COVID-19 booster doses

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Oxford Vaccine Group

Disclosures

- Act on behalf of University of Oxford as an investigator on vaccine relevant research funded/supported by vaccine manufacturers including
  - Pfizer
  - AZ
  - Janssen
  - GSK
  - MCM vaccines
  - Novavax

- I receive no personal financial benefit from this work

National Immunisation Schedule Evaluation Consortium

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Welcome to NISEC

Welcome to the website of the National Immunisation Schedule Evaluation Consortium (NISEC). NISEC is a collaboration between a network of Academic Clinical Research groups and the UK Health Security Agency, with a brief of conducting clinical research relevant to UK immunisation policy. NISEC is funded by the National Institute for Health Research Policy Research Programme (PR-R17-0916-22001), with additional funding for COVID-19 studies from the NIHR and Vaccine Task Force. On these pages you will find out more about who we are, our past and present studies, and these are influencing the UK Immunisation programme.

FUNDED BY NIHR | National Institute for Health Research

About NISEC

Learn more about the National Immunisation Schedule Evaluation Consortium

About NISEC >

Studies

Find out more about the current and past studies carried out by the Consortium

NISEC Studies >

Outputs & Impact

Find out more about the outputs from NISEC studies, and the Policy Impact of those outputs.

NISEC Outputs >

NISEC Membership

Find out more about the people and institutions that make up the Consortium

View Membership >

National Immunisation Schedule Evaluation Consortium

- NIHR funded consortium of Academic Units and UK HSA
- 6 new clinical trials launched in 2021 at request of Vaccine Task Force with funding support (+CEPI)
- Enrolled over 5500 participants
- Directly informed policy on
  - ‘Mix and match’ schedules
  - Concomitant influenza and COVID
  - Choice of third dose vaccines

Shaw et al, Lancet, 2021
- COMCOV

Liu et al Lancet, 2021
- COMCOV

Lazarus et al, Lancet, 2021
- COMFLUCOV

Munro et al, Lancet, 2021
- COV-Boost

Stuart et al, Lancet, 2021
- COMCOV2

Dejnirattisai et al, Lancet 2021
- COMCOV2, Omicron

www.nisec.ac.uk

NIHR | Oxford Biomedical Research Centre

Jonathan Van-Tam, UK DCMO

October 2020……

- We need to think ahead
- Multiple vaccines likely to become available, most of which are likely to be a two dose schedule
- Important for the UK and globally to consider what if:
    - There is a supply problem?
    - There is a safety signal?
    - An individual develops a contra-indication to the second dose?
    - It is not possible logistically to guarantee administration of the same vaccine for first and second doses?
        - Relevant for
            - UK
            - Global distribution

<u>Could</u> we give different vaccines for primary immunisation schedules?

<u>Should</u> we give different vaccines for primary immunisation schedules?

- Could this be a way to optimize vaccine responses?

- Theoretical benefits to delivering spike protein via multiple vaccine platforms within one schedule
  - ? Enhanced cross-variant protection

- <u>Novel</u> approach to vaccine use

- Particularly relevant to viral vector vaccines
  - ChAdOx1-nCOV-19 (Oxford/AstraZeneca)
  - Anti-vector immunity generated by first dose potentially impacts on immune response to second dose of same vaccine
  - Already have experience with heterologous prime/boost for different viral vectors
    - A26.Zebov/MVA-B-Filo
    - Sputnik V

    ….. but cross-platform schedules takes this to the next step

Challenges for mixed schedules

- No formal regulatory process
- Manufacturers generally reluctant
- Can complicate pharmacovigilance surveillance
- Locking in delivery to an optimal ‘mixed’ schedule likely to delay rather than enhance deployment
- Emphasis must be on:
  - Enhancing flexibility
  - Identifying any mixed schedules that should be avoided
    - excessive reactogenicity
    - poor immunogenicity

What have we learned?

Generating data on mixed schedules is important!

Germany halts use of AstraZeneca for under-60s

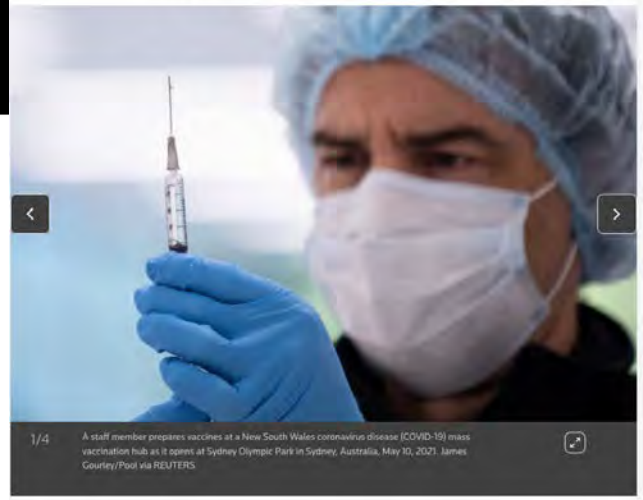
June 17, 2021
5:52 AM BST
Last Updated 5 months ago

Healthcare & Pharmaceuticals

Australia limits use of AstraZeneca COVID-19 vaccine to people over 60

3 minute read

Reuters



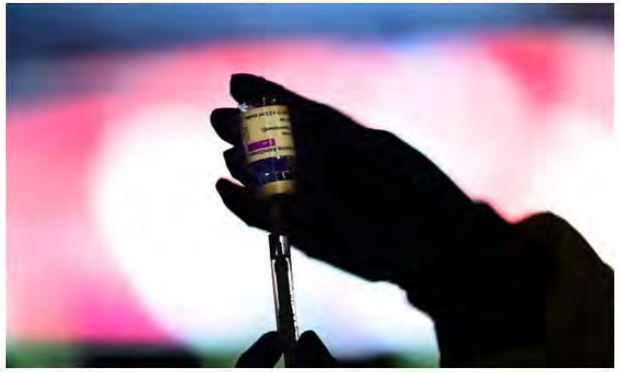
Coronavirus digest: Sweden halts AstraZeneca vaccine use

The list of European countries suspending the jab from the part-Swedish pharmaceutical giant is growing. Meanwhile, the WHO says lockdowns could be fatal for premature babies. Follow DW for the latest.

Canada suspends use of AstraZeneca Covid vaccine for those under 55

Immunisation panel says there is 'substantial uncertainty about the benefit' of the vaccine given risk of rare type of blood clot

