Emerging data on heterologous COVID-19 vaccine schedules

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SAGE Meeting
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World Health Organization

Overview

(1) Rapid review summary

(2) VE data

(3) Immunogenicity data: illustrative examples

(4) Immunogenicity data: synthesis

(5) Safety

Rationale for considering heterologous schedules

- Individual flexibility (e.g. after heightened dose-1 reactogenicity)
- Programmatic flexibility
  - Variable supply/access
  - Potential for enhanced safety/effectiveness

Rapid review summary

Article screening

Target profile

(1) N > 10 heterologous schedule recipients

(2) Mixed COVID-19 vaccine platforms

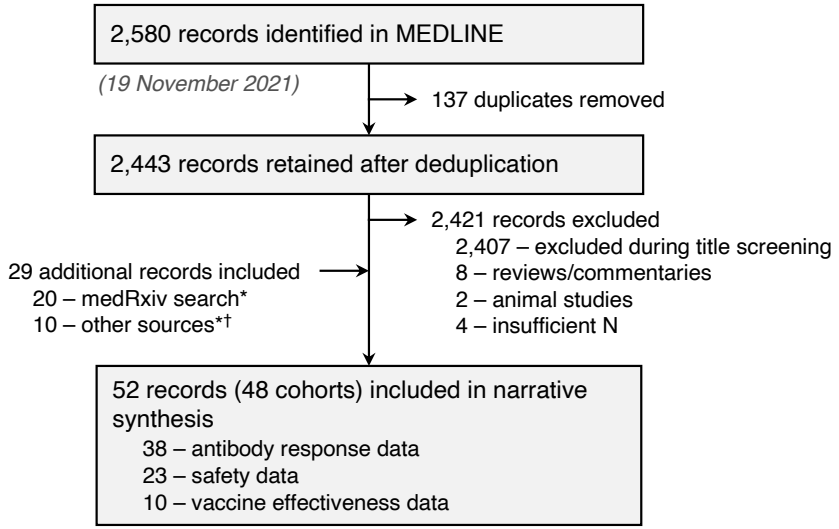
(3) WHO EUL vaccines (inc. Bharat)

