Interim recommendations for heterologous COVID-19 vaccine schedules

Interim guidance
16 December 2021

World Health Organization

Background

This interim guidance has been developed on the basis of the advice issued by the Strategic Advisory Group of Experts (SAGE) on Immunization at its meeting on 7 December 2021 *(1)*.

Declarations of interests were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the SAGE meeting website and SAGE Working Group website.

The guidance is based on the evidence outlined in this document, which was presented to SAGE on 7 December 2021.

All referenced documents are available on the SAGE COVID-19 webpage: https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials.

Methods

The details of the literature review and the summary of the available evidence serving as basis for this guidance are outlined below. The recommendations apply to all COVID-19 vaccines that have received a WHO Emergency Use Listing (EUL) as of 7 December 2021 (Ad26.COV2.S, BBV152, BNT162b2, ChAdOx1-S [recombinant], mRNA-1273, Sinopharm-BIBP, and Sinovac-CoronaVac). Due to the multiplicity of possible heterologous vaccine combinations, the limited direct evidence on the benefits of specific heterologous combinations against the primary outcome of interest (i.e. the level of protection conferred against severe COVID-19), and the lack of an established immune-correlate of protection against COVID-19, the available heterogenous body of evidence was deemed not to lend itself to formal GRADE[1]ing of evidence. Nevertheless, SAGE considered these indirect data from multiple sources as sufficient to proceed with issuing this good practice statement.[2]

Context

WHO, with support of SAGE and its COVID-19 Vaccines Working Group, is reviewing the emerging evidence on the use of heterologous schedules (also known as mix and match schedules).

This interim statement pertains to heterologous primary and heterologous boosting schedules. In a heterologous primary schedule, the vaccine product used for the second dose differs from that used for the first dose.[3] By contrast, heterologous boosting refers to the administration of a vaccine product that differs from the product(s) previously used for a homologous or heterologous primary vaccine series, once an initially sufficient immune response rate in a vaccinated population has waned over time.

This interim statement focuses on heterologous schedules combining multiple vaccine platforms (e.g. a vectored vaccine followed by an mRNA vaccine). Relevant safety signals that have been reported in relation to the heterologous usage of different products from the same vaccine platform (e.g. BNT162b2 followed by mRNA-1273) are also summarized.

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[1] GRADE: Grading of Recommendations, Assessment, Development and Evaluation.
[2] Good practice statements represent recommendations that guideline panels feel are important but that are not appropriate for formal ratings of quality of evidence. Good practice statements characteristically represent situations in which a large and compelling body of indirect evidence, made up of linked evidence including several indirect comparisons, strongly supports the net benefit of the recommended action *(2)*.
[3] Ad26.COV2.S can be given as a one-dose or two-dose primary series. For the purposes of this interim statement, a two-dose heterologous series involving Ad26.COV2.S alongside another COVID-19 vaccine is considered a heterologous primary series.

Rationale for heterologous schedules

The risks and benefits of COVID-19 vaccines, whether administered in a primary series or as booster doses, have largely been assessed using the same vaccine products throughout the dosing series. Accordingly, homologous vaccination is currently considered standard practice.

A common reason for considering heterologous COVID-19 vaccine schedules is lack of availability of the same vaccine product in settings with limited or unpredictable supply. Interchangeability of vaccine products would therefore allow for added programmatic flexibility. Other reasons for considering heterologous vaccine schedules include reducing reactogenicity, increasing immunogenicity, and enhancing vaccine effectiveness.

At present, heterologous schedules constitute off-label use in many countries, and should only be implemented with careful consideration of current vaccine supply, vaccine supply projections, and other access considerations, alongside the potential benefits and risks of the specific products being used.

Current state of knowledge

A rapid review was performed to summarize available data on the use of heterologous COVID-19 vaccine schedules involving a combination of WHO EUL COVID-19 vaccines from different platforms (see Annex 1 for literature review methods).

Vaccine effectiveness

Several observational studies have now reported on vaccine effectiveness (VE) following heterologous primary or boosting schedules involving WHO EUL COVID-19 vaccines (Annex 2). The majority have involved heterologous primary schedules using ChAdOx1-S followed by an mRNA vaccine. Short-term VE against infection or symptomatic disease following heterologous ChAdOx1-S/mRNA (estimates ranging from 61–91%) appears to be commensurate with, or marginally exceed that of, homologous ChAdOx1-S (43–89%), reaching levels similar to those observed after two doses of mRNA vaccine (69–90%). VE against hospitalization following heterologous ChAdOx1-S/mRNA was high (>95%) across studies in Canada, Chile, and Spain *(3-5)*.

VE following heterologous boosting has been reported in two studies to date. In the United Kingdom, heterologous boosting with BNT162b2 following a primary series of ChAdOx1-S had a VE against symptomatic disease of 93% (95% confidence interval [CI]: 92–94%) compared to unvaccinated individuals, and a relative VE of 87% (95% CI: 85–89%) compared to individuals who had received a primary series of ChAdOx1-S at least 140 days prior to onset but no booster dose. These estimates were similar to the VE and relative VE following a homologous booster dose of BNT162b2 following a primary series of BNT162b2 (94% [95% CI: 93–95%] and 84% [95% CI: 83–86%], respectively). In Chile, heterologous boosting with either ChAdOx1-S or BNT162b2 among Sinovac-CoronoVac primed individuals was associated with higher VE than homologous boosting against infection (90% for ChAdOx1-S; 93% for BNT162b2; and 68% for Sinovac-CoronoVac); symptomatic disease (93%, 95%, and 71%, respectively); hospitalization (96%, 89%, and 75%, respectively); and intensive care unit admission (98%, 90%, and 79%, respectively).

Immunogenicity

Data on the immunogenicity of heterologous schedules are available for a wider range of vaccine combinations and dosing regimens (Annex 3). These must be interpreted with caution given the lack of an established correlate of initial or long-term protection, as well as the confounding of schedule with dosing interval in several of the observational studies. Nonetheless, several consistent trends are emerging across the available studies:

- **Inactivated vaccines:** compared with homologous inactivated-only schedules, heterologous schedules have consistently shown enhanced immunogenicity when inactivated vaccines are administered either before or after vectored vaccines (post-vaccination heterologous/homologous binding antibody [Ig] ratios of 3–9 across 6 studies) or mRNA vaccines (Ig ratios of 11–33 across 4 studies). The majority of available studies involved administration of the inactivated vaccine prior to the vectored or mRNA vaccine (see Fig. 1 below). One cohort study reported higher antibody levels following Sinovac-CoronoVac/ChAdOx1-S (4-week interval) than ChAdOx1-S/Sinovac-CoronoVac (10-week interval), with both heterologous groups exhibiting higher antibody concentrations than homologous Sinovac-CoronoVac recipients (4-week interval) *(6)*.
- **Vectored vaccines:** compared with homologous vectored-only schedules, heterologous schedules have consistently shown enhanced immunogenicity when vectored vaccines are administered before or after mRNA vaccines (Ig ratios of 4–14 across 15 studies) but not inactivated vaccines (Ig ratios of 0.4–3 across 6 studies, of which 5 studies reported ratios of ≤1). The majority of studies involving mRNA vaccines assessed administration of a vectored vaccine followed by an mRNA vaccine. One clinical trial reported higher antibody concentrations following ChAdOx1-S/BNT162b2 than

BNT162b2/ChAdOx1-S, with both heterologous groups exhibiting higher antibody concentrations than homologous ChAdOx1-S recipients (all with 4-week intervals) *(7)*.