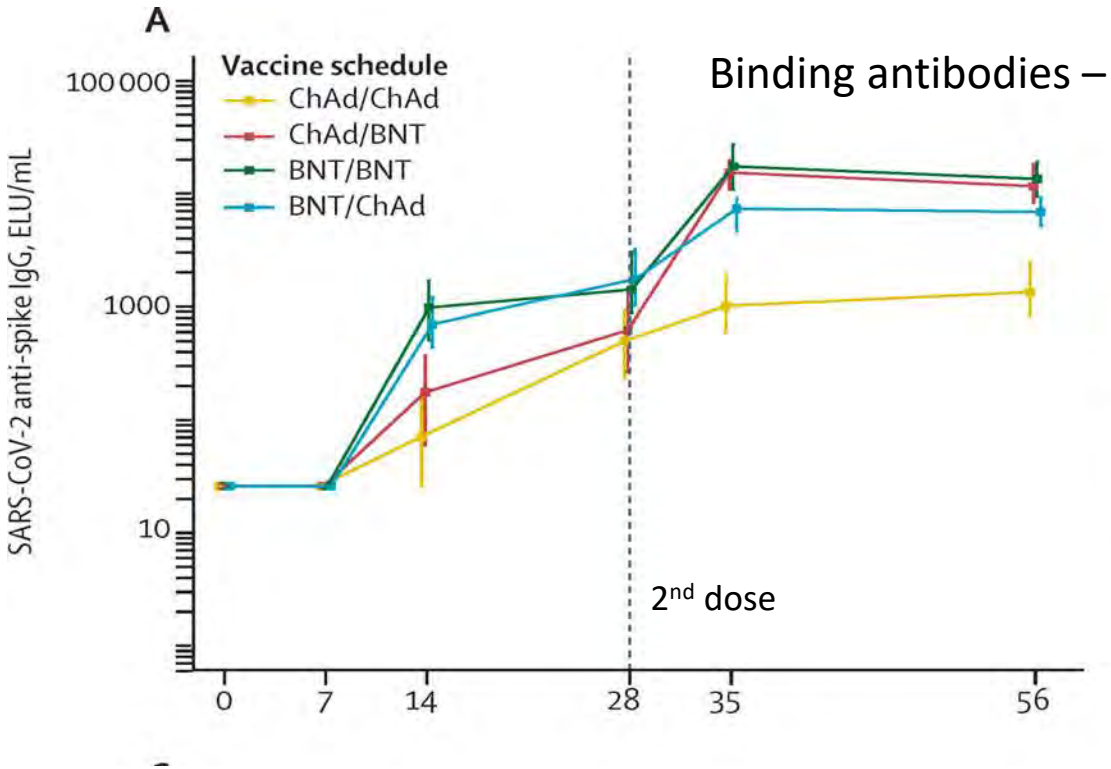
See all our coronavirus coverage



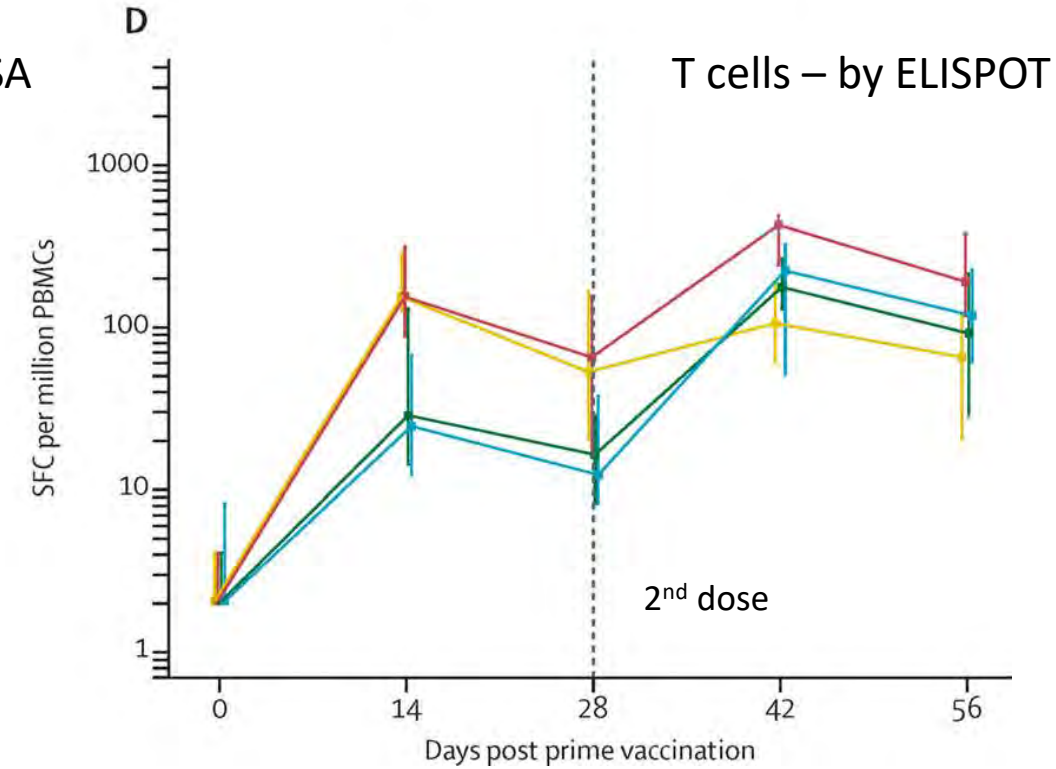
Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): a single-blind, randomised, non-inferiority trial

Xinxue Liu, Robert H Shaw*, Arabella S V Stuart*, Melanie Greenland, Parvinder K Aley, Nick J Andrews, J Claire Cameron, Sue Charlton, Elizabeth A Clutterbuck, Andrea M Collins, Tanya Dinesh, Anna England, Saul N Faust, Daniela M Ferreira, Adam Finn, Christopher A Green, Bassam Hallis, Paul T Heath, Helen Hill, Teresa Lambe, Rajeka Lazarus, Vincenzo Libri, Fei Long, Yama F Mujadidi, Emma L Plested, Samuel Provstgaard-Morys, Maheshi N Ramasamy, Mary Ramsay, Robert C Read, Hannah Robinson, Nisha Singh, David P J Turner, Paul J Turner, Laura L Walker; Rachel White, Jonathan S Nguyen-Van-Tam, Matthew D Snape, with the Com-COV Study Group†*

Binding antibodies – IgG by ELISA



T cells – by ELISPOT



COMCOV and COMCOV2: Summary of immunogenicity of primary immunisation at day 28 post 2nd dose

COMCOV2 (9 week interval, 63 year olds)	Anti-spike IgG	95% C.I.
BNT/Moderna	22953	(20589-25590)
ChAd/Moderna	20116	(18150-22296)
BNT/BNT	16929	(15025-19075)
BNT/Novavax	8886	(7393-10680)
ChAd/Novavax	5597	(4756-6586)
ChAd/ChAd	1971	(1718-2262)

COMCOV (12 week interval, 58 year olds)	Anti-spike IgG	95% C.I.
BNT/BNT	17534	(15005-20489)
ChAd/BNT	13517	(11536-15838)
BNT/ChAd	10553	(8892-12525)
ChAd/ChAd	2605	(2142-3169)

COMCOV2 (9 week interval)	T cell response	95% C.I.
ChAd/Novavax	189	(158-226)
ChAd/Moderna	149	(118-188)
BNT/Moderna	76	(58-99)
BNT/BNT	49	(39-63)
ChAd/ChAd	45	(34-61)
BNT/Novavax	29	(22-38)

COMCOV (12 week interval)	T cell response	95% C.I.
ChAd/BNT	113	(87-147)
BNT/BNT	48	(36-62)
BNT/ChAd	37	(28-50)
ChAd/ChAd	34	(26-43)

Xiu et al, Lancet 2021

Stuart et al Lancet 2021

Humoral immunity (ELISA)

- **Higher IgG with any schedule with an mRNA dose**
- Moderna 2nd dose more immunogenic than BNT 2nd dose following ChAd or BNT prime
- Heterologous ChAd/protein mid-ranked
- All combinations above ChAd/ChAd threshold

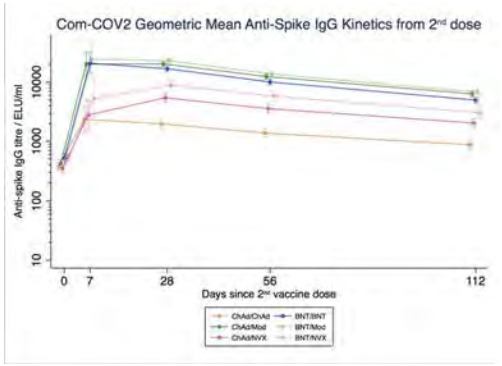
Cellular immunity (IFN-gamma secreting T cells, measured by ELISPOT)

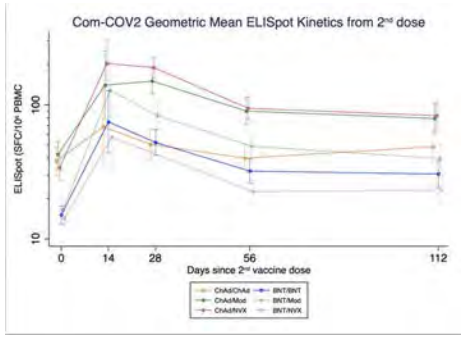
- **ChAd prime, followed by heterologous boost highly immunogenic**
- Homologous mRNA prime/boost is mid-ranked for cellular immunity, Moderna more immunogenic than BNT
- Single dose mRNA does not prime well for protein/matrix boost

Other data from COMCOV/COMCOV2: Mixed schedules

- No specific advantage for variants of concern
  - Beta
    - Neutralising activity reduced by 57-79% across all platforms
  - Delta
    - Neutralising activity reduced by 43-63% across all platforms
  - Omicron pending

- No difference in rate of Ab or T cell decline after primary immunisation





- Increased systemic reactions (e.g. chills, malaise) with mixed viral vector and mRNA vaccines
  - Not prohibitory
  - Minimized by increasing interval

- No safety concerns

Interim recommendations for heterologous COVID-19 vaccine schedules

Interim guidance

16 December 2021

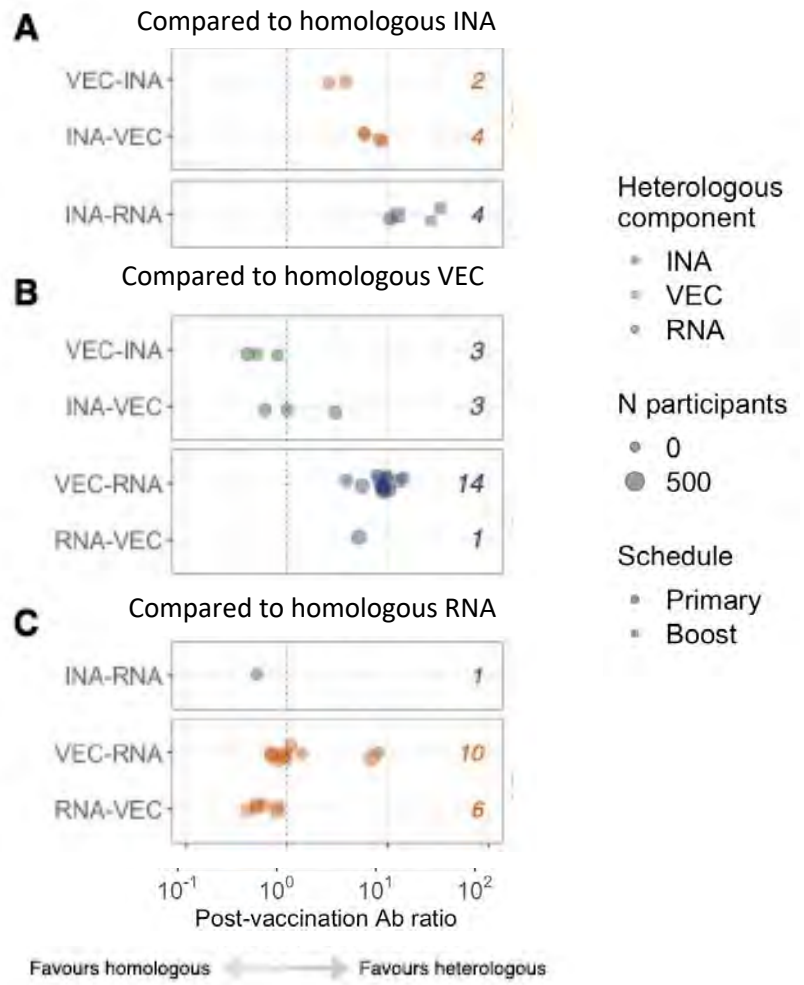
World Health Organization

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.