(4) Primary series or booster

Exclusion criteria

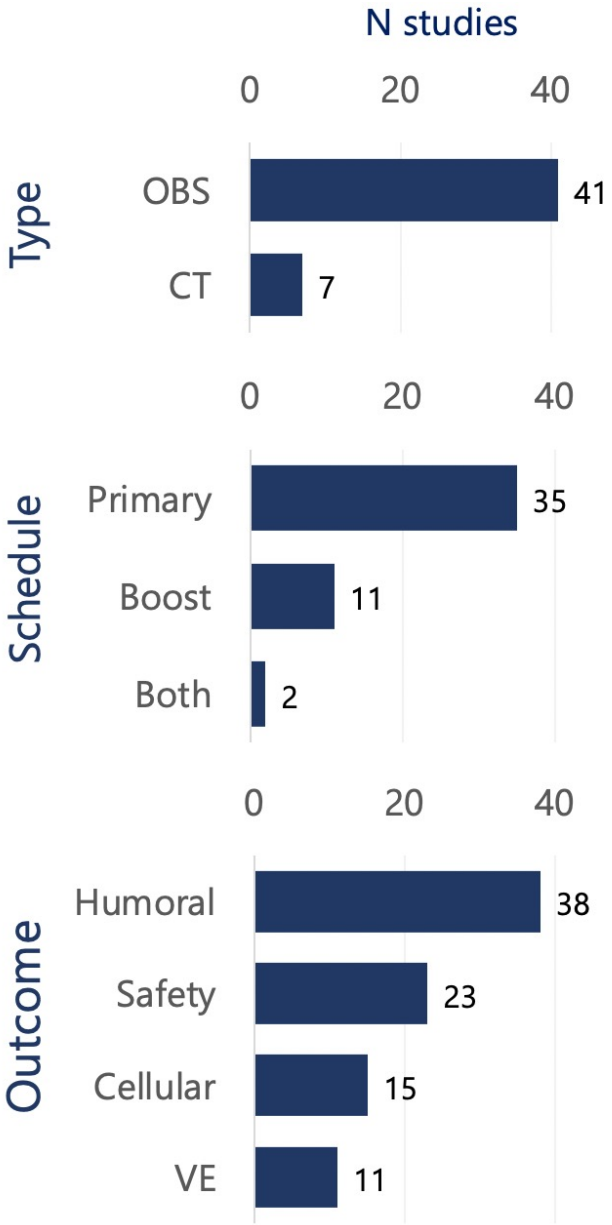
(1) Report exclusively on ICPs

(2) Report only on mixed RNA schedules

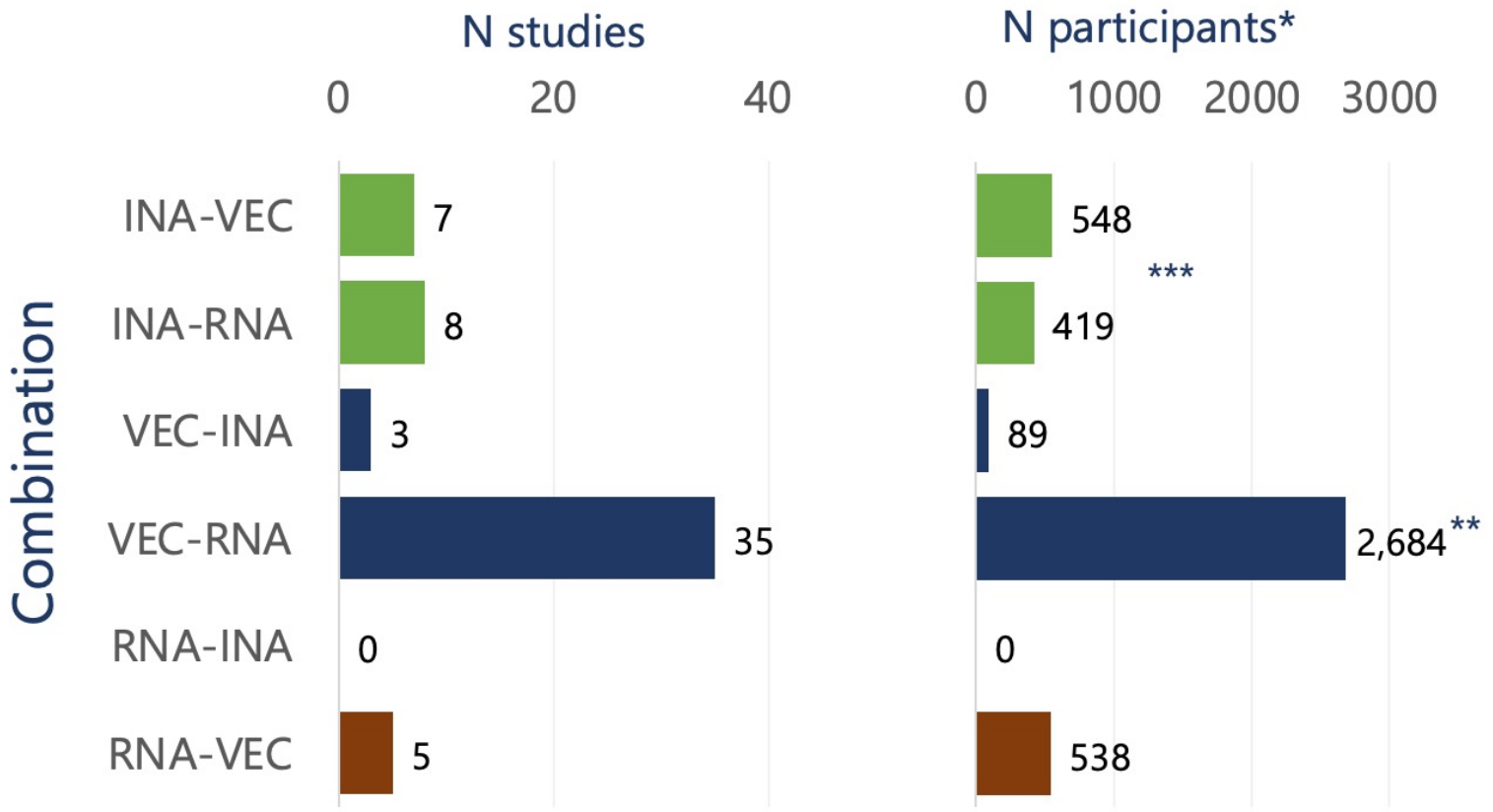


* Includes studies published after 19 November 2021

† Identified via bibliographies and expert recommendation



Rapid review summary



* N with humoral immunogenicity data receiving heterologous platforms

** >440,000 AZ/RNA recipients in VE studies

*** >2,6 million SV-AZ and SV-BNT recipients in VE studies

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VE data for heterologous priming schedules: severe disease

Study	Country	Vaccines	Interval (w)	Major variant (% cases)	Design	Outcome	Adjusted VE (95%)		
							AZ/RNA	AZ/AZ	RNA/RNA
Skowronski et al; medRxiv	Canada (BC data)*	AZ-RNA, AZ-AZ, RNA-RNA	≥3	Delta (91)	Test-negative	Hospitalisation	99 (98–100)	94 (90–96)	98 (97–98)
Martínez-Baz et al; EuroSurveillance	Spain	AZ-BNT, AZ-AZ, BNT-BNT	n.r.	n.r. (spans alpha/delta periods)	Cohort of close contacts of cases	Hospitalisation	100 (n.r.)	95 (79–99)	93 (88–96)
Preliminary data	Chile	AZ-RNA, AZ-AZ, RNA-RNA	n.r.	n.r.	Cohort	Hospitalisation	94 (94–95)	87 (79–92)	98 (89–100)
						ICU admission	97 (96–97)	95 (83–98)	96 (70–99)

* Equivalent data from Quebec.

- Short-term VE vs hospitalisation high (87–99%) for all heterologous/homologous groups

Chile data: https://cdn.who.int/media/docs/default-source/blue-print/chile_rafael-araos_who-vr-call_25oct2021.pdf?sfvrsn=7a7ca72a_7

VE data for heterologous priming schedules: infection/symptomatic disease

Study	Country	Vaccines	Interval (w)	Major variant (% cases)	Design	Outcome	Adjusted VE (95%)		
							AZ/RNA	AZ/AZ	RNA/RNA
Gram et al; medRxiv	Denmark	AZ-RNA	12	Alpha (n.r.)	Cohort	Infection	88 (83–92)	–	–
Skowronski et al; medRxiv	Canada (BC data)*	AZ-RNA, AZ-AZ, RNA-RNA	≥3	Delta (91)	Test-negative	Infection	90 (89–91)	71 (69–74)	90 (90–91)
Nordstrom et al; Lancet Reg Health Eur	Sweden	AZ-BNT, AZ-MOD, AZ-AZ, BNT-BNT, MOD-MOD	n.r.	Delta (n.r.)	Cohort	Symptomatic	67 (59–73) - BNT 79 (62-88) - MOD	50 (41–58)	78 (78–79) - BNT 87 (84–88) - MOD
Starrfelt et al; medRxiv	Norway	AZ-RNA, AZ-AZ, BNT-BNT, MOD-MOD	n.r.	n.r. (spans alpha/delta periods)	Cohort	Infection	61 (58–64)	43 (4–67)	70 (69–71) – BNT 78 (77–80) – MOD
Martínez-Baz et al; EuroSurveillance	Spain	AZ-BNT, AZ-AZ, BNT-BNT	n.r.	n.r. (spans alpha/delta periods)	Cohort of close contacts of cases	Infection	86 (70–93)	54 (48–60)	69 (66–72)
						Symptomatic	91 (71–97)	56 (48–63)	72 (69–75)
Poukka et al; medRxiv	Finland	AZ-RNA, AZ-AZ, RNA-RNA	n.r.	n.r. (spans alpha/delta periods)	HCW cohort	Infection (14–90d)	80 (82–86)	89 (73–95)	82 (79–85)
						Infection (91–180d)	62 (30–79)	63 (-166–95)	62 (55–68)
Preliminary data	Chile	AZ-RNA, AZ-AZ, RNA-RNA	n.r.	n.r.	Cohort	Infection	81 (80–81)	66 (61–71)	76 (72–79)
						Symptomatic	84 (84–85)	71 (66–76)	80 (77–83)
							61–91	43–89	62–90

* Equivalent data from Quebec.

- VE for heterologous AZ-RNA … similar to or marginally higher than AZ-AZ
  … similar to RNA-RNA

Chile data: https://cdn.who.int/media/docs/default-source/blue-print/chile_rafael-araos_who-vr-call_25oct2021.pdf?sfvrsn=7a7ca72a_7

VE data for heterologous boosting schedules: VEC-RNA

Preliminary VE data from England

Study	Country	Vaccines	Interval (w)	Major variant (% cases)	Design	Outcome	VE (95%)	
							AZ prime	BNT prime
Andrews et al; medRxiv	England	AZ-AZ-BNT, BNT-BNT-BNT	≥24	n.r. (spans delta period)	TND	Absolute VE*	93 (92–94)	94 (93–95)
						Relative VE**	87 (85–89)	84 (83–86)

* Relative to unvaccinated
** Relative to individuals who had received 2 x AZ or 2 x BNT at least 140 days before

VE data for heterologous boosting schedules: INA-RNA

Preliminary VE data from Chile

- Cohort nested within administrative database
- Priming with 2 doses of Sinovac-CoronaVac

Study	N	Infection	Symptomatic	Hospitalisation	ICU admission
CoronaVaC	165,000+	71 (65–76)	74 (68–79)	81 (73–87)	85 (70–96)
AZ	1.7M	91 (89–91	94 (93–94)	97 (96–98)	99 (97–99)
BNT	966,000+	93 (92–95)	95 (93–96)	91 (87–94)	93 (83–97)

Preliminary impact data from Bahrain

- SARS-CoV-2 positivity rates by vaccination group between 01 May 2021 and 11 September 2021

	2 x BIBP	2 x BNT162b2	2 x BIBP + BIBP	2 x BIBP + BNT162b2
% PCR+ out of tests undertaken (n/N)	0.76% (1,449/191,239)	0.29% (495/170,760)	0.22% (64/29,054)	0.07% (175/265,296)

Bahrain data: https://terrance.who.int/mediacentre/data/sage/SAGE_Slidedeck_Oct2021.pdf
Chile data: https://cdn.who.int/media/docs/default-source/blue-print/chile_rafael-araos_who-vr-call_25oct2021.pdf?sfvrsn=7a7ca72a_7