- **mRNA vaccines:** compared with homologous mRNA-only schedules, heterologous schedules have shown no clear evidence of enhanced immunogenicity when mRNA vaccines are administered before or after vectored vaccines (Ig ratio of 0.4–8 across 16 studies) or inactivated vaccines (Ig ratio of 0.5 in 1 study). The majority of studies (10 of 16) involving vectored vaccines documented post-vaccination Ig ratios in the range 0.7 to 1.4, implying approximate equivalence of the heterologous and homologous schedules.

These trends are consistent across observational studies and clinical trials (in which factors such as dosing interval could be better controlled), and are similar when considering neutralizing antibody concentrations as an endpoint (Annex 3). Several studies have also reported trends consistent with those described above for heterologous schedules combining WHO EUL vaccines with non-EUL vaccines *(8, 9)*.

Heterologous boosting using fractional doses of BNT162b2 has been explored in two recent studies *(9, 10)*, with promising immunogenicity results. WHO will review additional data on fractional doses as they become available.

Fig 1. Immunogenicity of heterologous schedules relative to (A) inactivated-only; (B) vectored-only; and (C) mRNA-only schedules‡
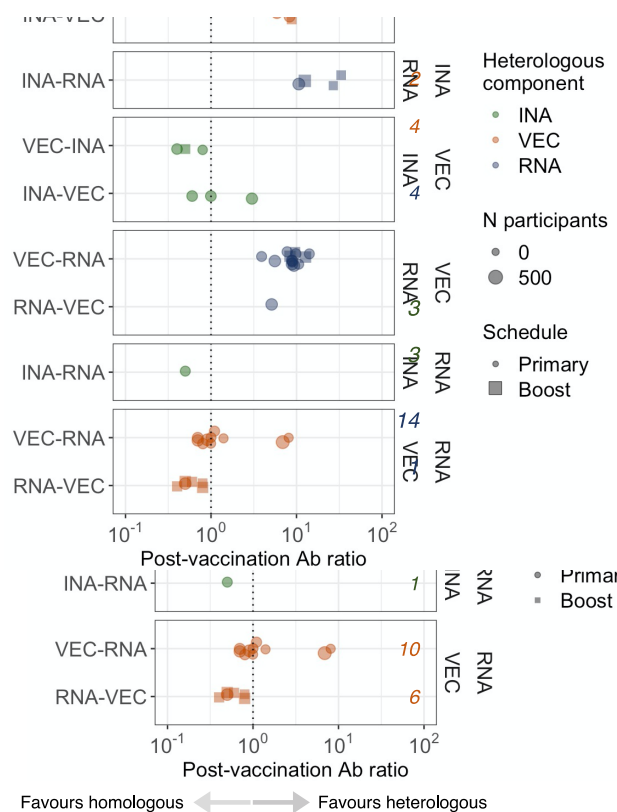
Ab: antibody; INA: inactivated vaccine; RNA: mRNA vaccines; VEC: vectored vaccine.

‡ Each point represents a separate estimate of the post-vaccination binding antibody ratio for heterologous vs homologous schedules, wherein a ratio of >1 favours heterologous vaccination. The order in which the vaccine platforms were administered is indicated on the left of each plot. The numbers in italics indicate the number of separate estimates for each heterologous combination (see Annex 3 for full details of each study, including post-vaccination antibody concentrations in both heterologous and homologous groups).

Safety

Limited safety data are available for the majority of heterologous product combinations. Where reported, heterologous schedules have typically shown transiently increased reactogenicity compared with homologous schedules *(11, 12)*, although results are inconsistent from study to study and the discrepancy between heterologous and homologous schedules has not always been observed *(13, 14)*. In particular, compared with homologous vaccination schedules, some studies have reported a higher frequency of local and systemic side effects (such as headache and fatigue) when ChAdOx1-S or Ad26.COV2.S are administered after mRNA

vaccines, or when BNT162b2 or mRNA-1273 are administered after vectored vaccines *(9, 15-17)*. The majority of side effects for both homologous and heterologous schedules are mild or moderate, typically resolving within 1–3 days of vaccination.

A very rare signal of myocarditis/pericarditis has been reported in association with the vaccines BNT162b2 and mRNA-1273. Current evidence suggests a likely causal association between myocarditis and these vaccines. A recent study of passive vaccine safety surveillance data in Canada documented higher rates of myocarditis/pericarditis when mRNA-1273 was administered as a heterologous second dose (after BNT162b2) than as a homologous second dose (after mRNA-1273) *(18)*. This discrepancy was not apparent if the second dose was given >30 days after the first dose. WHO will review additional data on the risk of myocarditis/pericarditis following mixed mRNA vaccine schedules as they become available.

No other major safety concerns have been identified for the use of heterologous schedules, although data are currently insufficient to determine whether rare adverse are altered by heterologous versus homologous usage across different WHO EUL COVID-19 vaccine combinations. Product-specific safety profiles based on homologous usage of each WHO EUL COVID-19 vaccine in the target age group are likely to apply to their use within heterologous schedules (as detailed in the product-specific recommendations), although side effects may be modestly different in the context of heterologous usage.

Recommendations (good practice statement)

Homologous schedules are considered standard practice based on substantial safety, immunogenicity, and efficacy data available for each WHO EUL COVID-19 vaccine. However, WHO supports a flexible approach to homologous versus heterologous vaccination schedules, and considers two heterologous doses of any EUL COVID-19 vaccine to be a complete primary series.[4,5] Heterologous vaccination should only be implemented with careful consideration of current vaccine supply, vaccine supply projections, and other access considerations, alongside the potential benefits and risks of the specific products being used.

Rapidly achieving high vaccination coverage with a primary vaccine series in priority-use groups, as defined in the WHO Prioritization Roadmap *(21)*, should continue to be the focus while vaccine supply remains constrained. Either homologous or heterologous schedules should be utilized to achieve high coverage according to the Roadmap in as timely a manner as possible. This process should not be delayed over considerations regarding the potential benefits of heterologous schedules.

