To mix or not to mix? Emerging evidence on heterologous COVID-19 vaccine schedules

Word count: 831

As of February 2022, 27 different COVID-19 vaccines have been authorised by one or more regulatory authorities for limited or widespread use.[1] Of these, eight vaccines have received a WHO Emergency Use Listing (EUL).[2] Although homologous vaccination remains standard practice, heterologous schedules that use more than one product in an individual's dosing series offer several potential benefits, including enhanced programmatic flexibility and improved immunogenicity.

We performed a comprehensive review of available data on the safety, immunogenicity, and effectiveness of heterologous vaccine schedules (see appendix pp1–3 for methods). We identified 48 studies that tested a combination of WHO EUL COVID-19 vaccines from different platforms. These included 7 controlled trials and 41 observational studies. Schedules involved a combination (in any order) of vectored/mRNA vaccines (36 studies), vectored/inactivated vaccines (8 studies), and inactivated/mRNA vaccines (8 studies). No protein-based vaccines had received a WHO EUL at the time of the review. A total of 37 studies considered heterologous primary schedules (involving more than one product during a two-dose primary series), while 13 considered heterologous boosting (among individuals who have previously received a complete homologous primary series). Most studies considered humoral immune response endpoints (38 studies), with a subset reporting on safety (23 studies) and vaccine effectiveness (VE; 11 studies).

The majority of VE studies (9 of 11) reported on heterologous primary schedules involving ChAdOx1-S followed by an mRNA vaccine (appendix pp5–7). VE against infection or symptomatic disease following this heterologous regimen (estimates ranging from 61–91%) was similar to or marginally greater than that of homologous ChAdOx1-S (43–89%), and commensurate with that of two mRNA vaccine doses (69–90%). Short-term VE against hospitalisation following heterologous ChAdOx1-S/mRNA was >95% across studies in Canada, Chile, and Spain.[3-5]

Two studies reported on VE following heterologous booster (third) doses. In the UK, administration of BNT162b2 at least 6 months after a primary series of ChAdOx1-S had a VE against symptomatic disease of 93% (95% CI 92–94%).[6] This was very similar to the VE of 94% (95% CI 93–95%) observed after a homologous booster dose of BNT162b2 among individuals primed with two doses of BNT162b2. Among individuals in Chile who received a primary series of the inactivated vaccine CoronaVac, heterologous, as opposed to homologous, boosting with ChAdOx1-S or BNT162b2 was associated with an absolute increase by 11–25% in VE against infection, symptomatic disease, hospitalisation, and intensive care unit admission (appendix pp5–7).[4]

Data on the immunogenicity of heterologous schedules are available for a wider range of vaccine combinations (appendix pp8–13 and figure). These findings must be interpreted with caution given the lack of an established correlate of initial or long-term protection. Differences in dosing interval between homologous and heterologous vaccine recipients were also apparent in several of the studies included. Despite these caveats, several consistent trends are emerging. Compared with homologous inactivated vaccine schedules, heterologous schedules have consistently shown enhanced immunogenicity when inactivated vaccines are administered before or after either vectored or mRNA vaccines (figure, top row). Vectored vaccines have shown enhanced immunogenicity (relative to homologous vectored vaccine schedules) when administered before or after mRNA but not inactivated vaccines (figure, middle row). By contrast, mRNA vaccines have shown no clear evidence of enhanced immunogenicity (relative to homologous mRNA vaccine schedules) when administered before or after vectored or inactivated vaccines (figure, bottom row). Notably, several studies have demonstrated approximate equivalence of the antibody response induced by heterologous vectored/mRNA versus homologous mRNA-only schedules.[7,8]

The order of vaccine products may also be important, albeit apparently less so than the combination. The UK Com-Cov study reported somewhat higher antibody concentrations following ChAdOx1-

S/BNT162b2 than BNT162b2/ChAdOx1-S.[9] However, both heterologous groups exhibited higher antibody concentrations than individuals who received two doses of ChAdOx1-S.