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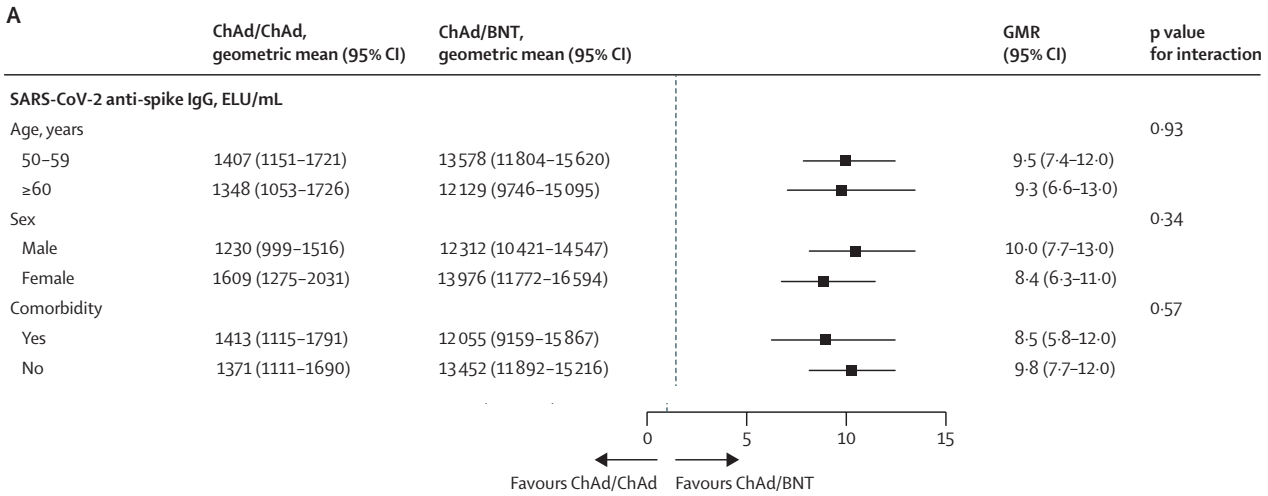
ComCov study: heterologous vs homologous primary vaccination

Overview

Study	Liu et al; Lancet
Country	UK
Study type	Single-blind RCT
Population	Adults, 18–65y



Groups (ranked by increasing post-D2 GM)

Dose 1	Dose 2	N	Day 28 S-IgG GM (95% CI)
AZ	AZ	104	1,392 (1,188–1,630)
BNT	AZ	104	7,133 (6,415–7,932)
AZ	BNT	109	12,906 (11,404–14,604)
BNT	BNT	109	14,080 (12,491–15,871)
	+4w		

Conclusions

- AZ/BNT and BNT/AZ > AZ/AZ
- Heterologous schedules more reactogenic than homologous counterpart; predominantly mild and transient
- Data on 12-week dose interval *in press*

Prospective cohort in Thailand: heterologous vs homologous boost

Overview

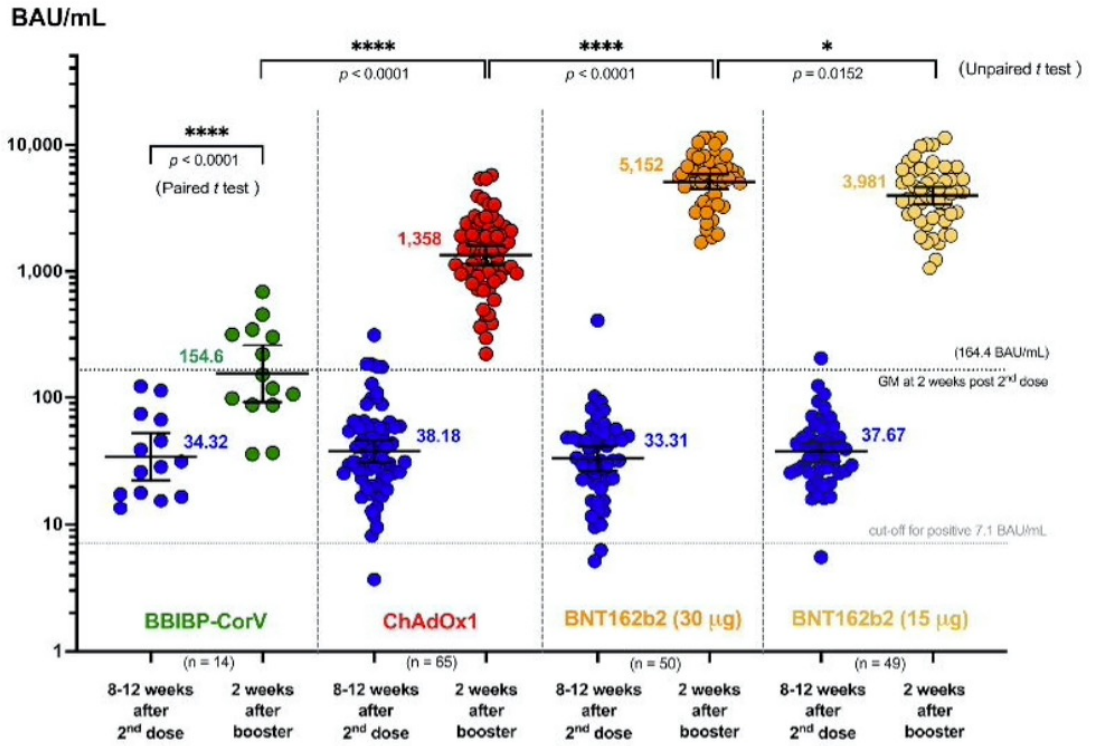
Study	Angkasekwinai et al; medRxiv
Country	Thailand
Study type	Cohort
Population	Adults, 18–60y

Groups (ranked by GMC)

Prime	Boost	N	Day 14 S-Ig GMT (95% CI)
2 x AZ	SP	23	128.1 (93.5–175.4)
2 x SV	SP	14	154.6 (92.1–259.5)
2 x AZ	AZ	50	246.4 (199.6– 304.2)
2 x SV	AZ	65	1,358 (1,142– 1,615)
2 x AZ	BNT 0.5	50	1,962 (1,625– 2,369)
2 x AZ	BNT	50	2,364 (2,006– 2,786)
2 x SV	BNT 0.5	50	3,981 (3,397–4,665)
2 x SV	BNT	50	5,152 (4,492–5,910)
	+2–3m		

- Primary interval 4w for SV and 8–10w for AZ
- SV-primed individuals younger

SV-primed:



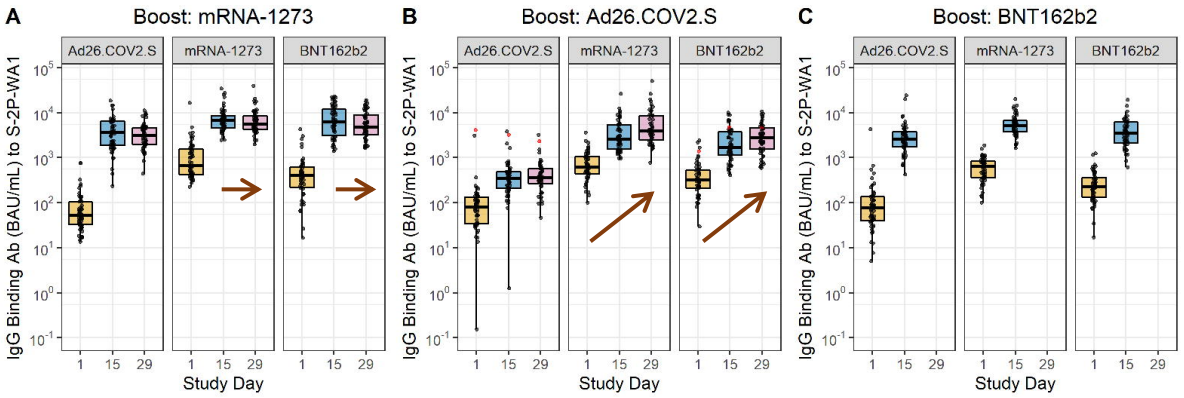
Conclusions

- RNA > AZ > SP boost for both AZ-primed and SV-primed

MixNMatch study: heterologous vs homologous boost

Overview

Study	Atmar et al; medRxiv
Country	USA
Study type	Non-randomised CT
Population	Adults, 19–85y