For countries considering heterologous schedules, WHO makes the following recommendations on the basis of equivalent or favourable immunogenicity or effectiveness for heterologous versus homologous schedules:

- Depending on product availability, countries implementing WHO EUL inactivated vaccines for initial doses may consider using WHO EUL vectored or mRNA vaccines for subsequent doses.
- Depending on product availability, countries implementing WHO EUL vectored vaccines for initial doses may consider using WHO EUL mRNA vaccines for subsequent doses.
- Depending on product availability, countries implementing WHO EUL mRNA vaccines for initial doses may consider using WHO EUL vectored vaccines for subsequent doses.

Recommendations as to the relative risks and benefits of homologous versus heterologous primary and booster doses will be reviewed as additional data become available.

WHO emphasizes the need for key gaps in the evidence to be addressed, including:

- Effectiveness and duration of protection of heterologous versus homologous vaccine schedules for specific WHO EUL product combinations, especially for heterologous schedules involving inactivated vaccines given the relative lack of available data for these.
- Long-term safety of heterologous schedules for specific WHO EUL product combinations, including surveillance for rare adverse events.
- Influence of the order of products and platforms on the safety, immunogenicity, and effectiveness of heterologous vaccination.
- Effectiveness of heterologous vaccination in relation to the time interval between (i) the first and second dose and (ii) the primary series and booster dose.
- Correlates of initial protection or duration of protection for homologous and heterologous schedules.
- Safety, immunogenicity, and effectiveness of fractional doses in the context of heterologous vaccination.
- Relative immunogenicity and effectiveness of heterologous versus homologous vaccine schedules against variants of concern, including the Omicron variant.

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[4] Ad26.COV2.S can be given as a one-dose or two-dose primary series, as defined in the product-specific recommendations *(19)*. Accordingly, a complete primary series may comprise one dose of Ad26.COV2.S, two doses of Ad26.COV2.S, or a heterologous series comprising one dose of Ad26.COV2.S and one dose of another WHO EUL COVID-19 vaccine.

[5] In moderately and severely immunocompromised individuals, WHO recommends an extended primary series including an additional dose *(20)*.

Annex 1. Search strategy for rapid review of COVID-19 vaccine response following heterologous primary or boosting schedules

A search in MEDLINE was performed to identify articles published between 1 July 2020 and 19 November 2021 using the search terms listed below.

Row	Term	Purpose
1	Coronavirus/ or Coronaviridae/ or SARS-CoV-2/ or coronaviridae infections/ or coronavirus infections/ or covid-19/	Controlled MEDLINE vocabulary terms for COVID-19
2	("covid*" or "COVID-19*" or COVID19* or "COVID-2019*" or "COVID2019*" or "SARS-CoV-2*" or "SARSCoV-2*" or "SARSCoV2*" or "SARS-CoV2*" or "SARSCov19*" or "SARS-Cov19*" or "SARSCov-19*" or "SARS-Cov-19*" or "SARSCov2019*" or "SARS-Cov2019*" or "SARSCov-2019*" or "SARS-Cov-2019*" or SARS2* or "SARS-2*" or "SARScoronavirus2*" or "SARS-coronavirus-2*" or "SARScoronavirus 2*" or "SARS coronavirus2*" or "SARScoronovirus2*" or "SARS-coronovirus-2*" or "SARScoronovirus 2*" or "SARS coronovirus2*" or (coronavirus* or coronovirus* or coronavirinae* or CoV) or ((corona* or corono*) adj1 (virus* or viral* or virinae*))).mp.	Free text terms for COVID-19 (adapted from *(22)*)
3	1 or 2	Combine articles identified by rows 1 or 2
4	Vaccines/ or COVID-19 Vaccines/ or immunization/ or immunization schedule/ or vaccination/	Controlled vocabulary terms for vaccine
5	(vaccin* or immunis* or immuniz*).mp.	Free text terms for vaccine
6	4 or 5	Combine articles identified by rows 4 or 5
7	(heterologous or prim* or boost* or mix*).mp.	Free text terms for heterologous schedules
8	3 and 6 and 7	Select articles identified by rows 3, 6, and 7
9	Limit 8 to dt="20200701-20211119"	Limit to studies uploaded from 1 July 2020

Duplicates were removed, and titles and abstracts were screened to identify articles reporting on safety, immunogenicity, and/or VE of heterologous vaccine schedules involving a combination of WHO EUL COVID-19 vaccines from different platforms. This included studies of heterologous primary schedules and heterologous booster doses.

Preprints in *medRxiv* were identified using the search strategy given below, implemented on 22 November 2021 with the package *medrxivr* using the programming language R.

Row	Term	Purpose
1	("coronavirus" or "COVID-19" or "SARS-CoV-2")	Free text terms for COVID-19
2	("vaccine" or "vaccines")	Free text terms for vaccine
3	("heterologous" or "mixed" or "mix" or "boost" or "booster" or "boosters")	Free text terms for heterologous schedules
4	1 and 2 and 3	Select articles identified by rows 1, 2, and 3

The search was extended by scanning the reference lists of included articles and by consulting experts in the field. Studies published after the formal searches described above were included, up to a final cut-off of 6 December 2021. Articles reporting heterologous vaccine outcomes for fewer than 10 individuals (excluding immunocompromised persons) were excluded. Data were extracted on study location, design, size, vaccine schedules, and dosing interval. For studies of VE, we extracted data on: start and end dates; duration of follow-up (average and range); variant profile; and adjusted VE estimates, stratified by vaccine schedule and outcome (infection, symptomatic disease, hospitalization, and/or intensive care unit admission). For studies reporting on antibody response, we extracted data on: timing of sample collection after the final dose; binding antibody assay endpoint (target and assay); neutralizing antibody assay endpoint (measurement and target); and average binding and neutralizing antibody levels, stratified by vaccine schedule.

Annex 2. Evidence of COVID-19 vaccine effectiveness for schedules involving heterologous platforms

The table below includes studies reporting estimates of VE following heterologous vaccine series involving a combination of WHO EUL COVID-19 vaccine. VE estimates for RNA vaccines (i.e. BNT162b2 and mRNA-1273) were combined where possible. Vaccination groups without a relevant heterologous comparator (e.g. those involving a single dose) were excluded.