Immunogenicity of heterologous schedules relative to (A) inactivated-only; (B) vectored-only; and (C) mRNA-only schedules‡



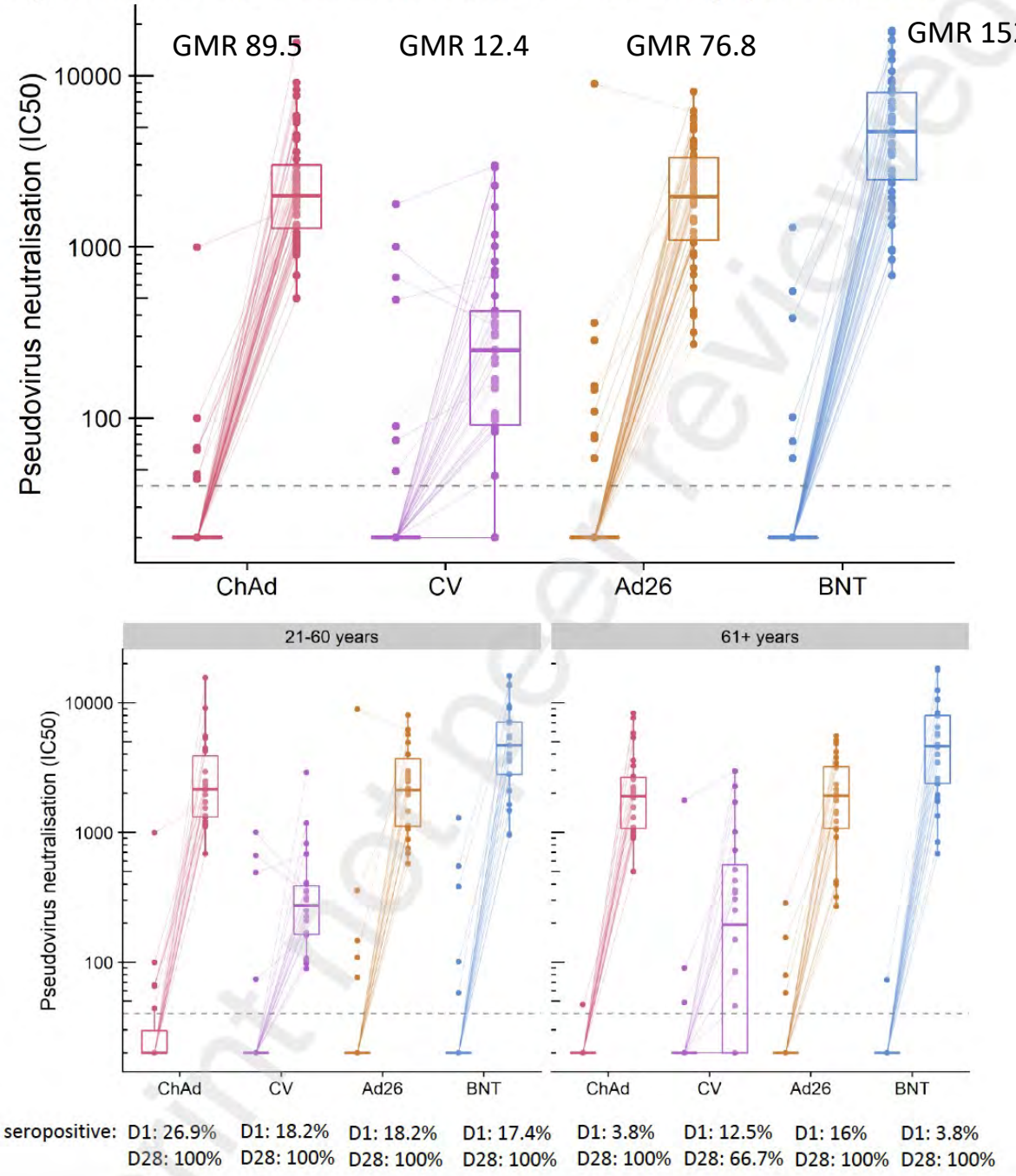
Ab: antibody; INA: inactivated vaccine; RNA: mRNA vaccines; VEC: vectored vaccine.

Binding antibody

Mixed schedules: 3rd dose boost immunisation

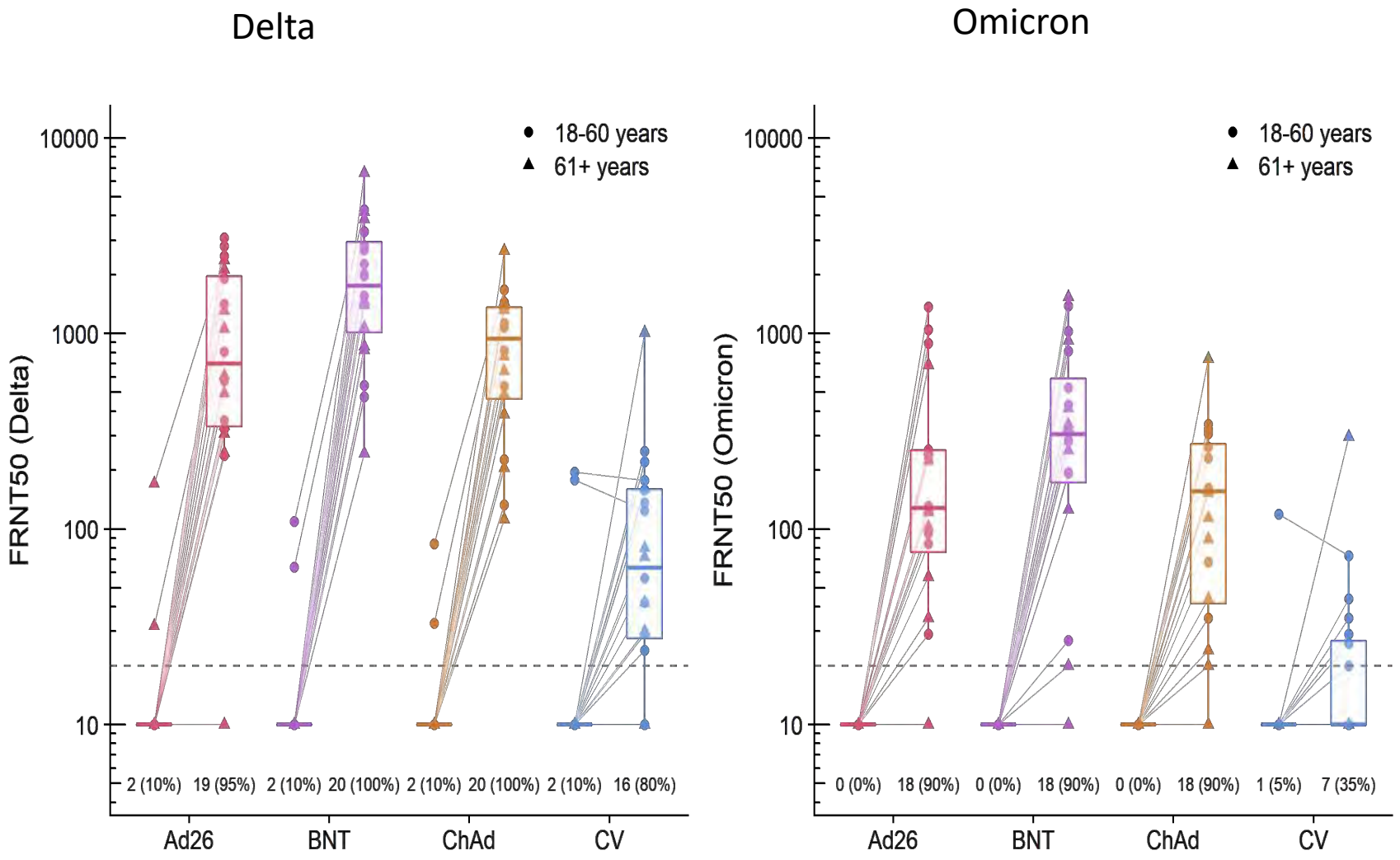
3rd dose after priming with Coronavac (CV) 6 months previously

