not described	ChAdOx1/BNT162b (n=41) ChAdOx1/mRNA=1273 (n=1)	ChAdOx1/ChAdOx1 (n = 9) BNT162b2 / BNT162b2 (n=8)	15 d after V2	IgG% ***all groups reached 100%*** IgG titers (anti-S and Anti RBD) ***titers in the heterologous groups 7-10x higher than the homologous ChAd and 10 to 175 times higher that the homologous BNT162b2*** Neutralization titers ***homologous ChA had 13 to 11 fold lower GMTs compared to heterologous or homo BNT*** Neutralization % ***similar across groups***	Very low	with missing samples post-D2
Tenbusch (Germany)	Preprint (July 2021)	Retrospective cohort	sera from assessed in 2 different laboratories	ChAdOx1/BNT162b2 (n = 232) ChAdOx1/BNT162b2 (n=250)	BNT162b2/BNT162b2 (n= 410) BNT162b2/BNT162b2 (n= 127) ChAdOx1/ChAdOx1 (n=250)	14 d after V2	Neutralizing antibody titers ***(results in table)***	Very low	sample selection not clarified

Barros-Martins (Germany)	Correspondence (June 2021)	Retrospective cohort	healthcare workers primed with ChAdOx, offered a choice of boost additional BNT homo group included in study	ChAdOx1/BNT162b2 74 days (n=55)	ChAdOx1/ChAdOx1 73 days (n=32) BNT162b2/BNT162b2 21 day interval (n=46)	16-17 d after V2	anti-S spike IgG titers (fold increase from preboost), for wild strain ***(11.5 fold inc vs 2.9)***, Alpha, Beta and Gamma neutralizing Ab titers post boost, for all strains for Wuhan ***: increased in both groups but higher titers in hetero*** for VOCs :***hetero with higher titers in all strains while ChA homo only had increase in Alpha but not in Beta and Gamma*** spike specific B cell positivity spike specific CD4 positivity ***increased in both groups but higher in hetero*** spike specific CD8	Very low	self-chosen 2nd dose comparison group BNT/BNT chosen by investigator without details with missing data in all groups
Behrens (Germany)	Correspondence (August 2021)	prospective cohort	Healthcare professionals and individuals with potential contact to SARS-CoV-2 (from CoCo study)	ChAdOx1/BNT162b2, mean 73.5 (71-85) days n = 11	ChAdOx1/ChAdOx1 mean 73.5 (71-85) days n = 12	15-17 d after V2	IgG (ELISA) 50% neutralization titer (VSV-pseudoviral assay) activity vs variants ***all heterologous indiviruals achieved NT50 = 25 against all variants with NT50>100 in 85% of vaccinees, unlike those who had homologous vaccination where a proportion of patients did not reach the 25***	Very low	balanced age no control of confounding factors

Benning (Germany)	Full publication (August 2021)	Prospective cohort	Health care workers (N= 166) heterologous group younger homologous ChA older than homologous BNT	ChAdOx1/BNT162b2 median 83d (77-94) interval (n=35)	ChAdOx1/ChAdOx1 median 82d (82-83) interval (n=17) BNT162b2/BNT162b2 median interval 20d (20-20) (n=82)	20 d (IQR 19-21) after V2	*(results in table)* TiTers - Full spike - S1 - RBD - S2 - nucleocapside Neutralizing antibodies Seropositivity - full spike - S1 - RBD - S2	Very low	only a small sample of were subjected to some of the immunologic studies
Dimeglio (France)	Preprint/correspondence (July 2021)	Prospective cohort	Healthcare workers with COVID-19 negative antibodies pre-vaccination >55yo with choice of homologous or hetero; those <55 all given BNT booster	ChAdOx1/BNT162b2	ChAdOx1/ChAdOx1 BNT162b2/BNT162b2	1 m after V2	NAb titers (Live virus-based assay) Nab seropositivity *in table* Nab titers *noted as not statistitcally significant across groups*	Very low	matched by age and gender for those >55 years old
Hammerschmidt (Germany)	Correspondence (August 2021)	Retrospective cohort	Healthcare professionals and individuals with potential contact to SARS-CoV-2	ChAdOx1/BNT162b2 2-3 months interval (n = 54)	BNT162b2/BNT162b2, 21 days interval (n = 30) ChAdOx1/ChAdOx1, 21 days interval (n = 31)	mean 17 (13-23) d after homologous ChAdOx1 prime-boost or heterologous BNT prime-boost mean 30 (15-65) d after homologous BNT162b2 prime-boost	NAb against Delta variant (sVNT, pVNT) *ChA/BNT with higher Nabs vs Alpha, beta and Gamma compared to BNT/BNT* *BNT/BNT higher Nabs vs Delta vs hetero...*	Very low	

Hillus (Germany)	Full publication (August 2021)	Prospective, observational cohort	health care workers in a tertiary care center (N=380 enrolled, excluded 26)) Excluded seropositive (PCR-confiremd or IgG detectable) only 30 selected samples tested for T-cell response	ChAdOx1/BNT162b2 71 d (IQR 70-73) (n = 104)	BNT162b2/BNT162b2 21 d (IQR 21-21) (n = 174) ChAdOx1/ChAdOx1 (n = 38)	3 weeks after V2	(Microarray-based immunoassay surrogate virus neutralization test (sVNT) and IGRA and ELISA) ***see tables for results*** Anti-full spike Anti-spike S1 reactivity Anti-spike RBD-IgG anti - N RBD binding inhibition (surrogate nutralization asssay) (pseudoneutralization assay) ID50 for Alpha and Beta T cell response ((IFN-gamma release assay)	Very low	use of electronic questionnaire for AEs Interim missing data, less samples with immunogenicity in homoBNT multivariate matching for sex and age between vaccine groups
Vallee (France)	Full publication (August 2021)	Retrospective crosssectional study	healthcare workers with not previous COVID infection BNT homo - younger	ChAdOx1/BNT162b2 12 weeks interval (n=130)	BNT162b2/BNT162b2 4 weeks interval (n=67)	30 and 60 d after V2	***IgG antibodies significantly higher with HETERO but no significant difference after adjustment for time between doses***	Very low	adjusted titers based on dosing interval

ChAdOx1/BNT162b2									
Study author (country)	**Type of study (date)**	**Study design**	**Population**	**Heterologous regimen (dosing interval)**	**Homologous regimen/comparator (dosing interval)**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Safety									
Borobia (Spain)	Full publication (July 2021)	RCT (Ph2)	Healthy, 18-60yo, received prim ChAdOx1 8-12 weeks prior to screening N = 676 Excluded clinically significant acute illness, T' at least 38'C, COVID-19 disease; pregnancy 2 withdrawals in vaccine group, 1 in control 7 exclusions from vaccine and 3 in control	ChAdOx1/BNT162b2 8-12 weeks (n = 441) 2 withdrew consent, 7excluded 1 lost to follow up	no second dose or ChAdOx (i.e. maintain observation) (n = 222) 1 withdrew consent 3 excluded	7 d reactogenicity 14 d after V2 planned 1 year	Solicited local and systemic adverse events Unsolicited adverse events ***31 with severe adverse events (malaise 23%, myalgia 19% and headcahe 16%***	Low	Open label Randomization list centrally generated by SAS, balanced wirhtdrawals and exclusions
GroB (Germany)	Preprint (July 2021)	Single cohort, self-controlled	Received ChAdOx1 as first dose (n = 26)	ChAdOx1/BNT162b2 56 days Interval (n = 26)	(no comparison) boost compared to prime	Not stated	Solicited local adverse events ***80.4%(23/26) with at least 1 mild or moderate symptoms*** most common AE : ***pain at injection site (84.6%), fatigue (84.6), chills (19.2)*** ***similar AE reports in prime and boost*** ***milder reaction to boost than prime*** Severe symptoms of fatigue (7.7) and headache (15.4%) Solicited systemtic adverse events	Low	