Study	Country	Group	Design	Start date	End date	Follow-up interval in days, median (range)	Major variant (% cases) [notes]	Outcome	Schedule (interval before last dose in weeks)a	Event rate, n/N (%) or n/person-years (incidence rate) if marked by *	VE (95% CI)
Gram et al. (23)[b]	Denmark	Primary	Cohort	9 Feb 2021	23 Jun 2021	133 (1–135)	Alpha (n.r.)	Infection	AZ-RNA (12)	29/7775 (0.004)*	88 (83–92)
Skowronski et al. (4)[c]	Canada	Primary	Test-negative case–control	30 May 2021	2 Oct 2021	76 (2–231)	Delta (91)	Hospitalization	AZ-RNA (≥3)	2/14 084 (0.01)	99 (98–100)
									AZ-AZ (≥3)	17/8077 (0.2)	94 (90–96)
									RNA-RNA (≥3)	178/230 188 (0.1)	98 (97–98)
						68 (0–250)		Infection	AZ-RNA (≥3)	404/14 084 (2.9)	90 (89–91)
									AZ-AZ (≥3)	645/8077 (8.0)	71 (69–74)
									RNA-RNA (≥3)	6595/230 188 (2.9)	90 (90–91)
Nordstrom et al. (24)[d]	Sweden	Primary	Cohort	19 Dec 2020	20 Feb 2021	76 (1–183)	Delta (n.r.)	Symptomatic	AZ-BNT (n.r.)	170/94 569 (0.2)	67 (59–73)
									AZ-MOD (n.r.)	17/16 402 (0.1)	79 (62–88)
									AZ-AZ (n.r.)	446/430 100 (0.1)	50 (41–58)
									BNT-BNT (n.r.)	5113/2 065 831 (0.2)	78 (78–79)
									MOD-MOD (n.r.)	312/248 234 (0.1)	87 (84–88)
Starrfelt et al. (25)[e]	Norway	Primary	Cohort	1 Jan 2021	27 Sep 2021	269 (n.r.)	n.r. [follow-up spans Alpha- and Delta-dominated periods]	Infection	AZ-RNA (n.r.)	702/132 630 (0.5)	61 (58–64)
									AZ-AZ (n.r.)	14/1438 (1.0)	43 (4–67)
									BNT-BNT (n.r.)	5548/2 494 177 (0.2)	70 (69–71)
									MOD-MOD (n.r.)	1038/420 588 (0.2)	78 (77–80)
									Mixed mRNA (n.r.)	428/625 060 (0.1)	85 (83–86)
Martínez-Baz et al. (5)[f]	Spain	Primary	Cohort of close contacts of positive cases	Apr 2021	Aug 2021	n.r.	n.r. [follow-up spans Alpha- and Delta-dominated periods]	Infection	AZ-BNT (n.r.)	7/119 (3.5)	86 (70–93)
									AZ-AZ (n.r.)	272/1539 (17.7)	54 (48–60)
									BNT-BNT (n.r.)	1070/7972 (13.4)	69 (66–72)
								Symptomatic	AZ-BNT (n.r.)	3/119 (2.5)	91 (71–97)
									AZ-AZ (n.r.)	173/1539 (11.2)	56 (48–63)
									BNT-BNT (n.r.)	645/7972 (8.1)	72 (69–75)
								Hospitalisation	AZ-BNT (n.r.)	0/119 (0.0)	100 (n.r.)
									AZ-AZ (n.r.)	2/1539 (0.1)	95 (79–99)
									BNT-BNT (n.r.)	20/7972 (0.3)	93 (88–96)

Poukka et al. (26)	Finland	Primary	Cohort of health-care workers	27 Dec 2020	26 Aug 2021	n.r. (14–180)	n.r. [follow-up spans Alpha- and Delta-dominated periods]	Infection (from 14 to 90 days after dose 2)	AZ-RNA (n.r.)	n.r.	80 (82–86)
									AZ-AZ (n.r.)	n.r.	89 (73–95)
									RNA-RNA (n.r.)	n.r.	82 (79–85)
								Infection (from 91 to 180 days after dose 2)	AZ-RNA (n.r.)	n.r.	62 (30–79)
									AZ-AZ (n.r.)	n.r.	63 (-166–95)
									RNA-RNA (n.r.)	n.r.	62 (55–68)
Pozzetto et al. (27)	France	Primary	Cohort of health-care workers	Jan 2021	8 May 2021	n.r.	n.r.	Infection	AZ-BNT (12)	10/2512 (0.4)	n. r.
									BNT-BNT (4)	81/10 609 (0.8)	n. r.
Prieto-Alhambra et al. (28)[g]	Spain	Primary	Cohort	1 Jun 2021	13 Oct 2021	n.r.	Delta (n.r.)	Infection	AZ-RNA (n.r.)	238/14 325 (1.7)	n. r.
									AZ-AZ (n.r.)	389/14 325 (2.7)	n. r.
Andrews et al. (29)[h]	England	Boost	Test-negative case–control	13 Sep 2021	29 Oct 2021	n.r.	n.r. [follow-up spans Delta-dominated period]	Symptomatic	AZ-AZ-BNT (≥24)	138/1266 (0.11)	93 (92–94)
									BNT-BNT-BNT (≥24)	518/5905 (0.09)	94 (93–95)
Preliminary data (30)	Bahrain	Boost	n.r.	1 May 2021	11 Sep 2021	n.r.	n.r.	Symptomatic	SP-SP-BNT (n.r.)	175/265 296 (0.07)	n.r.
									SP-SP-SP (n.r.)	64/29 054 (0.22)	n.r.
Araos et al. (3)[i]	Chile	Primary	Cohort	n.r.	n.r.	n.r.	n.r.	Infection	AZ-BNT (n.r.)	227/31 491 (0.007)*	80 (77–82)
									AZ-AZ (n.r.)	200/16 752 (0.012)*	68 (63–72)
									BNT-BNT (n.r.)	8651/625 499 (0.014)*	82 (81–82)
								Symptomatic	AZ-BNT (n.r.)	144/32 168 (0.004)*	83 (80–86)
									AZ-AZ (n.r.)	133/17 101 (0.008)*	73 (68–77)
									BNT-BNT (n.r.)	5628/633 358 (0.009)*	85 (85–86)
								Hospitalisation	AZ-BNT (n.r.)	1/33 847 (0.00003)*	99 (93–100)
									AZ-AZ (n.r.)	18/17 928 (0.001)*	88 (82–91)
									BNT-BNT (n.r.)	337/655 399 (0.001)*	95 (94–195)
								ICU admission	AZ-BNT (n.r.)	1/33 910 (0.00003)*	96 (78–99)
									AZ-AZ (n.r.)	3/18 051 (0.0002)*	95 (84–98)
									BNT-BNT (n.r.)	82/656 614 (0.0001)*	96 (95–97)
		Boost						Infection	SV-SV-AZ (n.r.)	428/153 954 (0.003)*	90 (89–91)
									SV-SV-BNT (n.r.)	82/33 025 (0.002)*	93 (91–94)
									SV-SV-SV (n.r.)	123/13 490 (0.009)*	68 (61–73)

									Symptomatic	SV-SV-AZ (n.r.)	249/155 226 (0.002)*	93 (92–94)
										SV-SV-BNT (n.r.)	51/33 393 (0.002)*	95 (93–96)
										SV-SV-SV (n.r.)	97/13 611 (0.007)*	71 (64–76)
									Hospitalization	SV-SV-AZ (n.r.)	53/158 216 (0.0003)*	96 (95–97)
										SV-SV-BNT (n.r.)	24/34 383 (0.001)*	89 (84–93)
										SV-SV-SV (n.r.)	34/13 908 (0.002)*	75 (65–82)
									ICU admission	SV-SV-AZ (n.r.)	8/158 522 (0.0001)*	98 (96–99)
										SV-SV-BNT (n.r.)	6/34 499 (0.0002)*	90 (78–95)
										SV-SV-SV (n.r.)	9/13 977 (0.001)*	79 (59–89)

AZ: AstraZeneca (ChAdOx1-S); BNT: Pfizer-BioNTech (BNT162b2); CI: confidence interval; d: days; ICU: intensive care unit; MOD: Moderna (mRNA-1273); n.r.: not recorded; RNA: mRNA vaccines (BNT162b2 or mRNA-1273); SP: Sinopharm (BIBP) SV: Sinovac (CoronaVac); VE: vaccine effectiveness.