Figure 4 Pseudovirus neutralisation titres before and 28 days post vaccination



Clemens et al, Lancet 2022

3rd dose after priming with Coronavac (CV) 6 months previously

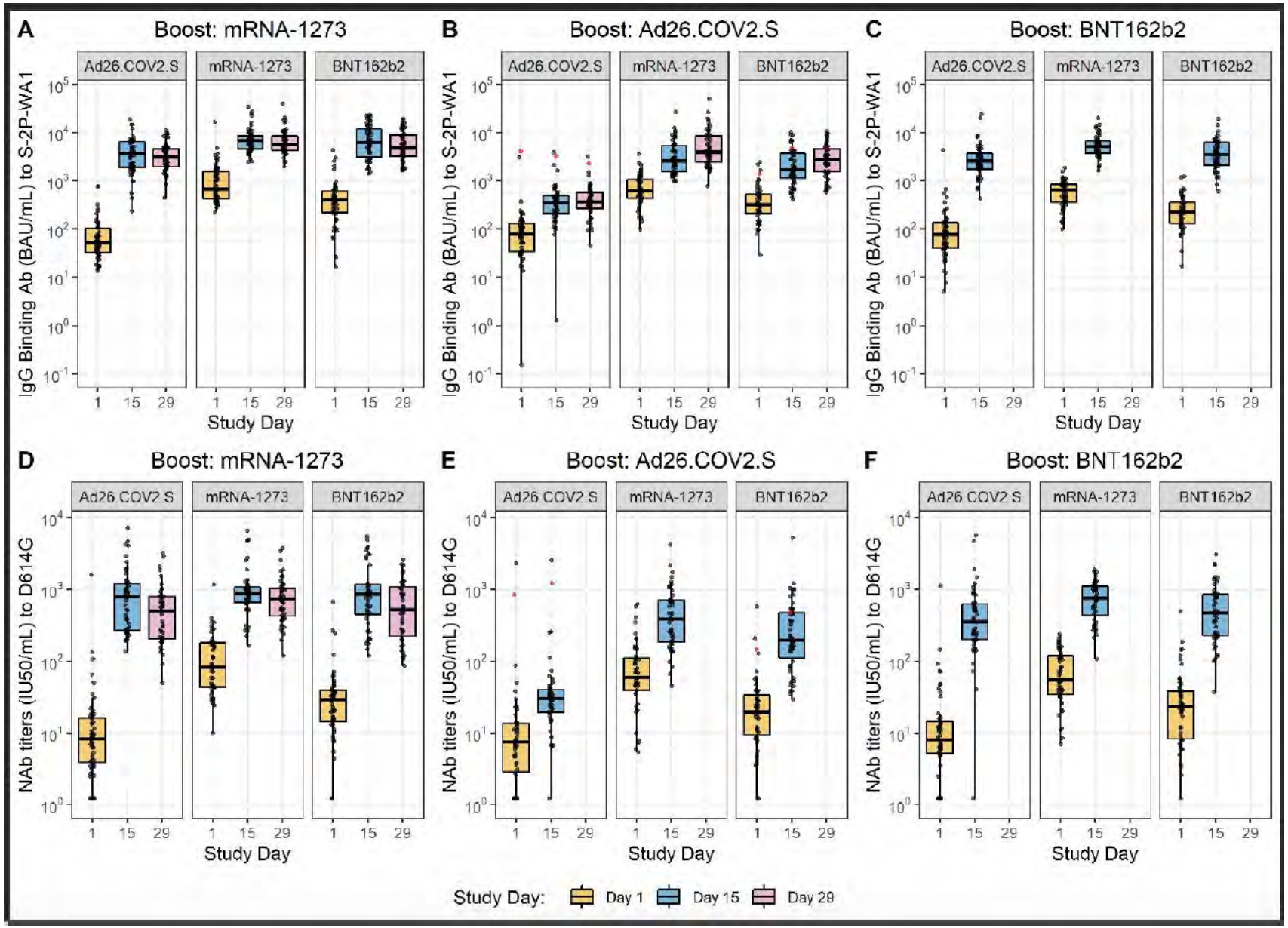


Clemens et al, Lancet 2022

NIH study

Binding IgG

Neutralising Ab



Atmar et al, Medi-archive 2021

COV-BOOST

Evaluating COVID-19 vaccine boosters

University of Southampton | NHS University Hospital Southampton NHS Foundation Trust

NISEC

Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial

Alasdair P S Munro, Leila Janani*, Victoria Cornelius*, Parvinder K Aley, Gavin Babbage, David Baxter, Marcin Bula, Katrina Cathie, Krishna Chatterjee, Kate Dodd, Yvanne Enever, Karishma Gokani, Anna L Goodman, Christopher A Green, Linda Harndahl, John Haughney, Alexander Hicks, Agatha A van der Klaauw, Jonathan Kwok, Vincenzo Libri, Martin J Llewelyn, Alastair C McGregor, Angela M Minassian, Patrick Moore, Mehmood Mughal, Yama F Mujadidi, Jennifer Murira, Orod Osanlou, Rostam Osanlou, Daniel R Owens, Mihaela Pacurar, Adrian Palfreeman, Daniel Pan, Tommy Rampling, Karen Regan, Stephen Saich, Jo Salkeld, Dinesh Saralaya, Sunil Sharma, Ray Sheridan, Ann Sturdy, Emma C Thomson, Shirley Todd, Chris Twelves, Robert C Read, Sue Charlton, Bassam Hallis, Mary Ramsay, Nick Andrews, Jonathan S Nguyen-Van-Tam, Matthew D Snape†, Xinxue Liu†, Saul N Faust†, on behalf of the COV-BOOST study group‡*

Chief Investigator Saul Faust

Evaluated a range of vaccines as '3rd dose' for participants primed in community with 2 doses of Oxford/AZ vaccine or Pfizer

- 3rd dose vaccines
  - Viral vectored
    - Oxford/AZ (ChAd)
    - Janssen (Ad26)
  - mRNA
    - Pfizer (BNT)
    - ½ dose Pfizer
    - Moderna (M1273)
      - *nb given at full (100 mcg) dose, rather than 50 mcg*
    - Curevac (CVnCOV)
  - Protein nanoparticle
    - Novavax (NVX)
    - ½ dose Novavax
  - Inactivated whole virus
    - Valneeva (VLA)
    - ½ dose Valneeva

Study Design

COV-BOOST
Evaluating COVID-19 vaccine boosters

Stage1

Eligible population

= 2,886

General cohort

= 2,236

Immunology cohort

= 650

25

Comprising 25 participants from each group

6 sites

Group A
= 888

- Pfz-BNT/Pfz-BNT = 444
  - Oxford-AZ = 111
  - Novavax = 111
  - Novavax-half = 111
  - Control = 111
- Oxford-AZ = 444
  - Oxford-AZ = 111
  - Novavax = 111
  - Novavax-half = 111
  - Control = 111

6 sites

Group B
= 1,110

- Pfz-BNT/Pfz-BNT = 555
  - Pfz-BNT/Pfz-BNT= 111
  - Valneva = 111
  - Valneva-half = 111
  - Janssen = 111
  - Control = 111
- Oxford-AZ = 555
  - Pfz-BNT/Pfz-BNT = 111
  - Valneva = 111
  - Valneva-half = 111
  - Janssen = 111
  - Control = 111