Liu (UK)	Preprint/correspondence (July 2021)	RCT (Ph2)	Adults > 50 y.o, with no or well-controlled, mild-moderate comorbidities (N=463) Excluded Previous lab-confirmed SARS-CoV-2 infection, history of anaphylaxis, history of allergy fo a vaccine ingredient, pregnancy, breastfeeding, intent to conceive, current use of anticoagulants	ChAdOx1/BNT162b2 28-day interval (n = 90) (n= 24, immuno) BNT162b2/ChAdOx1 28-day interval (n = 90) (n = 25, immuno)	ChAdOx1/ChAdOx1, 28-day interval (n = 90) (n = 25, immuno) BNT162b2/BNT162b2 28-day interval (n = 93) (n = 26, immuno)	7 d after immunization 28 d after immunization	Solicited local and systemic events Unsolicited adverse events Medically attended adverse events Blood biochemistry and hematology assessments ***both heterologous regimen had higher systemic reactions than homologous*** ***higher proportions of paracetamol use in the heterologous*** ***no thrombocytopenia***	Low	Participant-blind non-inferiority trial, IWRS clinical assessors unmasked only a sample of population with immunologic studies
Powell (UK)	RWE (August 2021)	Retrospective cohort	Adults aged 18-75 recorded to have received vaccination in the NIMS,who had received their second dose 21 days prior, with recorded mobile numbers, invited to the survey (n = 1313) Excluded ncomplete information, those who responded"not known" when asked about prior COVID 19 symptoms	ChAdOx1/BNT162b2 med 76d (n = 572) BNT162b2/ChAdOx1 med 76d (n = 167)	ChAdOx1/ChAdOx1 med 69d (n = 461) BNT162b2/BNT162b2 med 69d (n = 133)	Within 21 d from V2	Overall AE rates ***ChAd/BNT : 60.5%*** ***BNT/ChAd : 58.8%*** ***ChAd/ ChAd : 35.2%*** ***BNT/BNT : 29.3%*** Local reactogenicity ***ChAd/BNT : 51%*** ***BNT/ChAd : 54.4%*** ***ChAd/ ChAd : 32%*** ***BNT/BNT : 26.3%*** Systemic reactogenicity ***ChAd/BNT : 51.9%*** ***BNT/ChAd : 44.3%*** ***ChAd/ ChAd : 25.9%*** ***BNT/BNT : 25.6%*** ***HETERO more likely to report more severe AEs***	Low	database review Online survey questionnaire (response rate of 18.7%) (no protocol/ no clear methods) subgrouped by age, sex, previous infection, severe AR on prime

Benning (Germany)	Full publication (August 2021)	Prospective cohort	Health care workers (N= 166) heterologous group younger homologous ChA older than homologous BNT	ChAdOx1/BNT162b2 median 83d (77-94) interval (n=35)	ChAdOx1/ChAdOx1 median 82d (82-83) interval (n=17) BNT162b2/BNT162b2 median interval 20d (20-20) (n=82)	Not stated	Any reaction ***BNT/BNT = 83%*** ***Cha/BNT = 72%*** ***Cha/Cha = 29%*** Local reactogenicity ***Cha/Cha = 7%*** ***Cha/BNT = 52%*** ***BNT/BNT = 53%*** Systemic reactogenicity ***BNT/BNT = 76%*** ***Cha/BNT = 52%*** ***Cha/Cha = 29%***	Low	only a small sample of were subjected to some of the immunologic studies
Hillus (Germany)	Full publication (August 2021)	Prospective, observational cohort	health care workers in a tertiary care center (N=380 enrolled, excluded 26)) Excluded seropositive (PCR-confiremd or IgG detectable) only 30 selected samples tested for T-cell response	ChAdOx1/BNT162b2 71 d (IQR 70-73) (n = 104)	BNT162b2/BNT162b2 21 d (IQR 21-21) (n = 174) ChAdOx1/ChAdOx1 (n = 38)	1 d, 3 d, 5 d, 7 d after V1 and V2	Local Reactogenicity ***ChA/BNT : 80%*** ***BNT/BNT : 75%*** ***ChA/ChA : 60%*** Systemic Reaction rate: ***ChA/BNT : 49%*** ***BNT/BNT : 65%*** ***ChA/ChA : 39%*** ***fatigue, myalgia, headache and chills, and fever more common in HOMO vs hetero*** ***Severe AEs least common after hetero*** ***no lifethreateaning reactions***	Low	use of electronic questionnaire for AEs Interim missing data, less samples with immunogenicity in homoBNT multivariate matching for sex and age between vaccine groups

BNT162b2/ChAdOx1									
Study author (country)	**Type of study (date)**	**Study design**	**Population**	**Heterologous regimen (dosing interval)**	**Homologous regimen (dosing interval)**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Liu (UK)	Preprint/correspondence (July 2021)	RCT (Ph2)	Adults > 50 y.o, with no or well-controlled, mild-moderate comorbidities (N=463) Excluded Previous lab-confirmed SARS-CoV-2 infection, history of anaphylaxis, history of allergy fo a vaccine ingredient, pregnancy, breastfeeding, intent to conceive, current use of anticoagulants	ChAdOx1/BNT162b2 28-day interval (n = 90) (n= 24, immuno) BNT162b2/ChAdOx1 28-day interval (n = 90) (n = 25, immuno)	ChAdOx1/ChAdOx1, 28-day interval (n = 90) (n = 25, immuno) BNT162b2/BNT162b2 28-day interval (n = 93) (n = 26, immuno)	28 d after V2	ELISA) Anti-spike IgG* - ***see tables*** Anti-spike binding IgG† (IFN-γ ELISpot) Cellular responses IFN-γ Pseudotype virus neutralization assay (PNA)) NAb	Very low	Participant-blind non-inferiority trial, IWRS clinical assessors unmasked only a sample of population with immunologic studies
Safety									
Liu (UK)	Preprint/correspondence (July 2021)	RCT (Ph2)	Adults > 50 y.o, with no or well-controlled, mild-moderate comorbidities (N=463) Excluded Previous lab-confirmed SARS-CoV-2 infection, history of anaphylaxis, history of allergy fo a vaccine ingredient, pregnancy, breastfeeding, intent to conceive, current use of anticoagulants	ChAdOx1/BNT162b2 28-day interval (n = 90) (n= 24, immuno) BNT162b2/ChAdOx1 28-day interval (n = 90) (n = 25, immuno)	ChAdOx1/ChAdOx1, 28-day interval (n = 90) (n = 25, immuno) BNT162b2/BNT162b2 28-day interval (n = 93) (n = 26, immuno)	7 d after immunization 28 d after immunization	Solicited local and systemic events Unsolicited adverse events Medically attended adverse events Blood biochemistry and hematology assessments ***both heterologous regimen had higher systemic reactions than homologous*** ***higher proportions of paracetamol use in the heterologous*** ***no thrombocytopenia***	Low to moderate	Participant-blind non-inferiority trial, IWRS clinical assessors unmasked only a sample of population with immunologic studies