A key caveat across the included studies is the limited sample size for most heterologous product combinations and the lack of extensive safety data. Where reported, heterologous schedules have typically shown higher short-term reactogenicity compared with homologous schedules,[10,11] although not all studies have observed this discrepancy.[12,13] A recent study in Canada documented higher rates of myocarditis/pericarditis when mRNA-1273 was administered as a heterologous second dose within 30 days of BNT162b2 compared with after mRNA-1273, although it remains to be seen if this difference will be confirmed by additional studies. Further monitoring for rare adverse events associated with heterologous vaccination is essential. In the interim, product-specific safety profiles can be considered by policy makers contemplating the use of heterologous schedules, albeit with the knowledge that these may be modestly altered in the context of heterologous usage.

Heterologous schedules are poised to play an increasingly important role within the global COVID-19 vaccine strategy. In part, this will be driven by pragmatism as countries contend with variable supply for different vaccine products. However, independent of access considerations, the emerging VE and immunogenicity data highlight the value of heterologous schedules, depending on the platforms involved and the order of products used. A flexible approach to heterologous schedules is warranted as we seek to make optimal use of a diverse vaccine portfolio.

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Disclosures

EPKP is a consultant for the SAGE Working Group on COVID-19 vaccines. SD, MM, KLO'B, JH, and AW-S are staff of the WHO. The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

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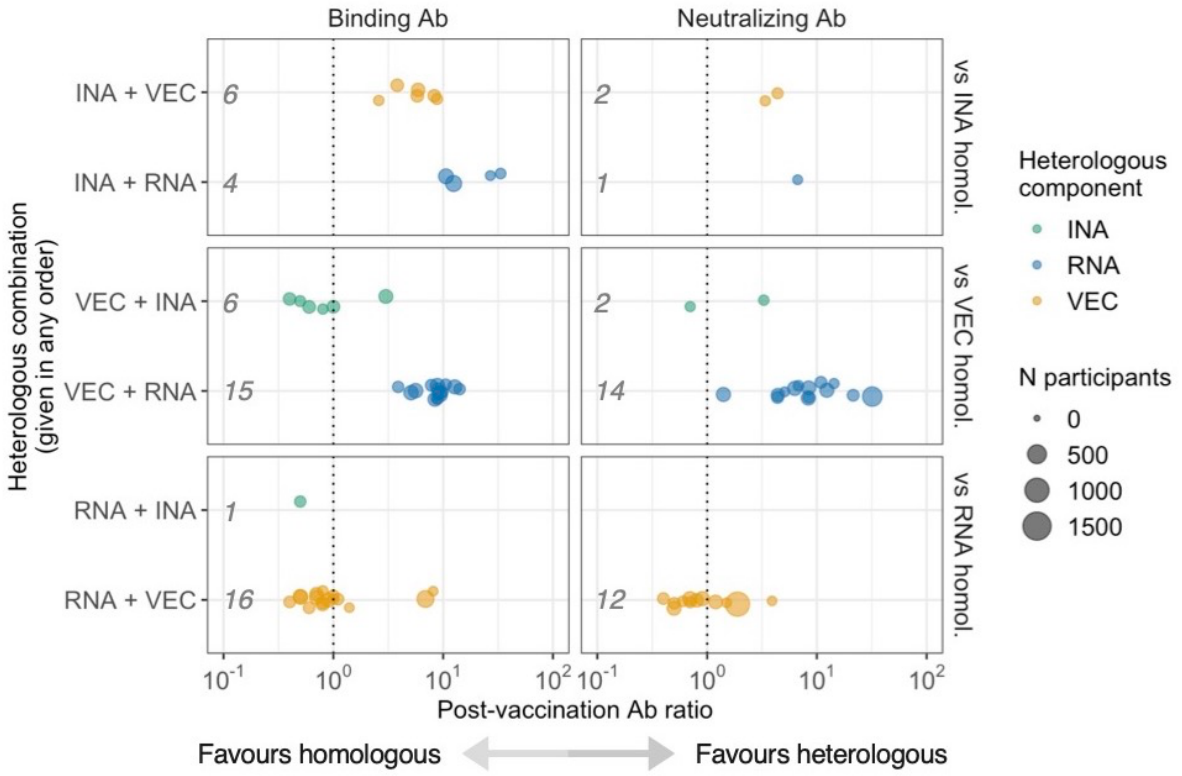
Figure legend

***Figure*: Comparative immunogenicity of COVID-19 vaccine schedules involving heterologous versus homologous platforms.** Post-vaccination antibody ratios are presented relative to homologous inactivated vaccine schedules (top row), homologous vectored vaccine schedules (middle row), and homologous mRNA vaccine schedules (bottom row). Study-specific data including citations details are provided in the appendix (p4 and pp7–13). The number of estimates available for each comparison is indicated in italics. Ab, antibody; INA, inactivated; VEC, vectored.