6 sites

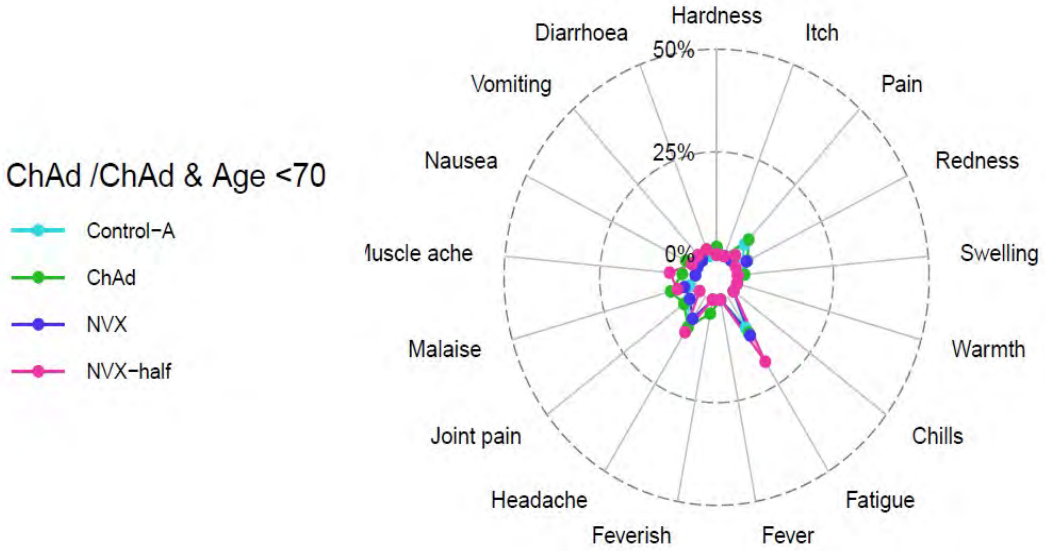
Group C
= 888

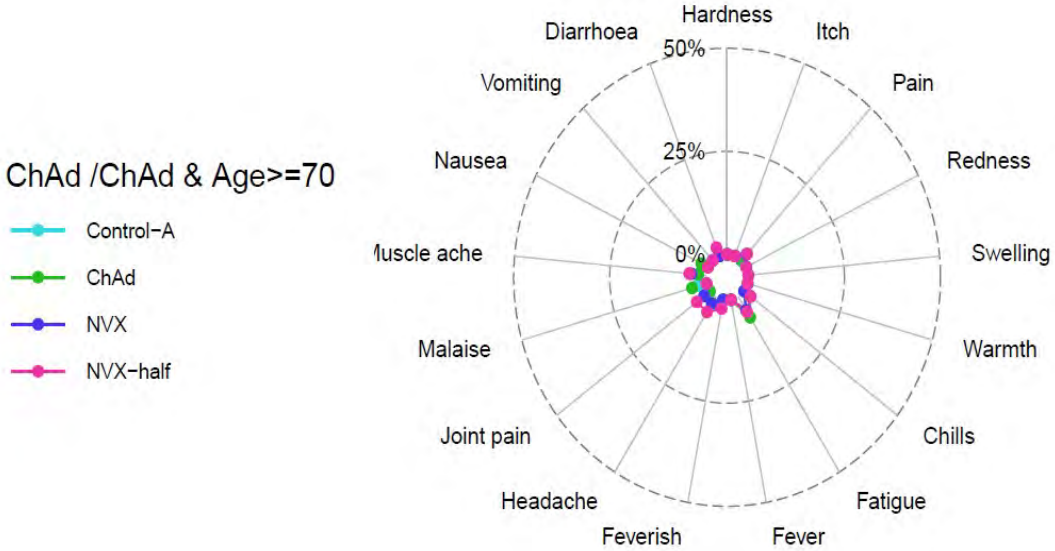
- Pfz-BNT/Pfz-BNT = 444
  - Moderna = 111
  - CureVac = 111
  - Pfz-BNT half = 111
  - Control = 111
- Oxford-AZ = 444
  - Moderna = 111
  - CureVac = 111
  - Pfz-BNT half = 111
  - Control = 111

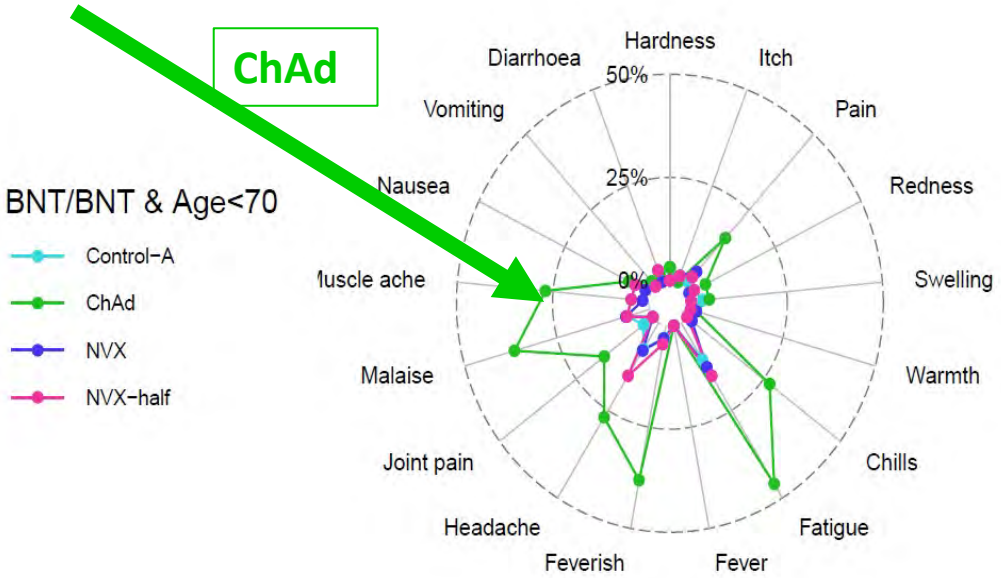
Baseline characteristics of people who took part

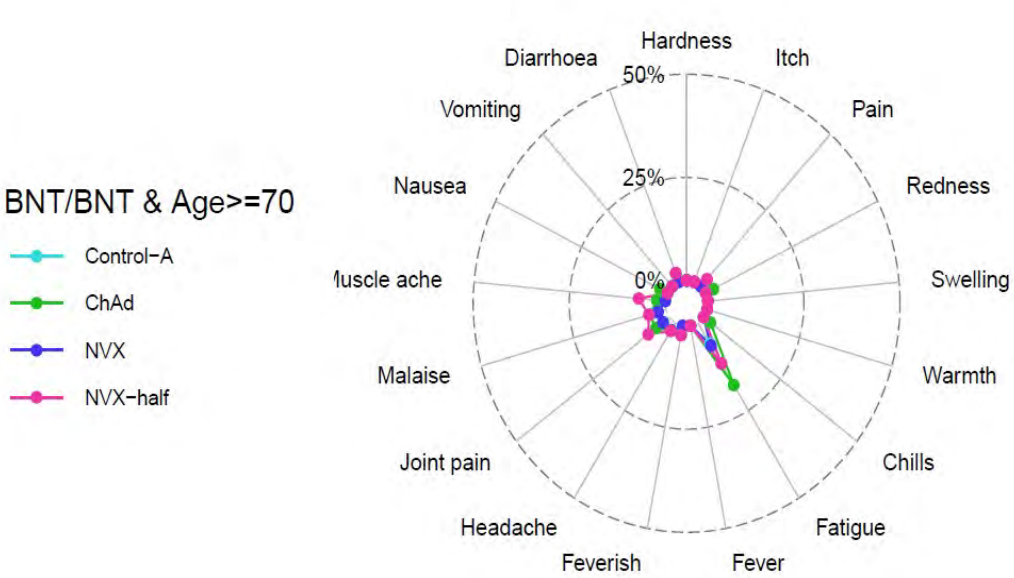
- People enrolled 10-12 weeks after their 2nd jab
- Included those aged 30-69, and those over 70
- Good age spread
- Included people with cardiovascular disorders, diabetes and respiratory conditions.
- Not people with immune problems