Powell (UK)	RWE (August 2021)	Retrospective cohort	Adults aged 18-75 recorded to have received vaccination in the NIMS,who had received their second dose 21 days prior, with recorded mobile numbers, invited to the survey (n = 1313) Excluded ncomplete information, those who responded"not known" when asked about prior COVID 19 symptoms	ChAdOx1/BNT162b2 med 76d (n = 572) BNT162b2/ChAdOx1 med 76d (n = 167)	ChAdOx1/ChAdOx1 med 69d (n = 461) BNT162b2/BNT162b2 med 69d (n = 133)	Within 21 d from V2	Overall AE rates ***ChAd/BNT : 60.5%*** ***BNT/ChAd : 58.8%*** ***ChAd/ ChAd : 35.2%*** ***BNT/BNT : 29.3%*** Local reactogenicity ***ChAd/BNT : 51%*** ***BNT/ChAd : 54.4%*** ***ChAd/ ChAd : 32%*** ***BNT/BNT : 26.3%*** Systemic reactogenicity ***ChAd/BNT : 51.9%*** ***BNT/ChAd : 44.3%*** ***ChAd/ ChAd : 25.9%*** ***BNT/BNT : 25.6%*** ***HETERO more likely to report more severe AEs***	Low to moderate	database review Online survey questionnaire (response rate of 18.7%) (no protocol/ no clear methods) subgrouped by age, sex, previous infection, severe AR on prime

ChAdOx1/mRNA-1273									
Study author (country)	**Type of study (date)**	**Study design**	**Population**	**Heterologous regimen (dosing interval)**	**Homologous regimen (dosing interval)**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Rose (Germany)	Preprint (July 2021)	Prospective cohort	not described	ChAdOx1/BNT162b (n=41) ChAdOx1/mRNA-1273 (n=1)	ChAdOx1/ChAdOx1 (n = 9) BNT162b2 / BNT162b2 (n=8)	15 d post V2	IgG% ***all groups reached 100%*** IgG titers (anti-S and Anti RBD) ***titers in the heterologous groups 7-10x higher than the homologous ChAd and 10 to 175 times higher that the homologous BNT162b2*** Neutralization titers ***homologous ChA had 13 to 11 fold lower GMTs compared to heterologous or homo BNT*** Neutralization % ***similar across groups***	Very low	with missing samples post-D2
Normark (US)	Correspondence (September 2021)	prospective cohort	healthcare workers (n=88) excluded 5 who had COVID prior	ChAdOx1/mRNA-1273 84 (IQR 82-86) (n=48)	ChAdOx1/ChAdOx1 70d (IQR 67-76) (n=35)	7 - 10 and 30 d after V2 (extracted 30 days)	***results in tables*** S-binding and RBD binding titers ***decreased neutralization of Beta, but HETERO significantly higher titers than HOMO***	Very low	interim report of ongoing study sl younger Homo Homo with more allergy and comorbid dosing interval longer in HOMO
Safety									
Normark (US)	Correspondence (September 2021)	prospective cohort	healthcare workers (n=88) excluded 5 who had COVID prior	ChAdOx1/mRNA-1273 84 (IQR 82-86) (n=48)	ChAdOx1/ChAdOx1 70d (IQR 67-76) (n=35)	7-10 d after V2	***higher pain with HETERO*** ***more systemic events with HETERO : Fever, fatigue, headcache, chills, other***	Low	interim report of ongoing study sl younger Homo Homo with more allergy and comorbid dosing interval longer in HOMO

ChAdOx1/BBV152									
Study author (country)	**Type of study (date)**	**Study design**	**Population**	**Heterologous regimen (dosing interval)**	**Homologous regimen (dosing interval)**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Kant (India)	Preprint (August 2021)	Prospective cohort	individuals under the national vaccination program	ChAdOx1/BBV152 (n = 18)	ChAdOX1/ChAdOx1 (n = 40) BBV152/BBV152 (n = 40)	60-70 d after V1	PRNT50 assay - ***see tables*** ELISA) Anti-RBD, anti-spike, N protein titers NAb titers against B.1, Alpha, Beta, and Delta strains	Very low	unclear on selection of the homologous groups
Safety									
Kant (India)	Preprint (August 2021)	Prospective cohort	individuals under the national vaccination program	ChAdOx1/BBV152 (n = 18)	ChAdOX1/ChAdOx1 (n = 40) BBV152/BBV152 (n = 40)	7 d after V2	Solicited local and systemic Aes (Cha/Cha vs Cov/Cov vs Cha/Cov) ***pain : 5 vs 7.5 vs 11.1 pyrexia : 15 vs 15 vs 11.1 malaise : 5 vs 15 vs. 5.5 paracetamol use : 7.5 vs 17.5 vs 11.1 overall frequency of AE in hetero similar to homo***	Low	unclear on selection of the homologous groups

mRNA-1273/BNT162b2									
Study author (country)	**Type of study (date)**	**Study design**	**Population**	**Heterologous regimen (dosing interval)**	**Homologous regimen (dosing interval)**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectivenss									
None									
Immunogenicity									
Vinh (Canada)	Preprint (September 2021)	Prospective cohort	>=65 year old, in long term care facility	mRNA-1273/BNT162b2	BNT162b2/BNT162b2 mRNA1273/mRNA1273	4 weeks	***similar levels of IgG were observed with no difference between HOMO and HETERO***	Very low	
Safety									
None									

CoronaVac/ChAdOx1									
Study author (country)	**Type of study (date)**	**Study design**	**Population**	**Heterologous regimen (dosing interval)**	**Homologous regimen (dosing interval)**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Yorsaeng (Thailand)	Preprint (September 2021)	Retrospective cohort	general population? Not described	CoronaVac/ChAdOx1 4 weeks (n=54)	CoronaVac/CoronaVac 3 weeks (n=80) ChAdOx1/ChAdOx1 10 weeks (n=80)	not specified	anti-S antibody titers	Very low	
Safety									
None									

CoronaVac/Ad5-nCoV									
Study author (country)	**Type of study (date)**	**Study design**	**Population**	**Heterologous regimen (dosing interval)**	**Homologous regimen (dosing interval)**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
None									
Immunogenicity									
Li (China)	Preprint (September 2021)	RCT	18-59 yo, healthy received two doses of CoronaVac in the past 3-6 months or one dose of CoronaVac in the past 1-2 months Excluded previous clinical or virologic COVID-19 diagnosis or infection, pregnant women	CoronaVac/Ad5 1-2 months (n=49) 2 patients discontinued	CoronaVac/CoronaVac 1-2 months (n=49) 1 patient discontinued	14 and 28 d after V2	neutralizing antibody titers (live viral assay) - seroconversion-***see table*** - GMT-***see table*** - Geometric mean fold increase ***23.4 vs 5.2*** IFN-Gamma titers - ***see table*** anti-RBD binding titer - ***see table***	Low	IWRS randomization participants, investigators, lab and outcome assessors blinded to treatment but not to th 3 or 2 dose regimen; (4-arm trial, 2 arms on booster after 2 doses of Coronavac)
Safety									
Li (China)	Preprint (September 2021)	RCT	18-59 yo, healthy received two doses of CoronaVac in the past 3-6 months or one dose of CoronaVac in the past 1-2 months Excluded previous clinical or virologic COVID-19 diagnosis or infection, pregnant women	CoronaVac/Ad5 1-2 months (n=49) 2 patients discontinued	CoronaVac/CoronaVac 1-2 months (n=49) 1 patient discontinued	28 days after V2	(Hetero vs Homo) ***any AE :25.5% vs 8.0%*** ***Inj site AE : 23.5 vs 2.0*** ***Pain at inj : 19.6 vs 2.0*** ***Any systemic : 11.8 vs 6.0*** ***Fever : 5.9 vs 2.0*** ***Fatigue : 7.8 vs 4.0*** ***low incidence of unsolicited adverse reactions*** ***no severe AE in both groups***	Low	IWRS randomization participants, investigators, lab and outcome assessors blinded to treatment but not to th 3 or 2 dose regimen; (4-arm trial, 2 arms on booster after 2 doses of Coronavac)