[a] Mean/median interval rounded to nearest week, or range if average interval not specified.
[b] VE estimate were adjusted for age, sex, heritage, hospital admission, and comorbidity.
[c] Median follow-up of 58 days for controls (range 0–265). Interval between doses varied from 3 to ≥16 weeks, with >70% in the range of 7–11 weeks. Data for British Columbia are displayed. Similar findings were reported for Quebec. Over 99% of heterologous vaccine recipients received ChAdOx1-S first. VE estimates were adjusted for age, sex, epidemiological week, and region. Combined rather than vaccine-specific VE are reported for mRNA vaccines.
[d] VE estimates were adjusted for age, sex, baseline vaccination date, home-maker service, place of birth, education, and diagnoses at baseline.
[e] VE estimates were adjusted for age, sex, country of birth, and crowded living conditions.
[f] VE estimates were adjusted for age group, sex, chronic conditions, contact setting, month, and vaccination status of index case.
[g] Vaccine groups were matched by age, sex, region, and date of second dose.
[h] Population comprised adults over 50 years of age. Absolute VE relative to unvaccinated individuals is reported. Relative VE for AZ-AZ-BNT vs AZ-AZ (140+ days since second dose) was 87% (95% CI: 85–89%); relative VE for BNT-BNT-BNT vs BNT-BNT (140+ days since second dose) was 84% (95% CI: 82–86%). VE estimates were adjusted for age, sex, deprivation, ethnic group, care home residence status, region, calendar week of onset, health and social care worker status, clinical risk group, extreme clinical vulnerability, immunosuppression status, and prior positive testing.
[i] VE estimates were adjusted for age and sex, among others (full list not specified in available data).

Annex 3. Evidence on the comparative immunogenicity of COVID-19 vaccine schedules involving heterologous versus homologous platforms

Summary tables of relative binding and neutralizing antibody concentrations for heterologous versus homologous vaccine schedules involving a combination of WHO EUL COVID-19 vaccines. Data are displayed for (A) inactivated vaccines; (B) vectored vaccines; and (C) mRNA vaccines.

Comparisons were included if antibody concentrations were reported for comparable heterologous and homologous schedules. Comparisons were excluded if they involved a different number of doses overall (e.g. JNJ-MOD vs MOD-MOD-MOD). Where antibody responses were reported at multiple timepoints, samples obtained 4 weeks after vaccination (or the nearest available timepoint) were selected. RBD-specific binding antibody concentrations and wild-type-specific neutralizing antibody concentrations were prioritized where multiple endpoints were reported. Some study arms are included in multiple comparisons (e.g. one homologous group used as a reference for multiple heterologous schedules).

(A) WHO EUL inactivated vaccines: heterologous vs homologous schedules

Study	Country	Group	Design	Heterologous schedule (interval before last dose in weeks)[a]	Homologous schedule (interval before last dose in weeks)[a]	Time of sampling after last dose (weeks)[a]	Ig endpoint (assay)	GMC (95% CI) or median concentration (IQR) (marked as *) [N]		Ig ratio	NAb endpoint (target)	GMC (95% CI) or median concentration (IQR) (marked as *) [N]		NAb ratio
								Heterologous	Homologous			Heterologous	Homologous	
Kant et al. (31)	India	Primary	OBS	AZ-BH (6)	BH-BH (4)	≥2	RBD-IgG (n.r.)	1866 (1003–3472) [18]	710 (461–1092) [40]	2.6	PRNT50 (B.1)	539.4 (263.9–1103) [18]	156.6 (105.2–233.1) [40]	3.4
Mahasirimo-ngkol et al. (32)	Thailand	Primary	OBS	SV-AZ (3.5)	SV-SV (3.5)	4	RBD-IgG (Abbott)	639 (63–726) [137]	108.2 (77–152) [32]	5.9	n.r.	n.r.	n.r.	n.r.
Wanlapakorn et al. (i) (6)	Thailand	Primary	OBS	SV-AZ (4)	SV-SV (4)	4–5	RBD-Ig (Roche)	573.4 (417.2–788.0) [44]	99.4 (77.5–127.3) [90]	5.8	% inhibition (sVNT pseudo-virus)	95.0*§ (86.8–97.8) [44]	48.8*§ (28.9–68.8) [90]	–
Wanlapakorn et al. (ii) (6)	Thailand	Primary	OBS	AZ-SV (10)	SV-SV (4)	4	RBD-Ig (Roche)	375.8 (304.9–463.3) [46]	99.4 (77.5–127.3) [90]	3.8	% inhibition (sVNT pseudo-virus)	50.0*§ (30.3–69.0) [40]	48.8*§ (28.9–68.8) [90]	–
Yorsaeng et al. (33)	Thailand	Primary	OBS	SV-AZ (4)	SV-SV (3)	4	S-Ig (Roche)	797.2 (598.7–1062) [54]	96.4 (76.1–122.1) [80]	8.3	n.r.	n.r.	n.r.	n.r.
Angkasek-winai et al. (i) (10)[b]	Thailand	Boost	OBS	SV-SV-AZ (8–12)	SV-SV-SP (8–12)	2	S-IgG (Abbott)	1358 (1142–5910) [65]	154.6 (92.1–259.5) [14]	8.8	PRNT50 (Delta)	271.2 (222.5–330.5) [65]	61.3 (35.1–107.0) [14]	4.4
Wanlapakorn et al. (iii) (34)	Thailand	Primary	OBS	SV-BNT (3)	SV-SV (3)	4	RBD-Ig (Roche)	1042 (828.6–1311) [66]	97.9 (82.6–116.1) [170]	10.6	% inhibition (sVNT pseudo-virus)	95.5*§ (93.0–96.6) [66]	66.6*§ (48.9–79.4) [170]	–
Angkasek-winai et al. (ii) (10)[b]	Thailand	Boost	OBS	SV-SV-BNT (8–12)	SV-SV-SP (8–12)	2	S-IgG (Abbott)	5152 (1142–1615) [50]	154.6 (92.1–259.5) [14]	33.3	PRNT50 (Delta)	411.1 (311.7–542.2) [30]	61.3 (35.1–107.0) [14]	6.7
Keskin et al. (35)	Turkey	Boost	OBS	SV-SV-BNT (24)	SV-SV-SV (24)	4	S-IgG (Abbott)	25 538 (18 502)* [27]	947.3 (1405.3)* [18]	27.0	n.r.	n.r.	n.r.	n.r.