Group A – moderate and severe reactions



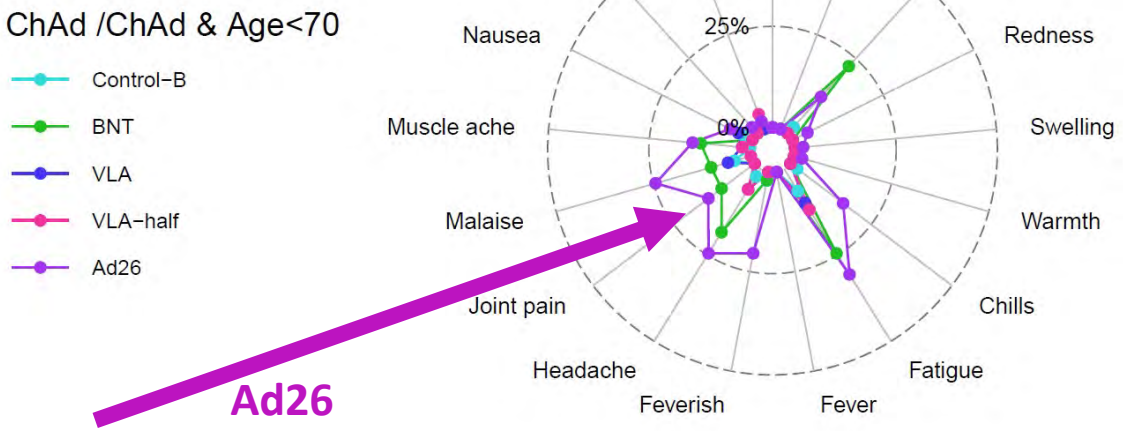




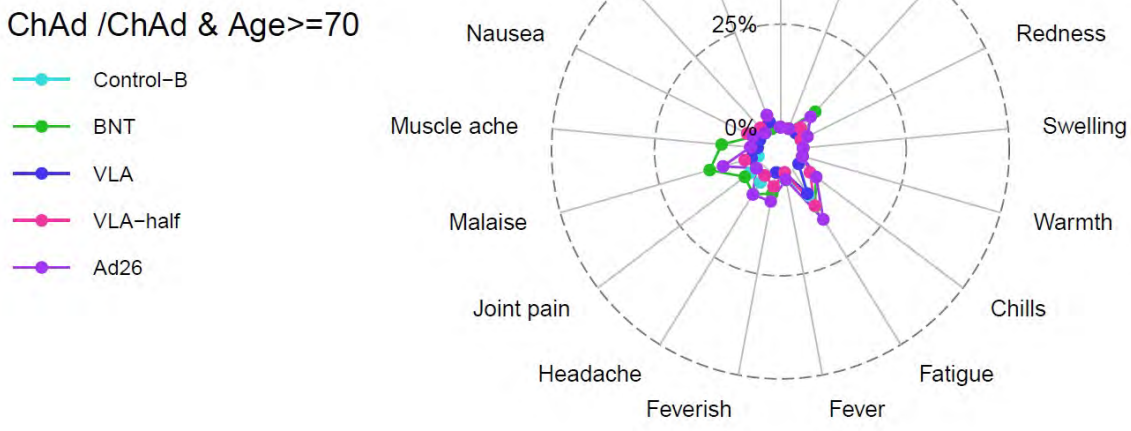


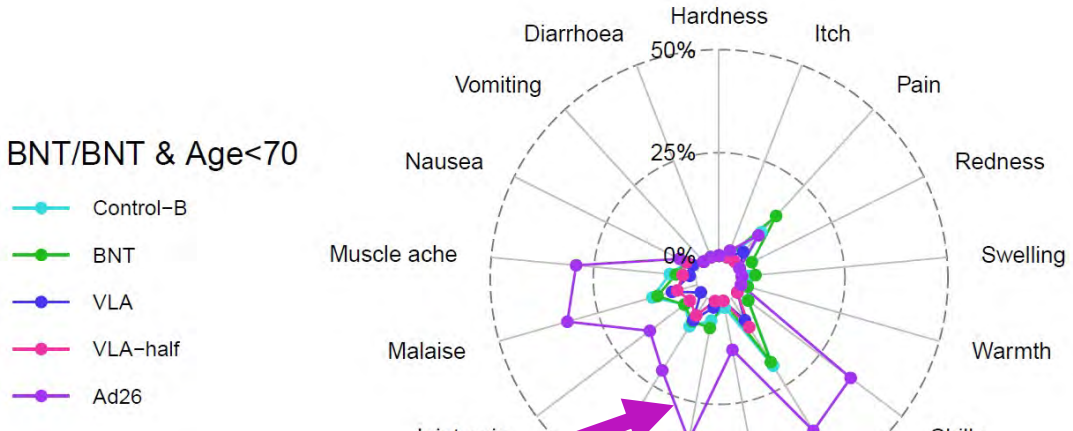
Munro et al Lancet 2021

Group B – moderate and severe

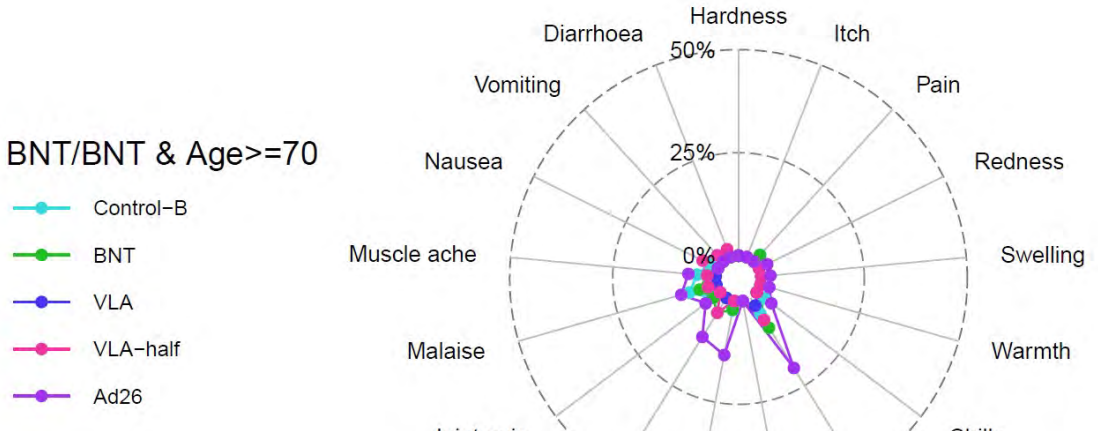


Ad26



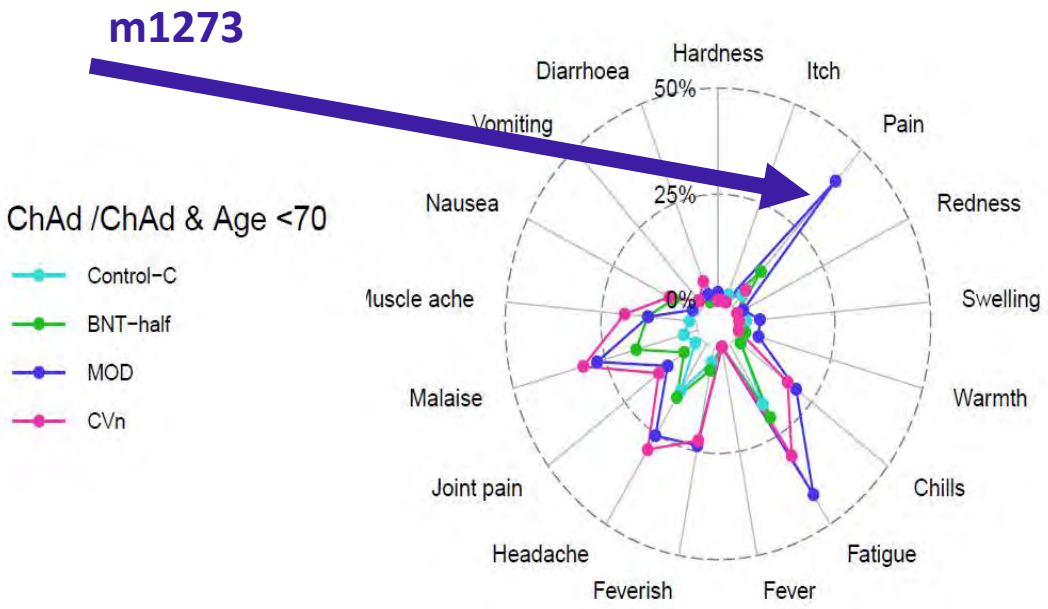


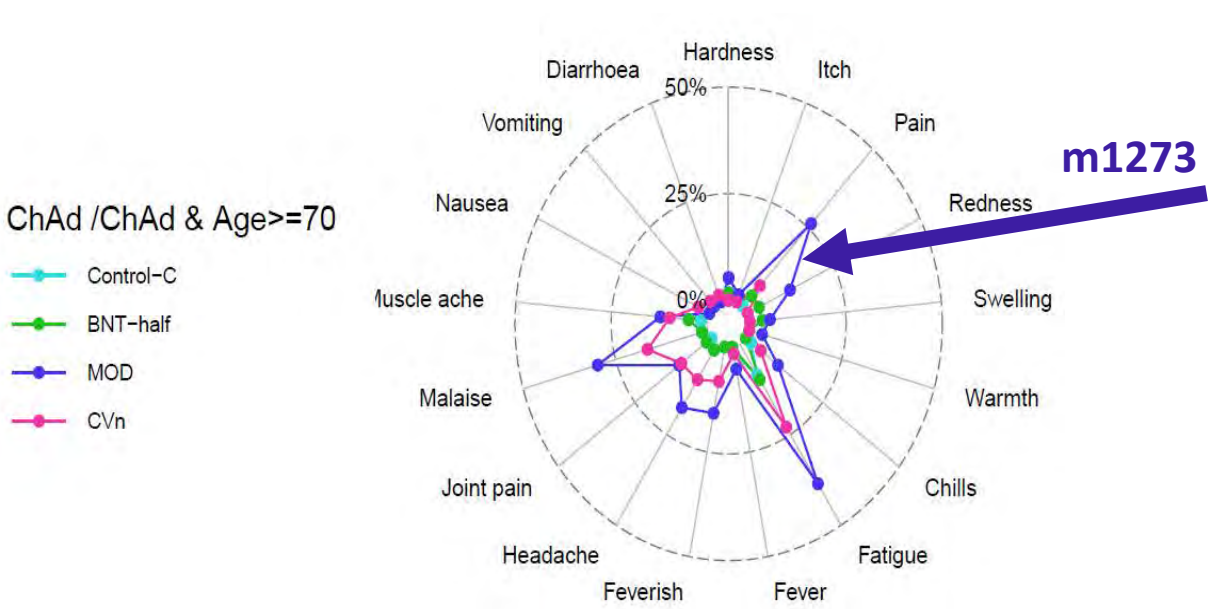
Ad26

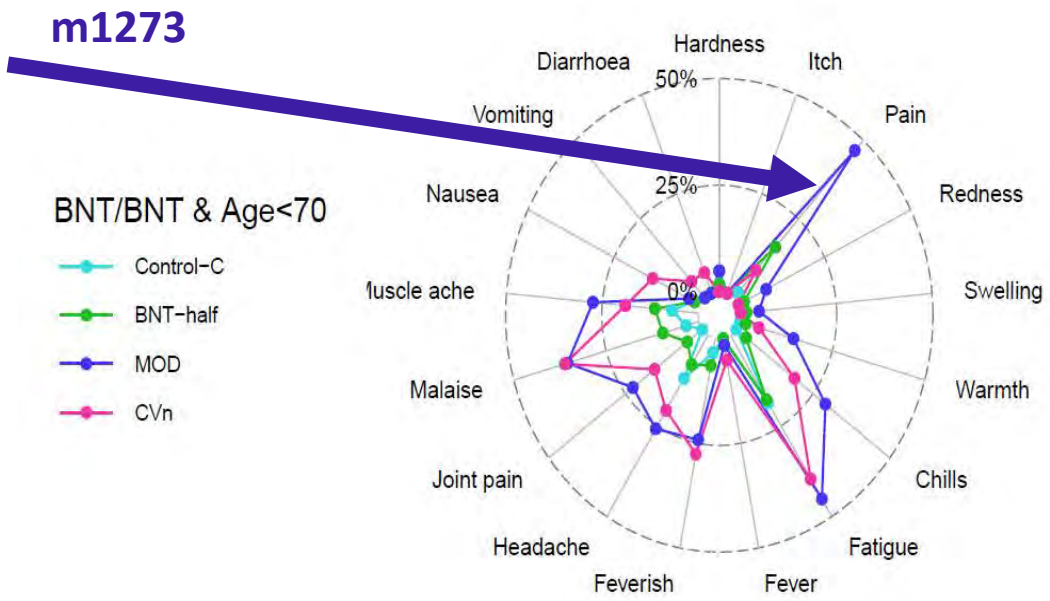


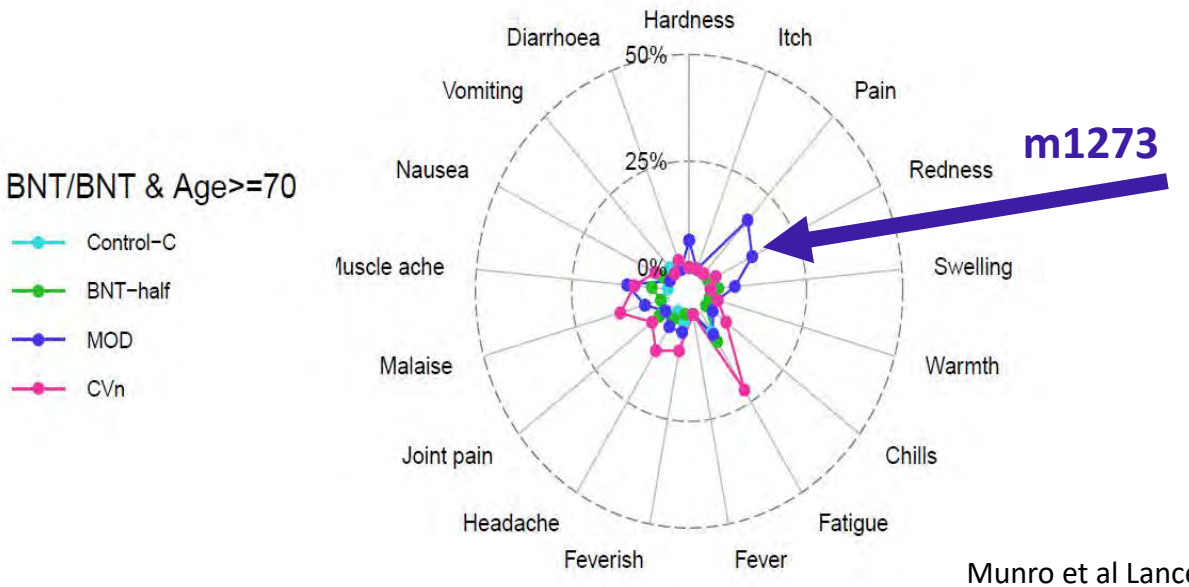
Munro et al Lancet 2021

Group C – moderate and severe









Munro et al Lancet 2021

Reactogenicity Summary 1

- Any grade local and systemic reactions similar after all vaccines
- Fatigue and headache the most common systemic reactions
- Pain the most frequent local reaction
- Overall, reactogenicity was greater in people aged 30-69 years compared with older participants regardless of the first vaccines received