ChAdOx1/BNT162b2 or mRNA-1273									
Study author (country)	**Type of study (date)**	**Study design**	**Population**	**Heterologous regimen (dosing interval)**	**Homologous regimen (dosing interval)**	**Follow-up**	**Outcomes**	**Certainty of evidence**	**Comments**
Clinical efficacy/effectiveness									
Gram (Denmark)	Preprint (July 2021)	Retrospective population-based cohort study	Vaccinated residents in Denmark N = 5,542,079	ChAdOx1/BNT162b2 (n = 88,050) ChAdOx1/mRNA-1273 (n = 48,501) results presented as ChAdOx1 / mRNA vaccine	ChAdOx1/- (n = 144,360) or no vaccination	Immediately after vaccination up to emigration, death, or June 23, 2021 whichever comes first 0-13 d and =/> 14 d after V2	VE against SARS-CoV-2 infection, *(0-13d)* *ChA/mRNA : 66% (59,72)* *(>=14d)* *ChA/mRNA : 88% (83,92)* COVID-19 related hospitalization *none* COVID 19 related death all cause hospitalization *(0-13d)* *Cha/mRNA :43% (36,49)* *(>=14d)* *Cha/mRNA : 50% (45,55)* all cause death *none occurred*	Low	controlled for calendar time, age, sex, heritage, comorbidity, and hospitaliation (for death)
Immunogenicity									
Schmidt (Germany)	Correspondence (July 2021)	Prospective cohort	216 immunocompetent individuals	ChAdOx1/mRNA-based (n = 97)	ChAdOx1/ChAdOx1 (n = 55) mRNA-based/mRNA-based (n = 64)	Median 14 d after vaccination after V2	***results in table*** Spike specfic IgG level (BAU/ml) Surrogate neutralization test (inhibitory activity) Cytokines interferon (IFN)-y Spike-specific CD4 , CD8	Very low	Homologous vector group older than other groups
Schmidt2 (Germany)	Full publication (August 2021)	Prospective cohort	40 solid transplant recipients 70 immunocompetent controls	ChAdOx1/mRNA-based (n = 20)	ChAdOx1/ChAdOx1 (n=9) mRNA-based/mRNA-based (n = 9)	Median 14 d after V2	***CD4 T cell levels after HOMO were lower than HETERO*** ***CD8 higher in hetero but not signifcant*** ***IgG and netrualizing Ab higher in Hetero and HomomRNA, thatn Homo vec***	Very low	matching across transplant vs immunocompetent, not based on vaccination
Safety									
Schmidt (Germany)	Correspondence (July 2021)	Prospective cohort	216 immunocompetent individuals	Vector vaccine/mRNA vaccine (n = 97)	Vector vaccine/Vector vaccine (n = 55) mRNA vaccine/mRNA vaccine (n = 64)	Within first week after D1 and D2	Local and systemic adverse events ***mRNA-boosted regimen less tolerated***	Low	Homologous vector group older than other groups

Appendix 6. Seropositivity

STUDY ID	Immunologic study (Test Used) (Time of Assessment)	HETERO Regimen (N) post-boost Seropositivity	HOMO Regimen (N) post-boost Seropositivity	Difference between Regimen after D2 (95% CI)
Benning	AntiS1 IgG positivity 20 days	ChAd/BNT (35) 97.0	ChAd/ChAd (17) 93.5	3.3% (-9.8 to 16.4)
		ChAd/BNT (35) 96.8	BNT/BNT (82) 97.0	-2.0% (-7.1 to 6.7)
	Full spike	ChAd/BNT (15) 100%	BNT/BNT (15) 100%	0.00%
	S1	ChAd/BNT (15) 100%	BNT/BNT (15) 100%	0.00%
	RBD	ChAd/BNT (15) 100%	BNT/BNT (15) 100%	0.00%
	S2	ChAd/BNT (15) 93%	BNT/BNT (15) 100%	-7.0% (-20 to 5.91)
Dimeglio	Nab (live virus based) (1 month) <55 y/o	ChAd/BNT (33) 75.7%	BNT/BNT (33) 87.8%	-12.1% (-31to 6.3)
	Nab (live virus based) (1 month) >55 y/o	ChAd/BNT (22) 95.4%	BNT/BNT (22) 68.2%	27.2% (5.86-48.5)
	Nab (live virus based) (1 month) >55 y/o	ChAd/BNT (22) 95.4%	ChAd/ChAd (22) 63.6%	31.8% (9.9-53.7)
Liu	Anti-spike (28days)	ChAd/BNT (108) 96%	ChAd/ChAd (105) 95%	1.0% (-4.6 to 6.6)
	Anti-spike (28days)	ChAd/BNT (108) 96%	BNT/BNT (110) 100%	-4.0% (-7.7 to -0.3)
	Anti-spike (28days)	BNT/ChAd (109) 100%	ChAd/ChAd (105) 95%	5.0% (8.3-9.2)
	Anti-spike (28days)	BNT/ChAd (109) 100%	BNT/BNT (110) 100%	0.00%
	Cellular Response (28 days)	ChAd/BNT (107) 100%	ChAd/ChAd (103) 98%	2.0% (-0.7 to 4.7)
	Cellular Response (28 days)	ChAd/BNT (107) 96%	BNT/BNT (109) 94%	7.0% (2.21-11.8)
	Cellular Response (28 days)	BNT/ChAd (108) 90%	ChAd/ChAd (103) 98%	- 8.0% (-14.2 to -1.73)
	Cellular Response (28 days)	BNT/ChAd (108) 90%	BNT/BNT (109) 94%	-3.0% (-10.4 to 4.4)

Hillus	RBD reactivity	ChAd/BNT (94) 100%	BNT/BNT (101) 99%	1.0% (-0.9 to 2.94)
	RBD reactivity	ChAd/BNT (94) 100%	ChAd/ChAd (36) 100%	0
	Nab (surrogate virus neutralization)	ChAd/BNT (94) 100%	ChAd/ChAd (36) 100%	0
	Nab (surrogate virus neutralization)	ChAd/BNT (94) 100%	BNT/BNT (101) 99%	1.0% (-0.9 to 2.94)
	Anti-S1	ChAd/BNT (94) 100%	ChAd/ChAd (36) 97%	3% (-2.57 to 8.57)
	Anti-S1	ChAd/BNT (94) 100%	BNT/BNT (101) 99%	1.0% (-0.9 to 2.94)
	Nab (surrogate virus neutralization)	ChAd/BNT (104) 97.1%	ChAd/ChAd (38) 92.4%	4.7% (-4.3 to 13.7)
	Nab (surrogate virus neutralization)	ChAd/BNT (104) 97.1%	BNT/BNT (174) 96.6%	0.5% (-3.7 to 4.7)
Li J	Neutralizing Antibody	CoV/Ad5 (50) 100%	CoV/CoV (50) 93.9%	6.1% (-0.5. to 12.73)
Schmidt	IFN gamma CD4	vector/mRNA (97) 0.17	mRNA/mRNA (55) 0.16	Median percentages, not GMTs
	IFN gamma CD4	vector/mRNA (97) 0.17	vector/vector (64) 0.04	Median percentages, not GMTs
	IFN gamma CD8	vector/mRNA (97) 0.28	mRNA/mRNA (55) 0.06	Median percentages, not GMTs
	IFN gamma CD8	vector/mRNA (97) 0.28	vector/vector (64) 0.04	Median percentages, not GMTs