| Pun Mok et al. (36) | China | Boost | CT | SV-SV-BNT (>4) | SV-SV-SV (>4) | 4 | RBD-Ig (in-house) | n.r. | n.r. | n.r. | % inhibition (sVNT pseudo-virus) | 96.8§ (n.r.) [40] | 57.8§ (n.r.) [40] | – |
| Preliminary data (30)c | Bahrain | Boost | CT | SP-SP-BNT (24) | SP-SP-SP (24) | 8 | S-Ig (n.r.) | 14 849 (n.r.) [153] | 1187.3 (n.r.) [152] | 12.5 | % inhibition (sVNT pseudo-virus) | 96.9§ (n.r.) [153] | 63.4§ (n.r.) [152] | – |

(B) WHO EUL vectored vaccines: heterologous vs homologous schedules

Study	Country	Group	Design	Heterologous schedule (interval before last dose in weeks)[a]	Homologous schedule (interval before last dose in weeks)[a]	Time of sampling after last dose (weeks)[a]	Ig endpoint (assay)	GMC (95% CI) or median concentration (IQR) (marked as *) [N]		Ig ratio	NAb endpoint (target)	GMC (95% CI) or median concentration (IQR) (marked as *) [N]		NAb ratio
								Heterologous	Homologous			Heterologous	Homologous	
Kant et al. (31)	India	Primary	OBS	AZ-BH (6)	AZ-AZ (6)	≥2	RBD-IgG (n.r.)	1866 (1003–3472) [18]	2260 (1881–2716) [40]	0.8	PRNT50 (B.1)	539.4 (263.9–1103) [18]	162 (76.74–342) [40]	3.3
Mahasirimongkol et al. (32)	Thailand	Primary	OBS	SV-AZ (3.5)	AZ-AZ (8–12)	4	RBD-IgG (Abbott)	639 (63–726) [137]	211.1 (162–249) [47]	3.0	n.r.	n.r.	n.r.	n.r.
Wanlapakorn et al. (i) (6)	Thailand	Primary	OBS	SV-AZ (3.5)	AZ-AZ (10)	4–5	RBD-Ig (Roche)	573.4 (417.2–788.0) [44]	933.7 (775.4–1124.0) [89]	0.6	% inhibition (sVNT pseudo-virus)	95.0*§ (86.8–97.8) [44]	77.2*§ (57.0–89.7) [90]	–
Wanlapakorn et al. (ii) (6)	Thailand	Primary	OBS	AZ-SV (10)	AZ-AZ (10)	4	S-Ig (Roche)	375.8 (304.9–463.3) [46]	933.7 (775.4–1124.0) [89]	0.4	% inhibition (sVNT pseudo-virus)	50.0*§ (30.3–69.0) [40]	77.2*§ (57.0–89.7) [90]	–
Yorsaeng et al. (33)	Thailand	Primary	OBS	SV-AZ (4)	AZ-AZ (10)	4	S-Ig (Roche)	797.2 (598.7–1062) [54]	818.1 (662.5–1010) [80]	1	n.r.	n.r.	n.r.	n.r.
Angkasekwinai et al. (i) (10)b	Thailand	Boost	OBS	AZ-AZ-SP (8–12)	AZ-AZ-AZ (8–12)	2	S-IgG (Abbott)	128.1 (93.5–175.4) [23]	246.4 (188.6–304.2) [50]	0.5	PRNT50 (Delta)	49.0 (37.6–64.1) [22]	69.1 (50.1–95.1) [30]	0.7
Atmar et al. (i) (17)d	USA	Boost	CT	JNJ-MOD (14)	JNJ-JNJ (18)	2	S-Ig (MSD)	3203.1 (2499.5–4104.9) [53]	326.0 (235.8–450.7) [50]	9.8	IU50/ml (D614G pseudo-virus)	676.1 (517.5–883.3) [53]	31.4 (22.3–44.3) [50]	21.5
Atmar et al. (ii) (17)d	USA	Boost	CT	JNJ-BNT (20)	JNJ-JNJ (18)	2	S-Ig (MSD)	2549.5 (2038.1–3189.3) [53]	326.0 (235.8–450.7) [50]	7.8	IU50/ml (D614G pseudo-virus)	341.3 (239.6–486.3) [53]	31.4 (22.3–44.3) [50]	10.9
Barros-Martins et al. (37)	Germany	Primary	OBS	AZ-BNT (10)	AZ-AZ (10)	2	RBD-IgG (Euro-immun)	625.7 (n.r.) [55]	160.9 (n.r.) [32]	3.9	Reciprocal titre (sVNT pseudo-virus)	4432*† (n.r.) [54]	529*† (n.r.) [31]	8.4