Binding Ab
Neutralizing Ab
Heterologous combination (given in any order)
INA + VEC
INA + RNA
VEC + INA
VEC + RNA
RNA + INA
RNA + VEC
6
4
2
1
6
15
2
14
1
16
12
vs INA homol.
vs VEC homol.
vs RNA homol.
10^{-1}
10^{0}
10^{1}
10^{2}
Post-vaccination Ab ratio
Favours homologous
Favours heterologous
Heterologous component
INA
RNA
VEC
N participants
0
500
1000
1500

147
148

Appendix

The material below is adapted with permission from the WHO's *Interim recommendations for heterologous COVID-19 vaccine schedules* (published under a CC BY-NC-SA 3.0 IGO license).[1]

Review methods

Search strategy for 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[2])
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

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.

Scope and eligibility criteria

Duplicates were removed, and titles and abstracts were screened to identify articles reporting on the safety, immunogenicity, and/or vaccine effectiveness (VE) of a heterologous COVID-19 vaccine schedule involving a combination of WHO Emergency Use Listing (EUL) COVID-19 vaccines from multiple platforms (e.g. a vectored vaccine followed by an mRNA vaccines). At the time of the search, the list of WHO EUL products included Ad26.COV2.S (Janssen), BIBP (Sinopharm), BNT162b2 (Pfizer/BioNTech), ChAdOx1-S (AstraZeneca), CoronaVac (Sinovac), Covaxin (Bharat), and mRNA-1273 (Moderna). Articles reporting heterologous vaccine outcomes for fewer than 10 individuals (excluding immunocompromised persons) were excluded. Multiple reports on the same population were combined under a single study ID during data extraction.

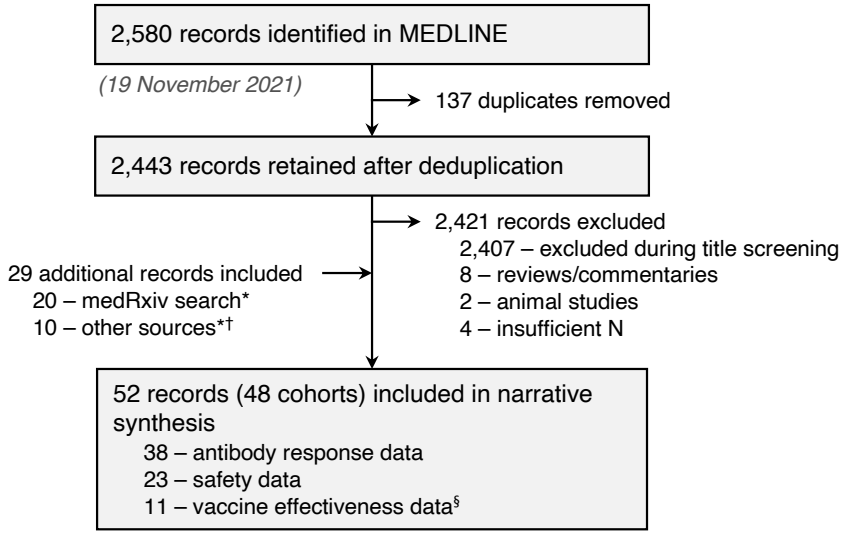
Data extraction

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, hospitalisation, 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); neutralising antibody assay endpoint (measurement and target); and average binding and neutralising antibody levels, stratified by vaccine schedule. We used Plot Digitizer[3] software to extract average (mean/median) antibody concentrations where these were not reported directly. We prioritised RBD-specific binding antibody concentrations and wild-type-specific neutralising antibody concentrations where multiple endpoints were reported. Where antibody responses were reported at multiple timepoints, samples obtained 4 weeks after vaccination (or the nearest available timepoint) were selected. Formal analysis of reactogenicity data was beyond the scope of this review, but key trends are summarised in the main text. Cellular immunity endpoints were beyond the scope of this review.