Appendix 8. Titer Levels

STUDY ID	Immunologic study (Test Used) (Time of Assessment)	HETERO Regimen (N) GMT (95% CI)	HOMO Regimen (N) GMT (95% CI)	GMR (Hetero:Homo) (95% CI)
Bennings	Anti-S1 IgG levels	ChAd/BNT (n =) 116.2 (IQR 61.8-170)	BNT/BNT (n =) 145.5 (100.0-291.1)	0.8
		ChAd/BNT (n =) 116.2 (61.8-170)	ChAd/ChAd (n =) 13.1 (7.0-29.0)	8.87
	Full spike MFI values	ChAd/BNT 24243	BNT/BNT 23849	1.02
	S1 MFI values	ChAd/BNT 19332	BNT/BNT 16955	1.14
	S2 MFI values	ChA/BNT 13138	BNT/BNT 9696	1.35
Liu	Anti-spike IgG	ChA/BNT (104) 12906	Cha/Cha (104) 1392	9.27
	Anti-spike IgG	BNT/ChA (109) 7133	BNT/BNT (109) 14080	0.51
	Anti-spike IgG	ChA/BNT (104) 12906	BNT/BNT (109) 14080	0.92
	Anti-spike IgG	BNT/ChA (109) 7133	Cha/Cha (104) 1392	5.12
	Neutralizing Antibodies (pseudotype assay NT50)	ChA/BNT (101) 515	Cha/ChAd (101) 61	8.5 (6.5-11)
	Neutralizing Antibodies (pseudotype assay NT50)	BNT/ChA (104) 383	BNT/BNT (102) 574	0.67 (0.51-0.88)
	Neutralizing Antibodies (pseudotype assay NT50)	ChA/BNT (101) 515	BNT/BNT (102) 574	0.9
	Neutralizing Antibodies (pseudotype assay NT50)	BNT/ChA (104) 383	Cha/ChAd (101) 61	6.3
	IFN-Gamma (ELISpot) 28 days after	ChAd/BNT (108) 184	ChAd/ChAd (104) 48	3.9 (2.9-5.3)
	IFN-Gamma (ELISpot) 28 days after	ChAd/BNT (108) 184	BNT/BNT (110) 80	2.3
	IFN-Gamma (ELISpot) 28 days after	BNT/ChAd (109) 97	ChAd/ChAd (104) 48	2.02
	IFN-Gamma (ELISpot) 28 days after	BNT/ChAd (109) 97	BNT/BNT (110) 80	1.2 (0.87-1.7)
Behrens	Anti-spike IgG (Quantivac) 16 days after	ChAd/BNT (11) 611.0	ChAd/ChAd (12) 171.9	3.55
Kant	Anti S1-RBD (Elisa) 9 weeks later	ChAd/CoV (18) 1866	ChAd/ChAd (40) 2260	0.83
	Anti S1-RBD (Elisa) 9 weeks later	ChAd/CoV (18) 1866	CoV/CoV (40) 710	2.63

	N-protein 9 weeks	ChAd/CoV (18) 1145	ChAd/ChAd (40) 353.7	3.24
	N-protein 9 weeks	ChAd/CoV (18) 1145	CoV/CoV (40) 742.4	1.54
	IgG titers (whole virus) 9 weeks	ChAd/CoV (18) 171.4	ChAd/ChAd (40) 111	1.54
	IgG (whole virus) 9 weeks	ChAd/CoV (18) 171.4	CoV/CoV (40) 86	1.99
	Neutralzing Antibodies (PRNT50) 9 weeks	ChAd/CoV (18) 539.4	ChAd/ChAd (40) 162	3.33
	Neutralzing Antibodies (PRNT50) 9 weeks	ChAd/CoV (18) 539.4	CoV/CoV (40) 156.6	3.44
Schmidt	Spike-specific IgG 14 days	vector/mRNA (97) 3630	mRNA/mRNA (55) 4932	0.74
	Spike-specific IgG 14 days	vector/mRNA (97) 3630	vector/vector (64) 404	8.99
Tenbusch	Neutralizing antibody (surrogate neutralization assay) 14 days	ChAd/BNT (232) 2798	BNT/BNT (410) 1730	1.62
	neutralizing antibody (surrogate neutralization assay) 14 days	ChAd/BNT (250) 6673	BNT/BNT (127) 2583	2.58
	neutralizing antibody (surrogate neutralization assay) 14 days	ChAd/BNT (250) 6673	ChAd/ChAd (66) 106	62.95
Hillus	Anti-spike IgG 3 weeks	ChAd/BNT () 5.6	BNT/BNT () 5.6	1.03
	Anti-spike IgG 3 weeks	ChAd/BNT () 5.6	ChAd/ChAd ( ) 4.9	1.14
	IFN-gamma (IGRA) 3 weeks	ChAd/BNT (91) 4762	BNT/BNT (66) 2026	2.35
	IFN- gamma (IGRA) 3weeks	ChAd/BNT (91) 4726	ChAd/ChAd (34) 1061	4.45
Normark	S-Binding 1 month	ChAd/Mod (48) 104083	ChAd/ChAd (35) 7381	14.1
	RBD-binding 7-10days	ChAd/Mod (48) 41680	ChAd/ChAd (35) 1224	34.05
Vallee	Anti-IgG 30-60 days	ChAd/BNT (130) 7268.6	BNT/BNT (67) 10,734.9	0.68
Yorsaeng	Anti-S IgG unspecified	CoV/ChAd (54) 797	CoV/CoV (80) 96.4	8.27

	Anti-S IgG unspecified	CoV/ChAd (54) 797	ChAd/ChAd (80) 818	0.97
Li J	Neutralizing antibodies (live viral netrualization assa) 28 days	CoV/Ad5 (50) 49.6	CoV/CoV (50) 10.6	4.68
	IFN-gamma 14 days	CoV/Ad5 (50) 65	CoV/CoV (50) 40	1.66
	Anti RBD-binding IgG 14 days	CoV/Ad5 (50) 941.8	CoV/CoV (50) 154.1	6.11