- Participants primed with BNT/BNT reported more frequent local and systemic reactions after receiving third dose
  - MOD (100 mcg),
  - ChAd and Ad26 as a third dose

Immunogenicity

We show anti-spike antibody and T-cell response by participant age at 28 days after the 3rd dose between study vaccines and controls for:

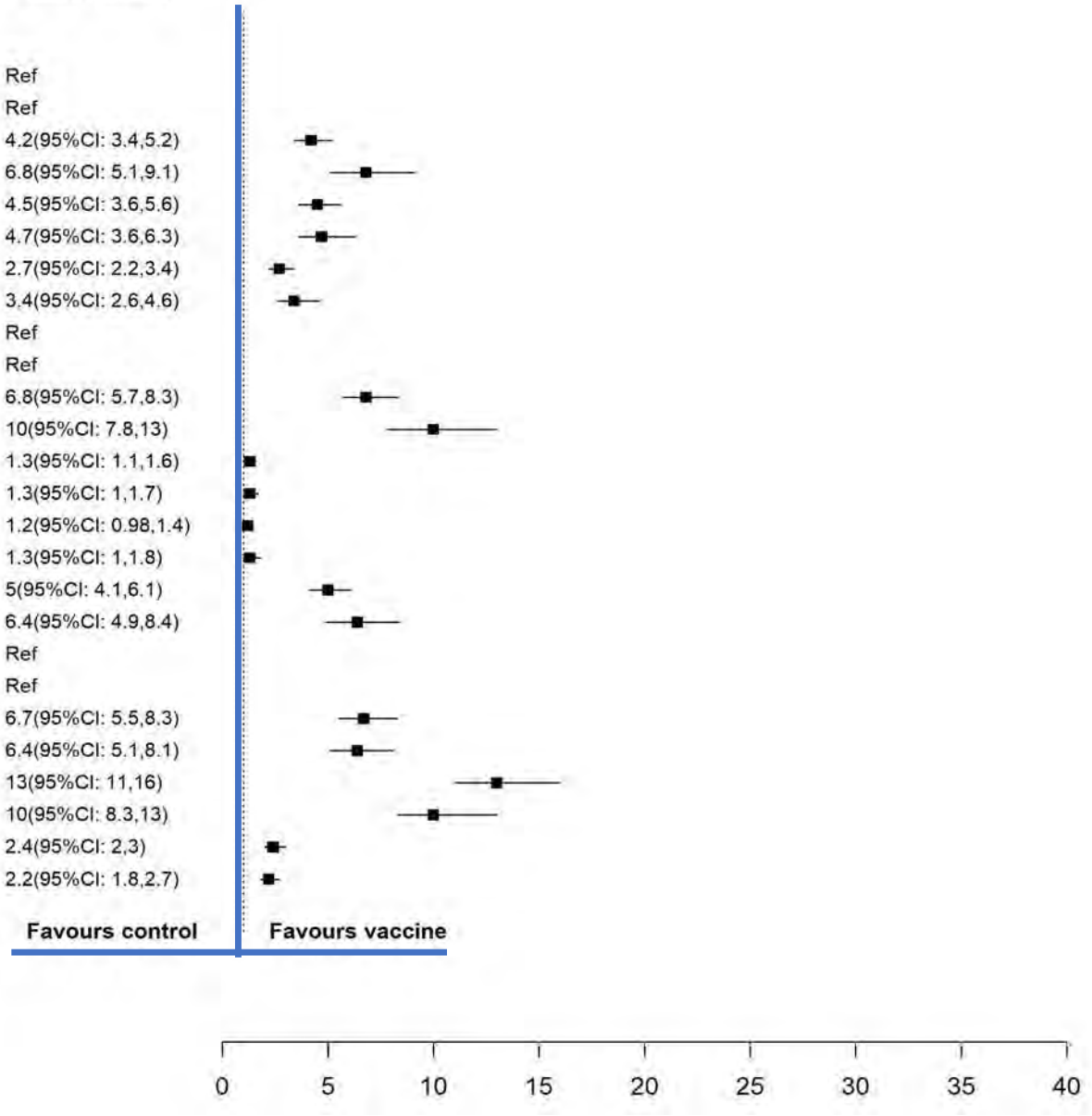
A) AZ/AZ primed population

B) Pfz-BNT/Pfz-BNT primed population

Across all three groups (A,B,C), we accounted for possible effects of participants' site, study baseline age, interval between 1st and 2nd dose, interval between 2nd and 3rd dose, and baseline immunogenicity. This was done using **Geometric Mean Ratios (GMRs)** of study vaccines by age group in each study group (A,B,C,).