Study	Country	Phase	Type	Heterologous	Homologous	Interval	Assay	Het. value	Hom. value	Ratio	Neut. assay	Het. neut.	Hom. neut.	Ratio
Benning et al. (14)	Germany	Primary	OBS	AZ-BNT (12)	AZ-AZ (12)	3	S1-IgG (Siemens)	116.2* (61.8–170) [35]	13.1* (7.0–29.0) [17]	8.9	% inhibition (sVNT pseudo-virus)	96.8*§ (96.7–96.9) [35]	93.5*§ (88.6–96.7) [17]	n.r.
Brehm et al. (38)	Germany	Primary	OBS	AZ-RNA (12)	AZ-AZ (12)	1	RBD-Ig (Roche)	9450* (n.r.) [106]	1069* (n.r.) [25]	8.8	n.r.	n.r.	n.r.	n.r.
Dimeglio et al. (39)d	France	Primary	OBS	AZ-BNT (12)	AZ-AZ (12)	4	n.r.	n.r.	n.r.	n.r.	n.r. (n.r.)	255*† (n.r.) [22]	50*† (n.r.) [22]	5.1
Havervall et al. (40)	Sweden	Primary	OBS	AZ-BNT (13)	AZ-AZ (12)	2–3	n.r.	n.r.	n.r.	n.r.	AU/ml (WT)	35*† (n.r.) [116]	25*† (n.r.) [82]	1.4
Hillus et al. (13)	Germany	Primary	OBS	AZ-BNT (10)	AZ-AZ (12)	3	RBD-IgG S/Co (SeraSpot)	5.6*§ (5.1–6.1) [104]	4.9*§ (4.3–5.6) [38]	–	% inhibition (sVNT pseudo-virus)	97.1*§ (96.9–97.3) [94]	92.4*§ (86.4–96.4) [36]	–
Liu et al. (i) (7)	United Kingdom	Primary	CT	AZ-BNT (4)	AZ-AZ (4)	4	S-IgG (Nexelis)	12 906 (11 404–14 604) [104]	1392 (1188–1630) [104]	9.3	NT50 (pseudo-virus)	515 (430–617) [101]	61 (50–73) [101]	8.4
Liu et al. (ii) (7)	United Kingdom	Primary	CT	BNT-AZ (4)	AZ-AZ (4)	4	S-IgG (Nexelis)	7133 (6415–7932) [109]	1392 (1188–1630) [104]	5.1	NT50 (pseudo-virus)	383 (317–463) [104]	61 (50–73) [101]	6.3
Normark et al. (41)	Sweden	Primary	OBS	AZ-MOD (11)	AZ-AZ (11)	4	S-Ig (n.r.)	104 083 (n.r.) [51]	7381 (n.r.) [37]	14.1	In-house Vero NT (Alpha)	1259† (n.r.) [20]	88† (n.r.) [34]	14.3
Sablerolles et al. (i) (42)	Netherlands	Primary	CT	JNJ-MOD (12)	JNJ-JNJ (12)	4	S-IgG (Liaison)	4180*† (n.r.) [122]	470*† (n.r.) [106]	8.9	PRNT50 (D614G)	1450*† (n.r.) [54]	326*† (n.r.) [50]	4.4
Sablerolles et al. (ii) (42)	Netherlands	Primary	CT	JNJ-BNT (12)	JNJ-JNJ (12)	4	S-IgG (Liaison)	2625*† (n.r.) [111]	470*† (n.r.) [106]	5.6	PRNT50 (D614G)	1450*† (n.r.) [53]	326*† (n.r.) [106]	4.4
Schmidt et al. (43)	Sweden	Primary	OBS	AZ-RNA (11)	AZ-AZ (11)	2	RBD-IgG (Euro-immun)	3630* (3721) [96]	404* (510) [55]	9	% inhibition (sVNT pseudo-virus)	100*†§ (100–100) [96]	84*†§ (61–96) [55]	–
Tenbusch et al. (44)	Germany	Primary	OBS	AZ-BNT (9)	AZ-AZ (9)	2	n.r.	n.r.	n.r.	n.r.	AU/ml (sVNT pseudo-virus)	3377* (n.r.) [482]	106* (n.r.) [66]	31.9
Thurm et al. (45)	Germany	Primary	OBS	AZ-RNA (11)	AZ-AZ (11)	4	S1-IgG (Thermo-Fisher)	1640 (1227–2053) [42]	154.4 (103.5–205.4) [38]	10.6	% inhibition (WT)	99.1§ (98.7–99.6) [42]	72.0§ (64.7–79.4) [38]	–
Angkasek-winai et al. (ii) (10)b	Thailand	Boost	OBS	AZ-AZ-BNT (8–12)	AZ-AZ-AZ (8–12)	2	S-IgG (Abbott)	2364 (2006–2786) [50]	246.4 (188.6–304.2) [50]	9.6	PRNT50 (Delta)	470.1 (395.5–558.9) [30]	69.1 (50.1–95.1) [30]	6.8
Munro et al (i) (9)f	UK	Boost	CT	AZ-AZ-BNT (11)	AZ-AZ-AZ (11)	4	S-IgG (Nexelis)	20 517 (17 718–23 757)	2457 (2058–2933) [99]	8.4	NT50 (WT	1621 (1314–1998) [93]	193 (161–231) [98]	8.4

Study	Country	Group	Design	Heterologous schedule (interval before last dose in weeks)[a]	Homologous schedule (interval before last dose in weeks)[a]	Time of sampling after last dose (weeks)[a]	Ig endpoint (assay)	GMC (95% CI) or median concentration (IQR) (marked as *) [N] Heterologous	Homologous	Ig ratio	NAb endpoint (target)	GMC (95% CI) or median concentration (IQR) (marked as *) [N] Heterologous	Homologous	NAb ratio
									[93]		pseudo-virus)			
Munro et al (ii) (9)[f]	UK	Boost	CT	AZ-AZ-MOD (11)	AZ-AZ-AZ (11)	4	S-IgG (Nexelis)	31 111 (26 363–36 714) [97]	2457 (2058–2933) [99]	12.7	NT50 (WT pseudo-virus)	2368 (2054–2730) [97]	193 (161–231) [98]	12.3

(C) WHO EUL RNA vaccines: heterologous vs homologous schedules

Study	Country	Group	Design	Heterologous schedule (interval before last dose in weeks)[a]	Homologous schedule (interval before last dose in weeks)[a]	Time of sampling after last dose (weeks)[a]	Ig endpoint (assay)	GMC (95% CI) or median concentration (IQR) (marked as *) [N]		Ig ratio	NAb endpoint (target)	GMC (95% CI) or median concentration (IQR) (marked as *) [N]		NAb ratio
								Heterologous	Homologous			Heterologous	Homologous	
Wanlapakorn et al. (34)	Thailand	Primary	OBS	SV-BNT (3)	BNT-BNT (3)	4–5	RBD-Ig (Roche)	1042 (828.6–1311) [66]	1963 (1378–2798) [19]	0.5	% inhibition (sVNT pseudo-virus)	95.5*§ (93.0–96.6) [66]	97.4*§ (96.3–97.7) [19]	–
Barros-Martins et al. (37)	Germany	Primary	OBS	AZ-BNT (10)	BNT-BNT (3)	2–4	RBD-IgG (Euro-immun)	625.7 (n.r.) [55]	574.1 (n.r.) [46]	1.1	Reciprocal titre (sVNT pseudo-virus)	4432*† (n.r.) [54]	6568*† (n.r.) [30]	0.7
Benning et al. (14)	Germany	Primary	OBS	AZ-BNT (12)	BNT-BNT (3)	3	S1-IgG (Siemens)	116.2* (61.8–170) [35]	145.5* (100.0–291.1) [82]	0.8	% inhibition (sVNT pseudo-virus)	96.8*§ (96.7–96.9) [35]	97.0*§ (96.1–98.0) [82]	–
Brehm et al. (38)	Germany	Primary	OBS	AZ-RNA (12)	RNA-RNA (6)	1–15	RBD-Ig (Roche)	9450* (n.r.) [106]	1388* (n.r.) [261]	6.8	n.r.	n.r.	n.r.	n.r.
Dimeglio et al. (39)[e]	France	Primary	OBS	AZ-BNT (12)	BNT-BNT (4)	4	n.r.	n.r.	n.r.	n.r.	n.r.	255*† (n.r.) [22]	168*† (n.r.) [22]	1.5
Glockner et al. (46)	Germany	Primary	OBS	AZ-RNA (12)	RNA-RNA (3)	4–5	S-IgG (Liaison)	1640 (1227–2053) [42]	1714 (1404–2025) [41]	1.0	n.r.	n.r.	n.r.	n.r.
Groß et al. (47)	Germany	Primary	OBS	AZ-BNT (8)	BNT-BNT (n.r.)	2	S-Ig (Roche)	8815* (n.r.) [26]	1086* (n.r.) [15]	8.1	NT50 (Alpha pseudo-virus)	2744* (n.r.) [25]	709* (n.r.) [14]	3.9
Havervall et al. (40)	Sweden	Primary	OBS	AZ-BNT (13)	BNT-BNT (3)	2–8	n.r.	n.r.	n.r.	n.r.	AU/ml (WT)	35*† (n.r.) [116]	30*† (n.r.) [101]	1.2
Hillus et al. (13)	Germany	Primary	OBS	AZ-BNT (10)	BNT-BNT (3)	3–4	RBD-IgG S/Co (SeraSpot)	5.6*§ (5.1–6.1) [104]	5.4*§ (4.8–5.9) [174]	–	% inhibition (sVNT pseudo-virus)	97.1*§ (96.9–97.3) [94]	96.6*§ (95.5–97.2) [101]	–
Liu et al. (i) (7)	United Kingdom	Primary	CT	AZ-BNT (4)	BNT-BNT (4)	4	S-IgG (Nexelis)	12 906 (11 404–14 604)	14 080 (12 491–15 871)	0.9	NT50 (pseudo-virus)	515 (430–617) [101]	574 (475–694) [102]	0.9