Appendix 9. Characteristics of Ongoing Studies

NCT Number	Title	Status	Study Results	Interventions	Outcome Measures	Sponsor/Collaborators	URL
NCT04988048	Collaborative Study to Evaluate Heterologous Vaccination Against Covid-19 in Argentina	Recruiting	No Results Available	Biological: COVID-19 vaccines	Antibody against Spike protein measurement by ELISA test|Incidence of adverse events by measurement of the number of reactions after vaccination|Neutralising Antibody against Spike protein and cellular immune response	Ministry of Public Health, Argentina|Russian Direct Investment Fund	https://ClinicalTrials.gov/show/NCT04988048
NCT04889209	Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) After Receipt of EUA Vaccines	Recruiting	No Results Available	Biological: Ad26.COV2.S|Biological: BNT162b2|Biological: mRNA-1273|Biological: mRNA-1273.211	Magnitude of SARS-CoV-2 specific antibody binding and neutralization titers|Occurrence of adverse events (AEs)|Occurrence of Adverse Events of Special Interest (AESIs).|Occurrence of New-Onset Chronic Medical Condition (NOCMCs).|Occurrence of Related Medically attended adverse events (MAAEs).|Occurrence of Serious Adverse Events (SAEs).|Occurrence of solicited reactogenicity adverse events (AEs)|Response rate of SARS-CoV-2 specific antibody binding and neutralization titers	National Institute of Allergy and Infectious Diseases (NIAID)	https://ClinicalTrials.gov/show/NCT04889209
NCT04833101	Study on Heterologous Prime-boost of Recombinant COVID-19 Vaccine (Ad5 Vector) and RBD-based Protein Subunit Vaccine	Active, not recruiting	No Results Available	Biological: recombinant Ad5 vectored COVID-19 vaccine|Biological: RBD-based protein subunit vaccine (ZF2001) against COVID-19|Biological: trivalent split influenza vaccine	Incidence of solicited adverse events within 7 days after vaccination.|GMT of neutralizing antibodies against live SARS-CoV-2 virus at Day 14 after the booster vaccination.|Incidence of adverse reactions within 28 days after vaccination.|Incidence of adverse events within 28 days after vaccination.|Incidence of unsolicited AE within 28 days after vaccination.|Incidence of serious adverse events(SAE) from the first dose to the 6 months after completing the last dose of vaccination.|GMT of binding antibodies against SARS-CoV-2 S and RBD protein measured by ELISA at day 14, day 28 after the second vaccination, and day 14, month 6 after the third vaccination.|Proportion of the participants with at least a four-fold increase of the binding antibodies against SARS-CoV-2 S and RBD protein at day 14, day 28 after the second vaccination, and day 14, month 6 after the third vaccination.|Fold increase of binding antibodies against SARS-CoV-2 S and RBD protein at day 14, day 28 after the second vaccination, and day 14, month 6 after the third vaccination.|GMT of neutralizing antibodies against live SARS-CoV-2 virus at day 28 after the second vaccination, and day 14, month 6 after the third vaccination|Proportion of the participants with at least a four-fold increase of neutralizing antibodies against live SARS-CoV-2 virus at day 14, day 28 after the second vaccination, and day	Jiangsu Province Centers for Disease Control and Prevention	https://ClinicalTrials.gov/show/NCT04833101

					14, month 6 after the third vaccination.|Fold increase of neutralizing antibodies against live SARS-CoV-2 virus at day 14, day 28 after the second vaccination and day 14, month 6 after the third vaccination.		
NCT05043259	Heterologous Prime-boost Immunization With an Aerosolised Adenovirus Type-5 Vector-based COVID-19 Vaccine (Ad5-nCoV) After Priming With an Inactivated SARS-CoV-2 Vaccine	Recruiting	No Results Available	Biological: inactive SARS-CoV-2 vaccine (Vero cell)|Biological: Low dose aerosolized Ad5-nCoV|Biological: High dose aerosolized Ad5-nCoV	Incidence of adverse reactions within 14 days after the booster dose.|GMT of neutralizing antibodies against live SARS-CoV-2 virus on day 14 after the booster dose.|Incidence of adverse events within 0-28 days after the booster dose.|Incidence of serious adverse events (SAE) till the 12 months after the booster dose.|GMT of neutralizing antibodies against live SARS-CoV-2 virus on day 7 and 28 after the booster dose.|Fold increase and seroconversion of neutralizing antibodies against live SARS-CoV-2 virus on day 14 after the booster vaccination.|GMT, fold increase and seroconversion of neutralizing antibodies against live SARS-CoV-2 virus at month 3, 6, and 12 after the booster dose.|GMT, fold increase and seroconversion of binding antibodies against SARS-CoV-2 RBD on day 7, day 14, day 28 after the booster dose.|GMT, fold increase and seroconversion of binding antibodies against SARS-CoV-2 RBD at month 3, 6, and 12 after the booster dose.|The levels of IFN- Î³â€• IL-2 and IL-	Jiangsu Province Centers for Disease Control and Prevention	https://ClinicalTrials.gov/show/NCT05043259

					13 secreted by specific T cells on day 7 and 14 after the booster vaccination.		
NCT05054621	Immunogenicity of COVID-19 Vaccine on Heterologous Schedule	Not yet recruiting	No Results Available	Biological: Heterologous prime-boost schedule with AZD1222 and MVC-COV1901|Biological: Homologous prime-boost schedule with two doses of AZD1222	Immunogenicity: Neutralizing antibody against SARS-CoV-2|Immunogenicityï¼šAnti-SARS-CoV-2 Spike antibody|Adverse events|Immunogenicity: Anti-SARS-CoV-2 Nucleocapsid antibody|Immunogenicity: T cell immunity	Chang Gung Memorial Hospital	https://ClinicalTrials.gov/show/NCT05054621
NCT04998240	Mix and Match Heterologous Prime-Boost Study Using Approved COVID-19 Vaccines in Mozambique	Not yet recruiting	No Results Available	Biological: BBIBP-CorV - Inactivated SARS-CoV-2 vaccine (Vero cell)|Biological: AZD1222 (replication-deficient Ad type 5 vector expressing full-length spike protein)	Geometric Mean Titers (GMTs) of anti-SARS-CoV-2 neutralizing antibodies|Incidence of SAEs and AESI observed at any time point during the entire study period|Incidence of solicited reactions within 7 days (local reactions) and 14 days (systemic reactions)|Incidence of unsolicited adverse events that are within 28 days after each vaccination|Incidence of changes in laboratory safety measures from baseline to day 28 after each vaccination|Geometric Mean Titers (GMTs) and Geometric Mean Fold Rise (GMFR)	International Vaccine Institute|The Coalition for Epidemic Preparedness Innovations (CEPI)|Instituto Nacional de SaÃºde (INS), Mozambique|University of Antananarivo|International Centre for Diarrhoeal Disease Research, Bangladesh|Harvard University|Heidelberg University	https://ClinicalTrials.gov/show/NCT04998240
NCT04760730	Safety and Immunogenicity Study in Adults of AZD1222 and rAd26-S	Not yet recruiting	No Results Available	Biological: AZD1222|Biological: rAd26-S	Antibody seroconversion rate (â‰¥ 4 fold increase from baseline) against SARS-CoV-2 Spike protein 29 days post second vaccination|Incidence of local and systemic solicited Adverse Events (AEs) for 7 days following each vaccination (Day 1 through	R-Pharm|AstraZeneca	https://ClinicalTrials.gov/show/NCT04760730

	Administered as Heterologous Prime Boost Regimen for the Prevention of Coronavirus Disease 2019 (COVID-19)				Day 7 for first vaccination and Day 29 through Day 35 for second vaccination)|Incidence of unsolicited AEs, Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs) through 29 days post each vaccination|Incidence of SAEs and AESIs after first vaccination until study end (Day 180)|Antibody seroconversion rate (â‰¥ 4 fold increase from baseline) against SARS-CoV-2 Spike protein 29 days post first vaccination|Antibody seroconversion rate (â‰¥ 4 fold increase from baseline) against Receptor Binding Domain (RBD) antigen|Geometric Mean Titre (GMT) and Geometric Mean Fold Rise (GMFR) of immunogenicity against Spike and RBD antigens at the day of vaccination (baseline), Day 15, 29 days post each vaccination and at study end (Day 180).|Antibody seroconversion rate (â‰¥ 4 fold increase from baseline) SARS-CoV-2 neutralising antibodies|GMT and GMFR of immunogenicity as measured by SARS-CoV-2 neutralising antibodies at day of vaccination (baseline), Day 15, 29 days post each vaccination and at study end (Day 180)		