Groups (ranked by increasing post-boost GMT)

Prime	Boost	N	Day 15 S-Ig GMT (95% CI)
1 x JNJ	JNJ	50	326 (235.8–450.7)
2 x BNT	JNJ	51	1904.7 (1497.8–2422.8)
1 x JNJ	BNT	53	2549.5 (2038.1–3189.3)
2 x MOD	JNJ	49	3029.4 (2433.2–3771.7)
1 x JNJ	MOD	53	3203.1 (2499.5–4104.9)
2 x BNT	BNT	50	3409.1 (2760.6–4209.8)
2 x MOD	BNT	51	5195.6 (4433.1–6089.3)
2 x BNT	MOD	50	6155.0 (4895.4–7738.7)
2 x MOD	MOD	51	6799.8 (5771.8–8010.9)
		+3-6m	

Conclusions

- Anamnestic response in all groups
- RNA boost > JNJ boost, but difference less pronounced at day 29
- No safety concerns identified

Heterologous boosting after mRNA

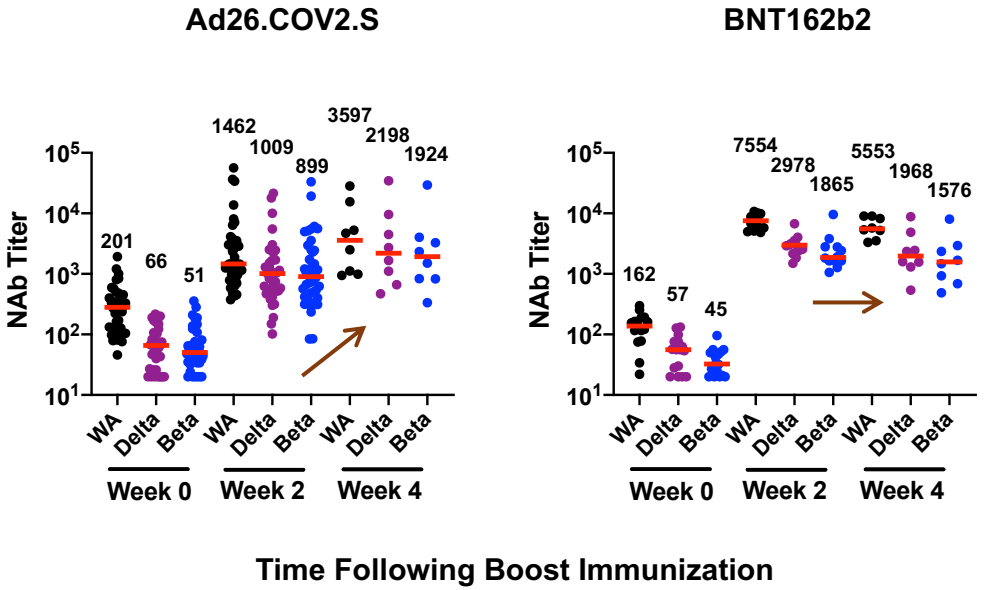
Overview

Study	Tan et al; Lancet
Country	USA
Study type	OBS
Population	Adults, 23–84y

Prime	Boost	N	Day 28 NAb median
2 x BNT	BNT	41	3,597
2 x BNT	JNJ	24	5,553

~8m

Antibody kinetics post-boost



Conclusions

- BNT > JNJ at week 2, but levels equivalent by week 4
- JNJ led to greater increases in CD8+ T cell responses than BNT

COV-BOOST study: heterologous vs homologous boost

Overview

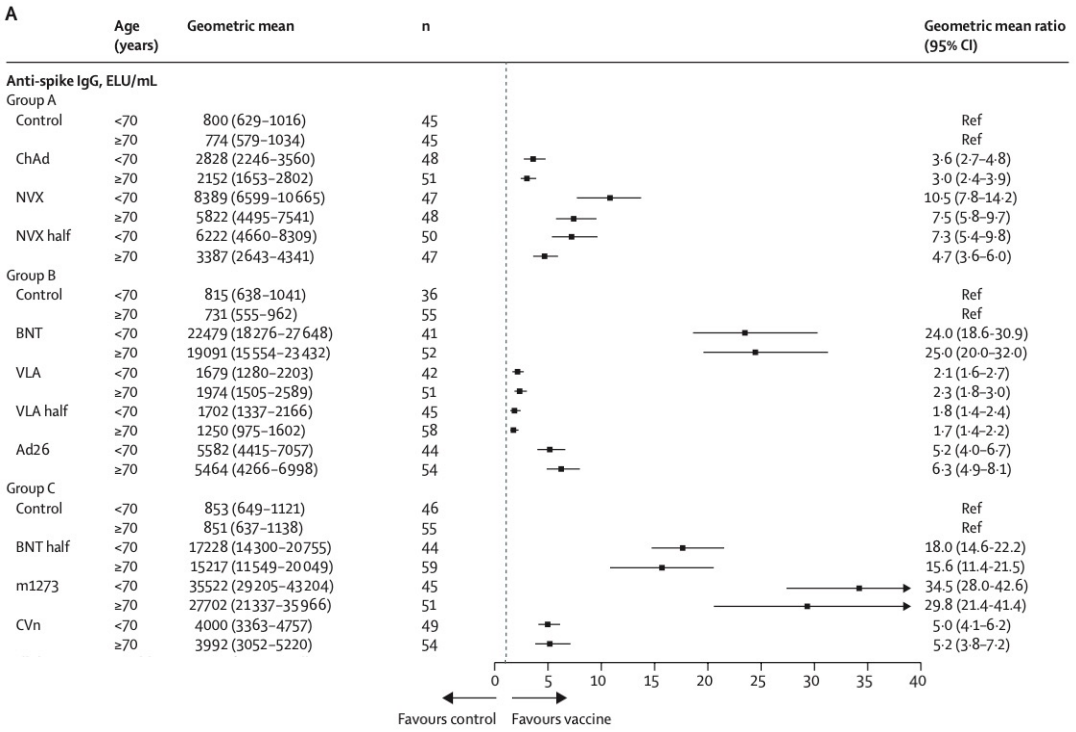
Study	Munro et al; Lancet
Country	UK
Study type	Observer-blind RCT
Population	Adults, 18–65y

EUL-only combinations (ranked by GMC)

Prime	Boost	N	Day 28 S-Ig GMT (95% CI)
2 x AZ	AZ	99	2457 (2058–2933)
2 x AZ	JNJ	98	5,517 (4,647–6,548)
2 x BNT	AZ	97	13,424 (11,702–15,399)
2 x AZ	BNT 0.5	103	16,045 (13,449–19,143)
2 x BNT	JNJ	87	17,079 (14,488–20,133)
2 x AZ	BNT	93	20,517 (17,718–23,757)
2 x BNT	BNT 0.5	92	23,082 (19,971–26,678)
2 x BNT	BNT	96	27,242 (24,148–30,731)
2 x AZ	MOD	97	31,111 (26,363–36714)
2 x BNT	MOD	91	33,768 (27,816–40,933)