Study	Country								[104]	[109]					
Liu et al. (ii) (7)	United Kingdom	Primary	CT	BNT-AZ (4)	BNT-BNT (4)	4	S-IgG (Nexelis)	7133 (6415–7932) [109]	14 080 (12 491–15 871) [109]	0.5	NT50 (pseudo-virus)	383 (317–463) [104]	574 (475–694) [102]	0.7
Pozzetto et al. (27)	France	Primary	OBS	AZ-RNA (12)	BNT-BNT (4)	4	RBD-IgG (Liaison	1068*† (814–1682) [31]	944*† (608–1394) [29]	1.0	% inhibition (sVNT pseudo-virus)	99*§ (89–100) [31]	62*§ (34–93) [29]	–
Schmidt et al. (43)	Sweden	Primary	OBS	AZ-RNA (11)	RNA-RNA (5)	2	RBD-IgG (Euro-immun)	3630* (3721) [96]	4932 (4239) [62]	0.7	% inhibition (sVNT pseudo-virus)	100*†§ (100–100) [96]	100*†§ (100–100) [62]	–
Tenbusch et al. (44)	Germany	Primary	OBS	AZ-BNT (9)	BNT-BNT (3)	2	n.r.	n.r.	n.r.	n.r.	AU/ml (sVNT pseudo-virus)	3377* (n.r.) [482]	1789* (n.r.) [537]	1.9
Thurm et al. (45)	Germany	Primary	OBS	AZ-RNA (11)	RNA-RNA (5)	4	S1-IgG (Thermo-Fisher)	2411 (1689–3441) [21]	1755 (1219–2527) [22]	1.4	% inhibition (WT)	99.1*§ (98.7–99.6) [42]	99.0*§ (98.3–99.6) [38]	–
Vallée et al. (48)	France	Primary	OBS	AZ-BNT (12)	BNT-BNT (4)	5–6	S-IgG (Abbott)	7268.6 (6501.3–8128.3) [130]	10 734.9 (9141.1–12 589.3) [67]	0.7	n.r.	n.r.	n.r.	n.r.
Atmar et al. (i) (17)d	USA	Boost	CT	MOD-MOD-JNJ (19)	MOD-MOD-MOD (16)	2	S-Ig (MSD)	3029.4 (2433.2–3771.7) [49]	6799.8 (5771.8–8010.9) [51]	0.4	IU50/ml (D614G pseudo-virus)	382.1 (290.5–502.5) [49]	901.8 (727.5–1117.8) [51]	0.4
Atmar et al. (ii) (17)d	USA	Boost	CT	BNT-BNT-JNJ (21)	BNT-BNT-BNT (24)	2	S-Ig (MSD)	1904.7 (1497.8–2422.2) [51]	3409.1 (2760.7–4209.8) [50]	0.3	IU50/ml (D614G pseudo-virus)	216.4 (157.8–296.9) [51]	446.7 (340.3–586.3) [50]	0.5
Munro et al (i) (9)f	UK	Boost	CT	BNT-BNT-AZ (16)	BNT-BNT-BNT (14)	4	S-IgG (Nexelis)	13 424 (11 702–15 399) [97]	27 242 (24 148–30 731) [96]	0.5	NT50 (WT pseudo-virus)	950 (802–1126) [98]	1789 (1520–2107) [95]	0.5
Munro et al (ii) (9)f	UK	Boost	CT	BNT-BNT-JNJ (15)	BNT-BNT-BNT (14)	4	S-IgG (Nexelis)	17 079 (14 488–20 133) [87]	27 242 (24 148–30 731) [96]	0.6	NT50 (WT pseudo-virus)	1441 (1188–1749) [75]	1789 (1520–2107) [95]	0.8

† approximate values extracted using Plot Digitizer software; § excluded from summary plot as metric is not a titre or concentration and is therefore not comparable to other ratios.

AU: arbitrary units; AZ: AstraZeneca (ChAdOx1-S); BH: Bharat (Covaxin); BNT: Pfizer-BioNTech (BNT162b2); CI: confidence interval; CT: clinical trial (randomized or non-randomized); EUL: Emergency Use Listing (WHO); GMC: geometric mean concentration; Ig: binding antibody; IQR: interquartile range; IU: international units; JNJ: Janssen (Ad26.COV2.S); MOD: Moderna (mRNA-1273); N: number; NAb: neutralizing antibody; NT: neutralization test; NT50: 50% neutralizing antibody titre; OBS: observational study; PRNT: plaque reduction neutralization test; RBD: receptor binding domain; RNA: mRNA vaccines (BNT162b2 or mRNA-1273); SP: Sinopharm (BIBP); SV: Sinovac (CoronaVac); sVNT: surrogate virus neutralization test; WT: wild-type.

Vaccine platform colour coding: green = inactivated; blue = mRNA; orange = vectored. The colour represents the heterologous component that differentiates the schedule from the homologous schedule being used as a reference.

[a] Average interval rounded to nearest week, or range if average interval not specified.

[b] The administration of SP to individuals who had previously received two doses of SV was considered a homologous boost for the purposes of this comparison. Separate groups received BNT doses at 30 μg (full dose) and 15 μg (fractional dose); the 30 μg recipients were included here, reflecting the formulation in the WHO EUL.

[c] Shared with SAGE on 5 October 2021.

[d] Comparisons involving different numbers of doses overall were excluded (e.g. JNJ-BNT vs BNT-BNT-BNT).

[e] Data for individuals aged >55 years (as opposed to <55 years) included given the presence of homologous RNA and homologous vectored comparators.

[f] Trial involved 18 study sites that were split into three groups, with multiple EUL and non-EUL COVID-19 vaccine products per group. Comparisons involving non-EUL vaccine products or fractional doses of EUL products were excluded. Some comparisons involved participants from separate study groups.

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WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 2 years after the date of publication.

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