Studies were included in the quantitative synthesis of antibody response rates if they reported post-vaccination antibody response data (binding or neutralising antibody concentrations) for comparable heterologous and homologous schedules. These were used to calculate the ratio of antibody concentrations between heterologous and homologous vaccine groups, whereby a ratio of >1 indicates higher antibody levels among heterologous vaccine recipients. Given the multiplicity of vaccine products and schedules involved, we did not seek to combine these ratios into pooled estimates. Comparisons were excluded if they involved a different number of doses overall (e.g. Ad26.COV2.S– BNT162b2 vs BNT162b2–BNT162b2–BNT162b2).

Ad26.COV2.S can be given as a one-dose or two-dose primary series. For the purposes of this review, a two-dose heterologous series involving Ad26.COV2.S alongside another COVID-19 vaccine was considered a heterologous primary series.



Supplementary Figure 1. Flow diagram. *Include studies published after 19 November 2021; † identified via bibliographies and expert recommendation; § includes studies reporting on SARS-CoV-2 infection rates by vaccine group without vaccine effectiveness estimates.

Supplementary Figure 2. Comparative immunogenicity of COVID-19 vaccine schedules involving heterologous versus homologous platforms. Post-vaccination antibody ratios are presented relative to (A) homologous inactivated vaccine schedules, (B) homologous vectored vaccine schedules, and (C) homologous mRNA vaccine schedules. Citations details are provided in the appendix (pp8–13). For studies in which the number of participants differed between binding and neutralising antibody measurements, we quote the higher number here. Some study arms are included in multiple comparisons (e.g. one homologous group used as a reference for multiple heterologous schedules). Ab, antibody; AZ, AstraZeneca (ChAdOx1-S); BH, Bharat (Covaxin); CT, clinical trial; INA, inactivated; OBS, observational; SP, Sinopharm (BIBP); SV, Sinovac (CoronaVac); VEC, vectored.

Supplementary Table 1. 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.[4b]	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.[5c]	Canada	Primary	Test-negative case–control	30 May 2021	2 Oct 2021	76 (2–231)	Delta (91)	Hospitalisation	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.[6d]	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.[7e]	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.[8f]	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.[9]	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.[10]	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.[11g]	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.[12h]	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[13]	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.[14i]	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)
								Hospitalisation	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).

Supplementary Table 2. 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 prioritised 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.[15]	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
Mahasirimongkol et al.[16]	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)[17]	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)[17]	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.[18]	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.
Angkasekwinai et al. (i)[19b]	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)[20]	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]	–
Angkasekwinai et al. (ii)[19b]	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.[21]	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.[22]	China	Boost	CT	SV-SV-BNT (>4)	SV-SV-SV (>4)	4	RBD-Ig (in-house)	n.r.	n.r.	n.r.	% inhibition (sVNT	96.8§ (n.r.) [40]	57.8§ (n.r.) [40]	–

											pseudo-virus)			
Preliminary data[13c]	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.[15]	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.[16]	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)[17]	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)[17]	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.[18]	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)[19b]	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)[23d]	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)[23d]	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.[24]	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

Benning et al.[25]	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 pseuo-virus)	96.8*§ (96.7–96.9) [35]	93.5*§ (88.6–96.7) [17]	n.r.
Brehm et al.[26]	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.[27d]	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.[28]	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.[29]	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)[30]	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)[30]	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.[31]	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)[32]	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)[32]	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.[33]	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.[34]	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.[35]	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)[19b]	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)[36f]	UK	Boost	CT	AZ-AZ-BNT (11)	AZ-AZ-AZ (11)	4	S-IgG (Nexelis)	20 517 (17 718–23 757) [93]	2457 (2058–2933) [99]	8.4	NT50 (WT pseudo-virus)	1621 (1314–1998) [93]	193 (161–231) [98]	8.4
Munro et al (ii)[36f]	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.[20]	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.[24]	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.[25]	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.[26]	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.[27e]	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.[37]	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.[38]	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.[28]	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.[29]	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)[30]	United Kingdom	Primary	CT	AZ-BNT (4)	BNT-BNT (4)	4	S-IgG (Nexelis)	12 906 (11 404–14 604) [104]	14 080 (12 491–15 871) [109]	0.9	NT50 (pseudo-virus)	515 (430–617) [101]	574 (475–694) [102]	0.9
Liu et al. (ii)[30]	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.[10]	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.[33]	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.[34]	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.[35]	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.[39]	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)[23d]	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)[23d]	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)[36f]	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)[36f]	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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