+2.5–3.5m

GMCs for different boosters following 2 x AZ



Conclusions

- AZ-AZ-RNA > AZ-AZ-AZ or AZ-AZ-JNJ
- BNT-BNT-AZ or BNT-BNT-JNJ < BNT-BNT-BNT
- Other non-EUL vaccines (Novavax, Valneva, Curevac) also included

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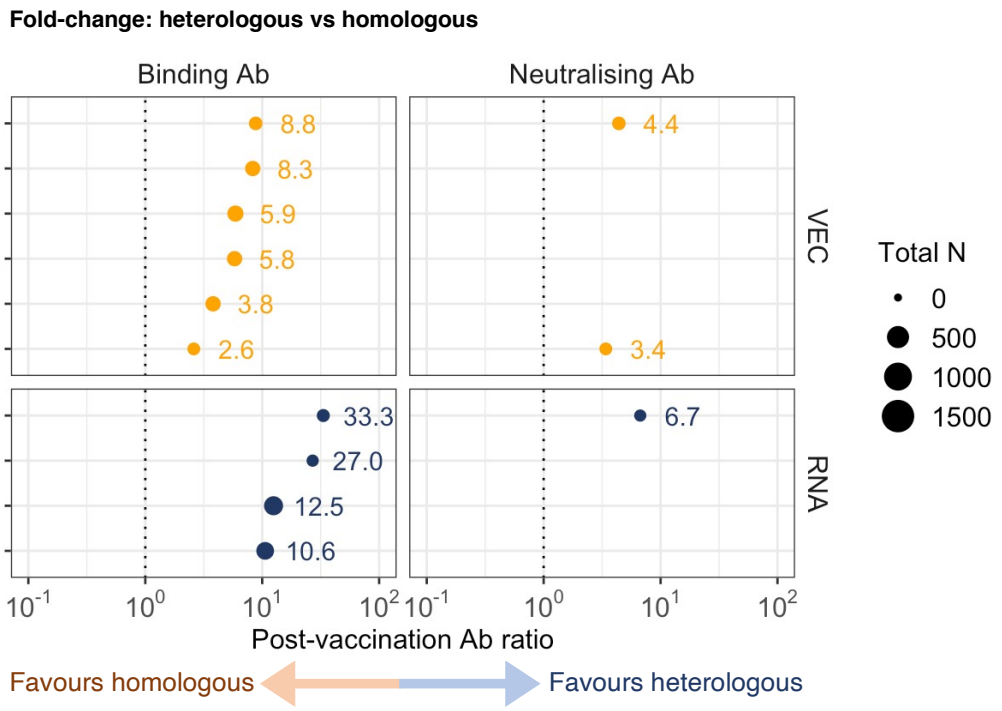
Heterologous/Homologous Ab ratio: inactivated vaccines

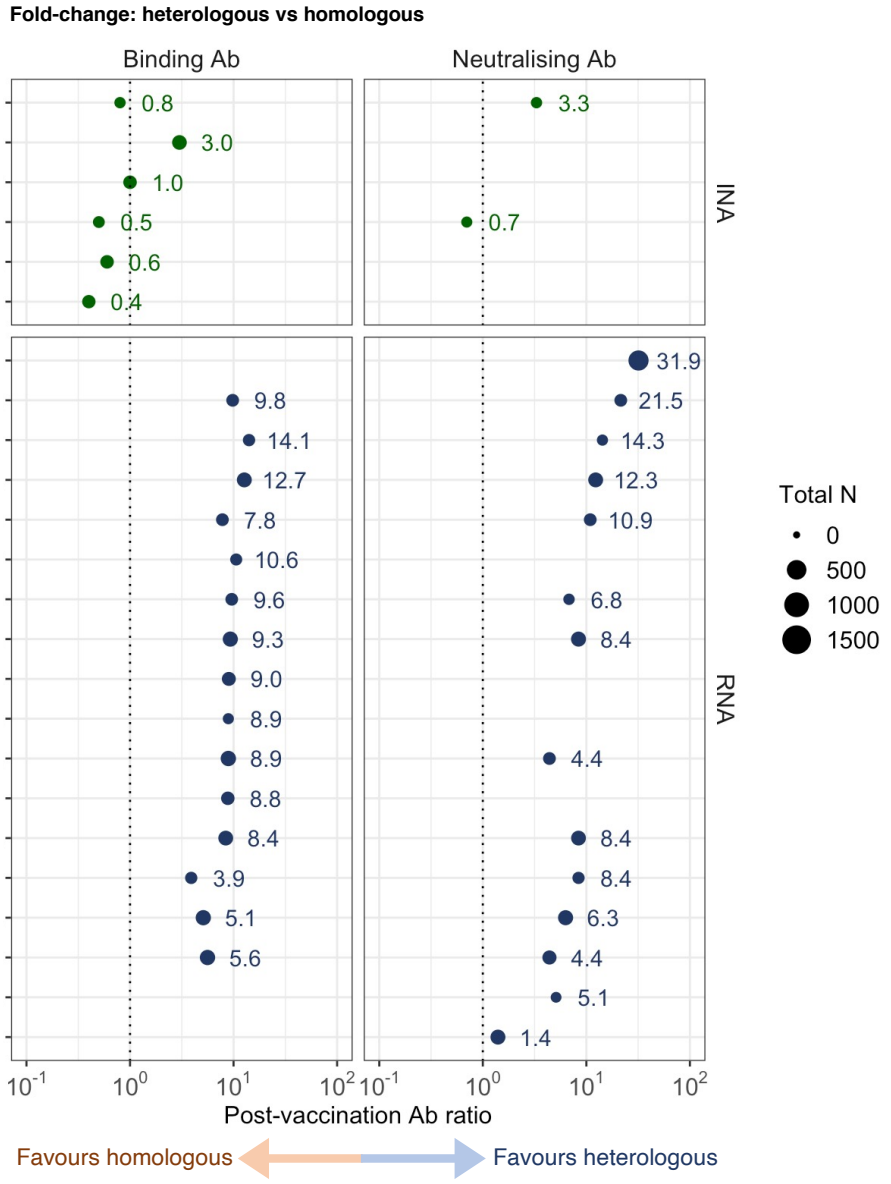
		Heterologous		Homologous	
Study	**Type**	**Schedule (final interval, w)**	***N***	**Schedule (final interval, w)**	***N***
Angkasekwinai; medRxiv	OBS	SV-SV-AZ (8-12)	*65*	SV-SV-SP (8-12)	*14*
Yorsaeng; medRxiv	OBS	SV-AZ (4)	*54*	SV-SV (3)	*80*
Mahasirimongkol; medRxiv	OBS	SV-AZ (3.5)	*137*	SV-SV (3.5)	*32*
Wanlapakorn; medRxiv (i)	OBS	SV-AZ (3.5)	*44*	SV-SV (4)	*90*
Wanlapakorn; medRxiv (ii)	OBS	AZ-SV (10)	*46*	SV-SV (4)	*90*
Kant; J Travel Med	OBS	AZ-BH (6)	*18*	BH-BH (4)	*40*
Angkasekwinai; medRxiv	OBS	SV-SV-BNT (8-12)	*50*	SV-SV-SP (8-12)	*14*
Keskin; J Med Virol	OBS	SV-SV-BNT (24)	*27*	SV-SV-SV (24)	*18*
Preliminary data (Bahrain)	CT	SP-SP-BNT (24)	*153*	SP-SP-SP (24)	*152*
Wanlapakorn; medRxiv (iii)	OBS	SV-BNT (3)	*66*	SV-SV (3)	*170*



Notes: Studies with homologous comparators included. AZ = AstraZeneca; BH = Bharat; BNT = BioNTech; JNJ = Janssen; MOD = Moderna; SP = Sinopharm; SV = Sinovac.