NCT05048940	Efficacy, Safety, and Immunogenicity of Vaccine Reimmunization With a Third Homologous Versus Heterologous Dose Against SARS-CoV-2 in Patients Undergoing Solid Organ Transplantation.	Not yet recruiting	No Results Available	Biological: Janssen vaccine|Biological: Spikevax (Moderna) vaccine	Changes in the production of anti-S1-RBD IgG antibodies.|Change in the presence of activated T cells specific for SARS-CoV-2 (Sprotein).|Changes in the phenotype of effector/memory/virgin B and T cell populations and subtypes of Th and NK cell populations.|Incidence of symptomatic/asymptomatic COVID infection after revaccination.|Number of patients with hospital admissions and/or visits to the emergency department for severe symptoms related to COVID-19 infection.	Instituto de InvestigaciÃ³n MarquÃ©s de Valdecilla	https://ClinicalTrials.gov/show/NCT05048940

NCT04684446	Study in Adults of AZD1222 and rAd26-S Administered as Heterologous Prime-Boost Regimen for the Prevention of COVID-19	Recruiting	No Results Available	Biological: AZD1222|Biological: rAd26-S	Antibody seroconversion rate (â‰¥ 4-fold increase from baseline) against SARS-CoV-2 neutralising antibodies 29 days post second vaccination.|Incidence of local and systemic solicited AEs for 7 days following each vaccination (Day 1 through Day 7 for first vaccination and Day 29 through Day 35 for second vaccination).|Incidence of unsolicited AEs, SAEs and AESIs through 29 days post each vaccination (ie, until Day 29 following the first vaccination and Day 57 following the second vaccination).|Incidence of SAEs and AESIs after first vaccination until study end (Day 180).|Antibody seroconversion rate (â‰¥ 4-fold increase from baseline) against SARS-CoV-2 Spike protein|Antibody seroconversion rate (â‰¥ 4-fold increase from baseline) against RBD antigen.|GMT and GMFR of immunogenicity against Spike and RBD antigens (MSD serology assay) at the day of vaccination (baseline), Day 15, 29 days post each vaccination and at study end (Day 180).|Antibody seroconversion rate (â‰¥ 4-fold increase from baseline) SARS-CoV-2 neutralising antibodies 29 days post first vaccination|GMT and GMFR of immunogenicity as measured by SARS-CoV-2 neutralising antibodies at day of vaccination (baseline), Day 15, 29 days post each vaccination and at study end (Day 180).|Intracellular cytokine staining, including quantification of Th1/Th2 responses, and flow cytometry for B- and T-cell responses from day of dosing baseline to 29 days post each vaccination and until study end|A binary response, whereby a participant is defined as a COVID-19 case if their illness (virologically confirmed [RT-PCR positive] and symptomatic) occurs	R-Pharm|AstraZeneca|Russian Direct Investment Fund|The Gamaleya National Center of Epidemiology & Microbiology	https://ClinicalTrials.gov/show/NCT04684446
NCT04907331	Heterologous SARS-CoV-2 Vaccination With ChAdOx-1 and BNT162b2	Recruiting	No Results Available	Biological: Vaxzevria|Biological: Comirnaty	Neutralizing antibodies|T cells|vaccine failures	Medical University Innsbruck|Medical University of Graz|Medical University of Vienna	https://ClinicalTrials.gov/show/NCT04907331
NCT05027672	Strategies for Combining the First Component of Sputnik V With Other Adenoviral or mRNA-based Vaccines.	Active, not recruiting	No Results Available	Drug: Gam-COVID-Vac (rAd26) / Gam-COVID-Vac (rAd5)	ELISA assessment of concentration of IgG anti Spike (UI/ml) at 28 days.|Serious adverse events Adverse events of special interest|Neutralising antibodies against SARS-CoV-2	Ministerio de Salud de Ciudad AutÃ³noma de Buenos Aires	https://ClinicalTrials.gov/show/NCT05027672

NCT04569383	Safety and Immunogenicity of the Candidate Vaccine MVA-SARS-2-S and a Booster Vaccination With a Licensed Vaccine Against COVID-19	Active, not recruiting	No Results Available	Biological: MVA-SARS-2-S vaccinations (days 0 & 28)|Biological: Comirnaty	Percentage of Participants Experiencing Solicited Local or Systemic Reactogenicity as Defined by the Study Protocol|Immunogenicity. Number of participants who seroconverted	UniversitÃ¤tsklinikum Hamburg-Eppendorf|German Center for Infection Research|Philipps University Marburg Medical Center|Ludwig-Maximilians - University of Munich	https://ClinicalTrials.gov/show/NCT04569383
NCT04993560	Safety and Efficacy of COVID-19 Prime-boost Vaccine in Bahrain	Recruiting	No Results Available	Biological: BBIBP-CorV|Biological: BNT162b2	Change from Baseline Immunogenicity at 8 weeks|Reactogenicity	Royal College of Surgeons in Ireland - Medical University of Bahrain|The National Taskforce for Combatting COVID-19-Kingdom of Bahrain|Bahrain Defence Force Royal Medical Services|Ministry of Health, Bahrain|Bahrain International Exhibition & Convention Centre	https://ClinicalTrials.gov/show/NCT04993560
NCT04776317	Chimpanzee Adenovirus and Self-Amplifying mRNA Prime-Boost Prophylactic Vaccines Against SARS-CoV-2 in Healthy Adults	Recruiting	No Results Available	Biological: ChAdV68-S|Biological: ChAdV68-S-TCE|Biological: SAM-LNP-S|Biological: SAM-LNP-S-TCE|Other: Sodium Chloride, 0.9%	Occurrence of Adverse Events of Special Interest (AESIs)|Occurrence of clinical safety laboratory adverse events by severity grade|Occurrence of Serious Adverse Events (SAEs)|Occurrence of solicited local reactogenicity adverse events (AEs)|Occurrence of solicited systemic reactogenicity adverse events (AEs)|Occurrence of unsolicited adverse events (AEs)|Geometric mean fold rise from baseline in titer measured by a SARS-CoV-2 neutralization assay|Geometric mean fold rise from baseline in titer of receptor-binding domain (RBD) specific Immunoglobulin G (IgG)|Geometric mean fold rise from baseline in titer of Spike-specific Immunoglobulin G (IgG)|Geometric mean titer measured by a SARS-CoV-2 neutralization assay|Geometric mean titer of receptor-binding domain (RBD) specific Immunoglobulin G (IgG)|Geometric mean titer of Spike-specific Immunoglobulin G (IgG)|Percent of cells expressing a cytokine by cell type (CD4+ or CD8+), cytokine set (Th1 or Th2 cytokine for CD4+ and CD8+ cytokine for CD8+ or other combinations of interest) and peptide pool (covering spike and T cell epitope regions)|Percentage of subjects who	National Institute of Allergy and Infectious Diseases (NIAID)|Gritstone Oncology, Inc.	https://ClinicalTrials.gov/show/NCT04776317

					seroconverted for RBD from wild-type virus and emergent viral strains|Percentage of subjects who seroconverted for spike protein from wild-type virus and emergent viral strains|Percentage of subjects who seroconverted for wild-type virus and emergent viral strains|Rate of spot-forming cell per million cells by peptide pool|Responder status, derived from the intracellular cytokine staining (ICS) cell counts for each set of applicable cytokines and each peptide pool|Responder status, determined by interferon (IFN) gamma Enzyme Linked Immunospot Assay (ELISpot) for each peptide pool|Th1/Th2 cytokine balance of T cell response		