Heterologous/Homologous Ab ratio: vectored vaccines

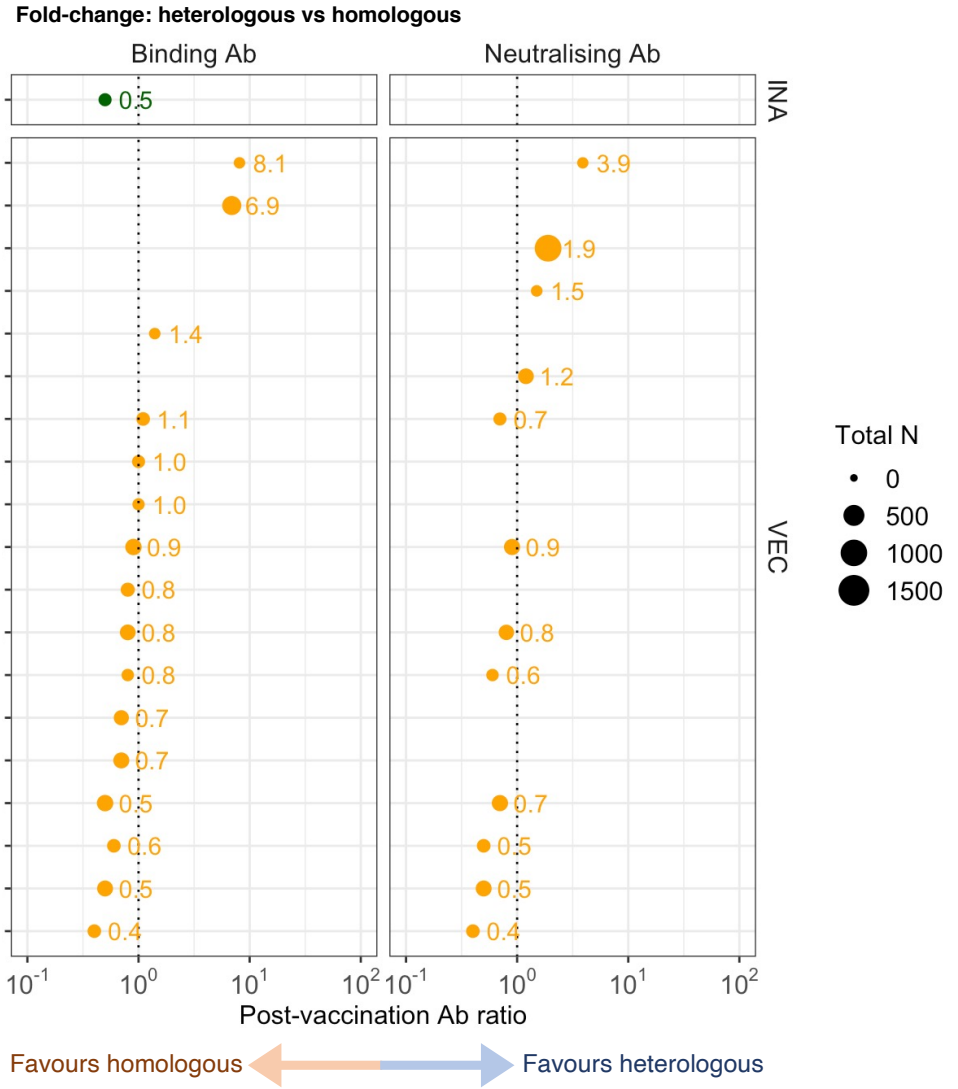
		Heterologous		Homologous	
Study	**Type**	**Schedule (final interval, w)**	***N***	**Schedule (final interval, w)**	***N***
Kant; J Travel Med	OBS	AZ-BH (6)	*18*	AZ-AZ (6)	*40*
Mahasirimongkol; medRxiv	CT	SV-AZ (3.5)	*137*	AZ-AZ (8–12)	*47*
Yorsaeng; medRxiv	OBS	SV-AZ (4)	*54*	AZ-AZ (10)	*80*
Angkasekwinai; medRxiv	OBS	AZ-AZ-SP (8-12)	*23*	AZ-AZ-AZ (8-12)	*50*
Wanlapakorn; medRxiv (i)	OBS	SV-AZ (3.5)	*44*	AZ-AZ (10)	*89*
Wanlapakorn; medRxiv (ii)	OBS	AZ-SV (10)	*46*	AZ-AZ (10)	*89*
Tenbusch; Lancet ID	OBS	AZ-BNT (9)	*482*	AZ-AZ (9)	*66*
Atmar; medRxiv (i)	CT	JNJ-MOD (14)	53	JNJ-JNJ (18)	*50*
Normark; N Eng J Med	OBS	AZ-MOD (11)	51	AZ-AZ (11)	*37*
Munro; Lancet (i)	CT	AZ-AZ-MOD (11)	*97*	AZ-AZ-AZ (11)	*99*
Atmar; medRxiv (ii)	CT	JNJ-BNT (20)	53	JNJ-JNJ (18)	*50*
Thurm; medRxiv	OBS	AZ-RNA (11)	*42*	AZ-AZ (11)	*38*
Angkasekwinai; medRxiv	OBS	AZ-AZ-BNT (8-12)	*50*	AZ-AZ-AZ (8-12)	*50*
Liu; Lancet (i)	CT	AZ-BNT (4)	*109*	AZ-AZ (4)	*104*
Schmidt; Nat Med	OBS	AZ-RNA (11)	*96*	AZ-AZ (11)	*55*
Benning; Vaccines	OBS	AZ-BNT (12)	*35*	AZ-AZ (12)	*17*
Sablerolles; medRxiv (i)	CT	JNJ-MOD (12)	*122*	JNJ-JNJ (12)	*106*
Brehm; Int J Hyg Env H	OBS	AZ-RNA (12)	*106*	AZ-AZ (12)	*25*
Munro; Lancet (ii)	CT	AZ-AZ-BNT (11)	*93*	AZ-AZ-AZ (11)	*99*
Barros-Martins; Nat Med	OBS	AZ-BNT (10)	*55*	AZ-AZ (10)	*32*
Liu; Lancet (ii)	CT	BNT-AZ (4)	*109*	AZ-AZ (4)	*104*
Sablerolles; medRxiv (ii)	CT	JNJ-BNT (12)	*111*	JNJ-JNJ (12)	*106*
Dimeglio; Clin Infect Dis	OBS	AZ-BNT (12)	*22*	AZ-AZ (12)	*22*
Havervall; medRxiv	OBS	AZ-BNT (13)	*116*	AZ-AZ (12)	*82*



Notes: Studies with homologous comparators included. AZ = AstraZeneca; BH = Bharat; BNT = BioNTech; JNJ = Janssen; MOD = Moderna; SP = Sinopharm; SV = Sinovac.

Heterologous/Homologous Ab ratio: RNA vaccines

		Heterologous		Homologous	
Study	**Type**	**Schedule (final interval, w)**	***N***	**Schedule (final interval, w)**	***N***
Wanlapakorn; medRxiv	CT	SV-BNT (3)	*66*	BNT-BNT (3)	*19*
Groß; medRxiv	OBS	AZ-BNT (8)	*26*	BNT-BNT (n.r.)	*15*
Brehm; Int J Hyg Env H	OBS	AZ-RNA (12)	*106*	RNA-RNA (6)	*261*
Tenbusch; Lancet ID	OBS	AZ-BNT (9)	*482*	BNT-BNT (3)	*537*
Dimeglio; Clin Infect Dis	OBS	AZ-BNT (12)	*22*	BNT-BNT (4)	*22*
Thurm; medRxiv	OBS	AZ-RNA (11)	*42*	RNA-RNA (5)	*38*
Havervall; medRxiv	OBS	AZ-BNT (13)	*116*	BNT-BNT (3)	*101*
Barros-Martins; Nat Med	OBS	AZ-BNT (10)	*55*	BNT-BNT (3)	*46*
Glockner; Viruses	OBS	AZ-RNA (12)	*42*	RNA-RNA (3)	*41*
Pozzetto; Nature	OBS	AZ-RNA (12)	*31*	BNT-BNT (4)	*29*
Liu et al; Lancet (i)	CT	AZ-BNT (4)	*104*	BNT-BNT (4)	*109*
Benning; Vaccines	OBS	AZ-BNT (12)	*35*	BNT-BNT (3)	*82*
Munro; Lancet (i)	CT	BNT-BNT-JNJ (15)	*87*	BNT-BNT-BNT (14)	*96*
Tan; medRxiv	OBS	BNT-BNT-JNJ (34)	*41*	BNT-BNT-BNT (36)	*24*
Schmidt; Nat Med	OBS	AZ-RNA (11)	*96*	RNA-RNA (5)	*62*
Vallée; J Clin Med	OBS	AZ-BNT (12)	*130*	BNT-BNT (4)	*67*
Liu; Lancet (ii)	CT	BNT-AZ (4)	*109*	BNT-BNT (4)	*109*
Atmar; medRxiv (i)	CT	MOD-MOD-JNJ (19)	*49*	MOD-MOD-MOD (16)	*51*
Munro; Lancet (ii)	CT	BNT-BNT-AZ (16)	*98*	BNT-BNT-BNT (14)	*96*
Atmar; medRxiv (ii)	CT	BNT-BNT-JNJ (21)	*51*	BNT-BNT-BNT (24)	*50*



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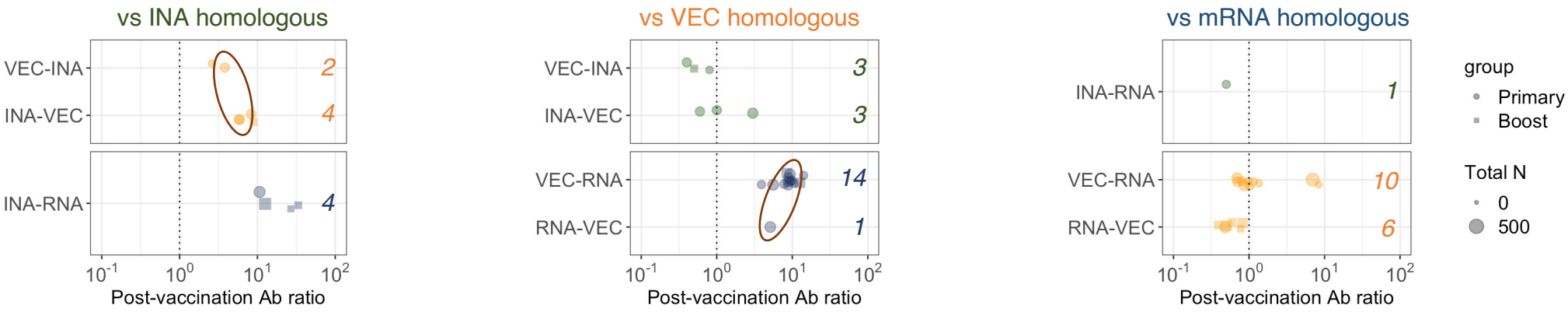
Heterologous/Homologous Ab ratio

Does order matter?



- One study reported higher Ab levels for SV-AZ than AZ-SV, but both higher than SV-SV (Wanlapakorn; medRxiv)
- One study reported higher Ab levels for AZ-BNT than BNT-AZ, but both higher than AZ-AZ (Liu; Lancet)

- Order may matter based on preliminary data, but possibly not as much as combination

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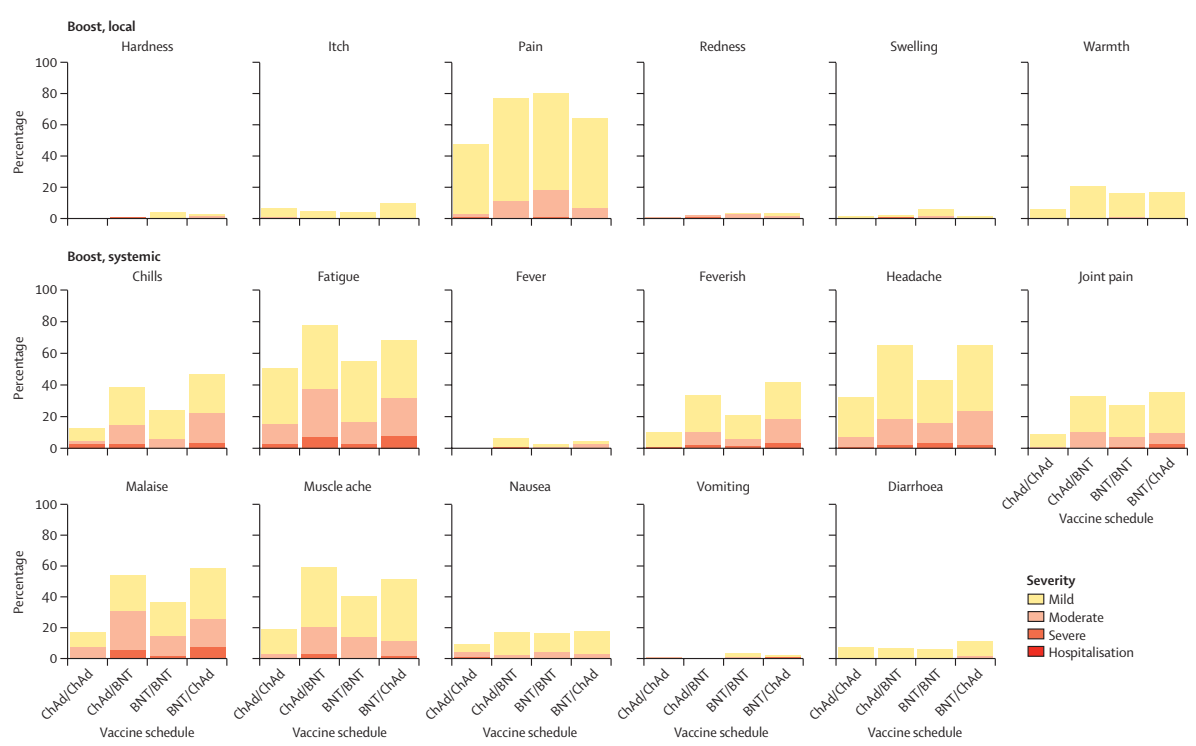
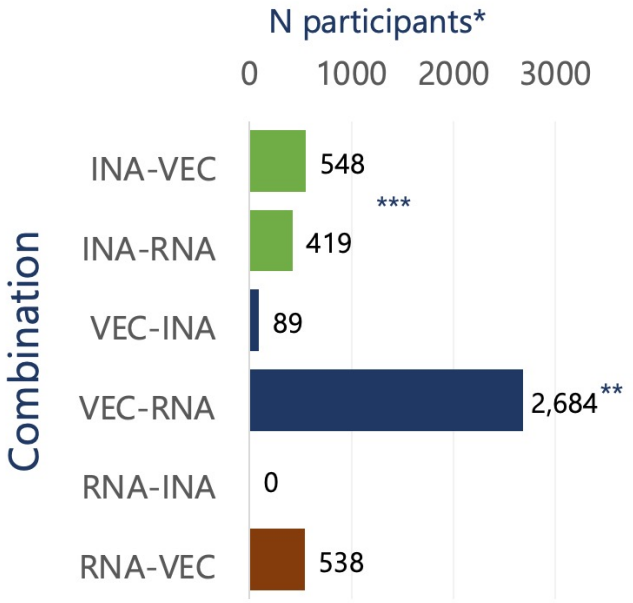
Safety – mixed platforms