NCT04927936	A Trial Among HealthCare Workers (HCW) Vaccinated With Janssen Vaccine: the SWITCH Trial	Recruiting	No Results Available	Biological: Vaccination once with Janssen vaccine (only priming)|Biological: Vaccination with Janssen vaccine followed with Janssen vaccine (homologous boosting).|Biological: Vaccination with Janssen vaccine followed with Moderna vaccine (heterologous boosting).|Biological: Vaccination with Janssen vaccine followed with Pfizer vaccine (heterologous boosting).	Determination of antibodies by a quantitative IgG assay (LIAISON SARS-CoV-2 TrimericS IgG essay) 28 days after booster	Erasmus Medical Center|Leiden University Medical Center|University Medical Center Groningen|Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)	https://ClinicalTrials.gov/show/NCT04927936

NCT04860739	Vaccination With COMIRNATY in Subjects With a VAXZEVRIA First Dose	Active, not recruiting	No Results Available	Drug: COMIRNATY	To assess the humoral immune response against SARS-CoV-2, 14 days after a vaccination with COMIRNATY in subjects that received a previous single dose of VAXZEVRIA, as compared with no dosing.|To assess the humoral immune response against SARS-CoV-2, 28 days after a vaccination with COMIRNATY in subjects that received a previous single dose of VAXZEVRIA (antibodies)|To assess the humoral immune response against SARS-CoV-2, 28 days after a vaccination with COMIRNATY in subjects that received a previous single dose of VAXZEVRIA (Virus neutralization)|To assess the occurrence of symptomatic molecularly confirmed COVID-19 and severity of COVID-19 signs and symptoms after the administration of a dose of COMIRNATY in subjects that received a prior single dose of VAXZEVRIA|To evaluate the safety of a dose of COMIRNATY in subjects that received a previous single dose of VAXZEVRIA (solicited adverse events)|To evaluate the safety of a dose of COMIRNATY in subjects that received a previous single dose of VAXZEVRIA (unsolicited adverse events)|To evaluate the safety of a dose of COMIRNATY in subjects that received a previous single dose of VAXZEVRIA (serious adverse events)|To evaluate the safety of a dose of COMIRNATY in subjects that received a previous single dose of VAXZEVRIA (Medically-attended adverse events)|To assess the humoral immune response against viral variants of SARS-CoV-2, 14 and 28 days after a dose of COMIRNATY in subjects that received a previous single dose of VAXZEVRIA	Spanish Clinical Research Network - SCReN|Instituto de Salud Carlos III	https://ClinicalTrials.gov/show/NCT04860739

NCT04952727	Study on Sequential Immunization of Inactivated COVID-19 Vaccine and Recombinant COVID-19 Vaccine (Ad5 Vector) in Elderly Adults	Recruiting	No Results Available	Biological: Recombinant SARS-CoV-2 Ad5 vectored vaccine|Biological: Inactive SARS-CoV-2 vaccine (Vero cell)	Incidence of adverse reactions within 28 days after the booster dose.|GMT of neutralizing antibodies against live SARS-CoV-2 virus on day 14 after the booster dose.|Incidence of solicited AE within 14 days after the booster dose|Incidence of unsolicited AE within 28 days after the booster dose.|Incidence of serious adverse events (SAE) till the 6 months after the booster dose.|GMT of binding antibodies against SARS-CoV-2 S and N protein on day 14, day 28 and month 6 after the booster dose.|GMT of neutralizing antibodies against live SARS-CoV-2 virus on day 28 and month 6 after the booster dose.|Fold increase of binding antibodies against SARS-CoV-2 S and N protein on day 14, day 28 and month 6 after the booster vaccination.|Fold increase of neutralizing antibodies against live SARS-CoV-2 virus on day	Jiangsu Province Centers for Disease Control and Prevention|CanSino Biologics Inc.	https://ClinicalTrials.gov/show/NCT04952727

					14, day 28 and month 6 after the booster vaccination.|Proportion of the participants with at least a four-fold increase of the binding antibodies against SARS-CoV-2 S and N protein on day 14, day 28 and month 6 after the booster vaccination.|Proportion of the participants with at least a four-fold increase of neutralizing antibodies against live SARS-CoV-2virus on day 14, day 28 and month 6 after the booster vaccination.|Specific T cell responses on day 14 after the booster vaccination.		

NCT04892459	Study on Sequential Immunization of Inactivated SARS-CoV-2 Vaccine and Recombinant SARS-CoV-2 Vaccine (Ad5 Vector)	Active, not recruiting	No Results Available	Biological: Recombinant SARS-CoV-2 Ad5 vectored vaccine|Biological: Inactive SARS-CoV-2 vaccine (Vero cell)	Incidence of adverse reactions within 28 days after the booster dose.|GMT of neutralizing antibodies against live SARS-CoV-2 virus on day 14 after the booster dose.|Incidence of solicited AE within 14 days after the booster dose|Incidence of unsolicited AE within 28 days after the booster dose.|Incidence of serious adverse events (SAE) till the 6 months after the booster dose.|GMT of binding antibodies against SARS-CoV-2 S and N protein on day 14, day 28 and month 6 after the booster dose.|GMT of neutralizing antibodies against live SARS-CoV-2 virus on day 28 and month 6 after the booster dose.|Fold increase of binding antibodies against SARS-CoV-2 S and N protein on day 14, day 28 and month 6 after the booster vaccination.|Fold increase of neutralizing antibodies against live SARS-CoV-2 virus on day 14, day 28 and month 6 after the booster vaccination.|Proportion of the participants with at least a four-fold increase of the binding antibodies against SARS-CoV-2 S and N protein on day 14, day 28 and month 6 after the booster vaccination.|Proportion of the participants with at least a four-fold increase of neutralizing antibodies against live SARS-CoV-2 virus on day 14, day 28 and month 6 after the booster vaccination.|Specific T cell responses on day 14 after the booster vaccination.	Jiangsu Province Centers for Disease Control and Prevention|CanSino Biologics Inc.	https://ClinicalTrials.gov/show/NCT04892459
NCT04894435	Mix and Match of the Second COVID-19 Vaccine Dose for Safety and Immunogenicity	Recruiting	No Results Available	Biological: mRNA-1273 SARS-CoV-2 vaccine|Biological: BNT162b2|Biological: ChAdOx1-S [recombinant]|Other: 0, 28 day schedule|Other: 0, 112 day schedule	Antibody response to SARS-CoV-2 S protein|Durability of antibody response to SARS-CoV-2 S over 12 months|Pseudoneutralization assay, T cell testing, Antibody dependent cellular cytotoxicity (ADCC), Antibody avidity, RNA seq|Incidence of grade 3 solicited local and systemic adverse events, SAEs, AEFIs, MAAEs, AESIs in the 7 days following vaccine receipt.|Acceptability of vaccines as determined by participant-completed questionnaire.	Canadian Immunization Research Network|Canadian Center for Vaccinology|BC Children's Hospital Research Institute|Children's Hospital Research Institute of Manitoba|CHU de Quebec-Universite Laval|Ottawa Hospital Research Institute|Ontario Agency for Health Protection and Promotion|University of	https://ClinicalTrials.gov/show/NCT04894435

						Toronto|Massachusetts General Hospital|Interior Health	