Example: Com-COV study (Shaw et al; Lancet)



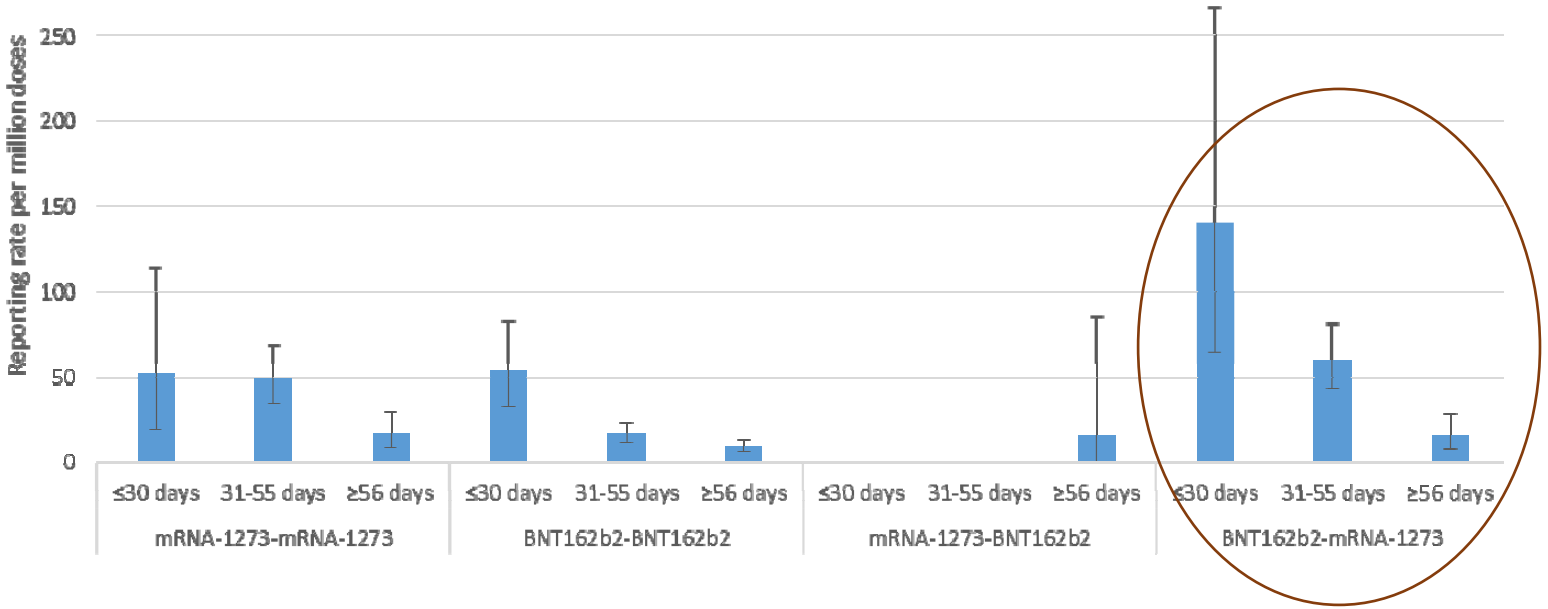


- No major safety concerns, though tendency towards greater reactogenicity for heterologous vs homologous schedules
- One study reporting high rates of AEs requiring medical attention for BNT/AZ (19%) and AZ/BNT (10%), but subject to recruitment bias (Powell et al; Euro Surveill)
- Modest overall sample size, especially when broken down by vaccine product pairings

Safety – mixed mRNA

Passive safety surveillance data from Ontario (Buchan et al; medRxiv, 5 Dec 2021)

Myocarditis/pericarditis rates among people who completed 2-dose series on/after 1 June 2021



- 297 instances meeting inclusion criteria across >19 million doses
- 70% associated with second dose; 77% in males
- 98% led to emergency department visit; 71% led to hospital admission

Conclusions

- Evidence supports flexible approach to heterologous schedules
- Preliminary VE data:
  - Vector/RNA > Vector alone (primary)
  - Vector/RNA ~ RNA alone (primary)
  - Inactivated/RNA and Inactivated/Vector > Inactivated alone (booster)

- Immunogenicity data:
  - Inactivated/RNA and Inactivated/Vector > Inactivated alone
  - Vector/RNA > Vector alone
  - Vector/RNA ~ RNA alone

- Tendency towards greater reactogenicity

Interim recommendations for heterologous COVID-19 vaccine schedules

Dr Folake Olayinka
7th December 2021

World Health Organization

Good Practice Statement

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 GRADEing of evidence.

Nevertheless, SAGE considered these indirect data from multiple sources as sufficient to proceed with issuing this good practice statement.

Rationale for Heterologous Schedules

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.

Recommendations (good practice statement) – i

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.*

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.

***Footnotes:**

Ad26.COV2.S can be given as a one-dose or two-dose primary series, as defined in the product-specific EUL. 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.

In moderately and severely immunocompromised individuals, WHO recommends an extended primary series including an additional dose.

Recommendations (good practice statement) – ii

Rapidly achieving high vaccination coverage with a primary vaccine series in priority-use groups, as defined in the WHO Prioritization Roadmap, should continue to be the focus while vaccine supply remains constrained.

Either homologous or heterologous schedules should be utilised 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.

Recommendations (good practice statement) – iii

For countries considering heterologous schedules, WHO makes the following recommendations:

- Depending on product availability, countries implementing WHO EUL inactivated vaccines may consider using WHO EUL vectored or mRNA vaccines for heterologous vaccination; and

- Depending on product availability, countries implementing WHO EUL vectored vaccines may consider using WHO EUL mRNA vaccines for heterologous vaccination.

Optional 3rd bullet point:

- Depending on product availability, countries implementing WHO EUL mRNA vaccines may consider using WHO EUL vectored vaccines for heterologous vaccination.

Recommendations (good practice statement) – iv

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

Note that WHO is currently not recommending booster doses for the general vaccination eligible population.

Evidence gaps

- safety, effectiveness, and duration protection of heterologous versus homologous vaccine doses for specific WHO EUL product combinations;
- 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;
- correlate of initial protection or duration of protection for homologous and heterologous schedules; and
- safety, immunogenicity, and effectiveness of fractional doses in the context of heterologous vaccination.