BNT/BNT + dose 3 GMR d28 - Anti Spike IgG

		GM (95%CI)	GMR (95%CI)
Anti-spike IgG, ELU/ml			
Control-A	***<70***	3160(2603-3835) [n=59]	Ref
	70+	1954(1413-2702) [n=51]	Ref
ChAd	***<70***	12440(10420-14852) [n=57]	4.2(95%CI: 3.4,5.2)
	70+	14961(12065-18551) [n=40]	6.8(95%CI: 5.1,9.1)
NVX	***<70***	12635(10032-15915) [n=54]	4.5(95%CI: 3.6,5.6)
	70+	9130(6783-12289) [n=47]	4.7(95%CI: 3.6,6.3)
NVX-half	***<70***	9054(7281-11260) [n=56]	2.7(95%CI: 2.2,3.4)
	70+	7920(6031-10401) [n=42]	3.4(95%CI: 2.6,4.6)
Control-B	***<70***	3843(3095-4770) [n=51]	Ref
	70+	2571(2029-3257) [n=43]	Ref
BNT	***<70***	24781(21353-28760) [n=51]	6.8(95%CI: 5.7,8.3)
	70+	30326(25054-36709) [n=45]	10(95%CI: 7.8,13)
VLA	***<70***	4996(4189-5959) [n=55]	1.3(95%CI: 1.1,1.6)
	70+	3365(2703-4189) [n=44]	1.3(95%CI: 1,1.7)
VLA-half	***<70***	3766(3183-4457) [n=53]	1.2(95%CI: 0.98,1.4)
	70+	3668(2817-4775) [n=45]	1.3(95%CI: 1,1.8)
Ad26	***<70***	17312(13678-21911) [n=43]	5(95%CI: 4.1,6.1)
	70+	16855(13360-21264) [n=44]	6.4(95%CI: 4.9,8.4)
Control-C	***<70***	3194(2492-4094) [n=50]	Ref
	70+	2865(2271-3615) [n=48]	Ref
BNT-half	***<70***	25583(20932-31268) [n=51]	6.7(95%CI: 5.5,8.3)
	70+	20310(16564-24903) [n=41]	6.4(95%CI: 5.1,8.1)
MOD	***<70***	44547(38424-51645) [n=47]	13(95%CI: 11,16)
	70+	25118(17698-35650) [n=44]	10(95%CI: 8.3,13)
CVn	***<70***	8224(6983-9685) [n=49]	2.4(95%CI: 2,3)
	70+	6958(5266-9193) [n=42]	2.2(95%CI: 1.8,2.7)



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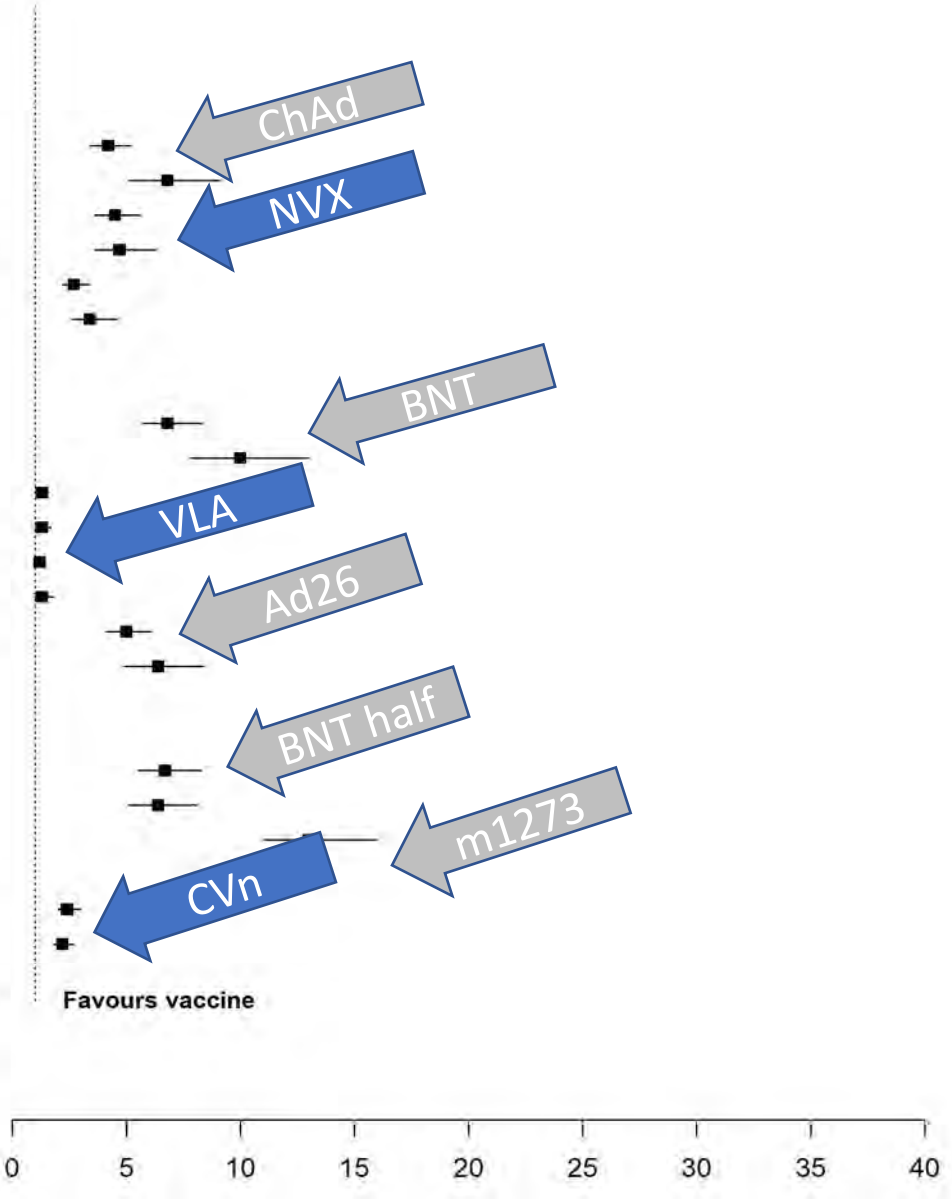
BNT/BNT + dose 3 GMR d28 - Anti Spike IgG

		GM (95%CI)	GMR (95%CI)
Anti-spike IgG, ELU/ml			
Control-A	*<70*	3160(2603-3835) [n=59]	Ref
	70+	1954(1413-2702) [n=51]	Ref
ChAd	*<70*	12440(10420-14852) [n=57]	4.2(95%CI: 3.4,5.2)
	70+	14961(12065-18551) [n=40]	6.8(95%CI: 5.1,9.1)
NVX	*<70*	12635(10032-15915) [n=54]	4.5(95%CI: 3.6,5.6)
	70+	9130(6783-12289) [n=47]	4.7(95%CI: 3.6,6.3)
NVX-half	*<70*	9054(7281-11260) [n=56]	2.7(95%CI: 2.2,3.4)
	70+	7920(6031-10401) [n=42]	3.4(95%CI: 2.6,4.6)
Control-B	*<70*	3843(3095-4770) [n=51]	Ref
	70+	2571(2029-3257) [n=43]	Ref
BNT	*<70*	24781(21353-28760) [n=51]	6.8(95%CI: 5.7,8.3)
	70+	30326(25054-36709) [n=45]	10(95%CI: 7.8,13)
VLA	*<70*	4996(4189-5959) [n=55]	1.3(95%CI: 1.1,1.6)
	70+	3365(2703-4189) [n=44]	1.3(95%CI: 1,1.7)
VLA-half	*<70*	3766(3183-4457) [n=53]	1.2(95%CI: 0.98,1.4)
	70+	3668(2817-4775) [n=45]	1.3(95%CI: 1,1.8)
Ad26	*<70*	17312(13678-21911) [n=43]	5(95%CI: 4.1,6.1)
	70+	16855(13360-21264) [n=44]	6.4(95%CI: 4.9,8.4)
Control-C	*<70*	3194(2492-4094) [n=50]	Ref
	70+	2865(2271-3615) [n=48]	Ref
BNT-half	*<70*	25583(20932-31268) [n=51]	6.7(95%CI: 5.5,8.3)
	70+	20310(16564-24903) [n=41]	6.4(95%CI: 5.1,8.1)
MOD	*<70*	44547(38424-51645) [n=47]	13(95%CI: 11,16)
	70+	25118(17698-35650) [n=44]	10(95%CI: 8.3,13)
CVn	*<70*	8224(6983-9685) [n=49]	2.4(95%CI: 2,3)
	70+	6958(5266-9193) [n=42]	2.2(95%CI: 1.8,2.7)



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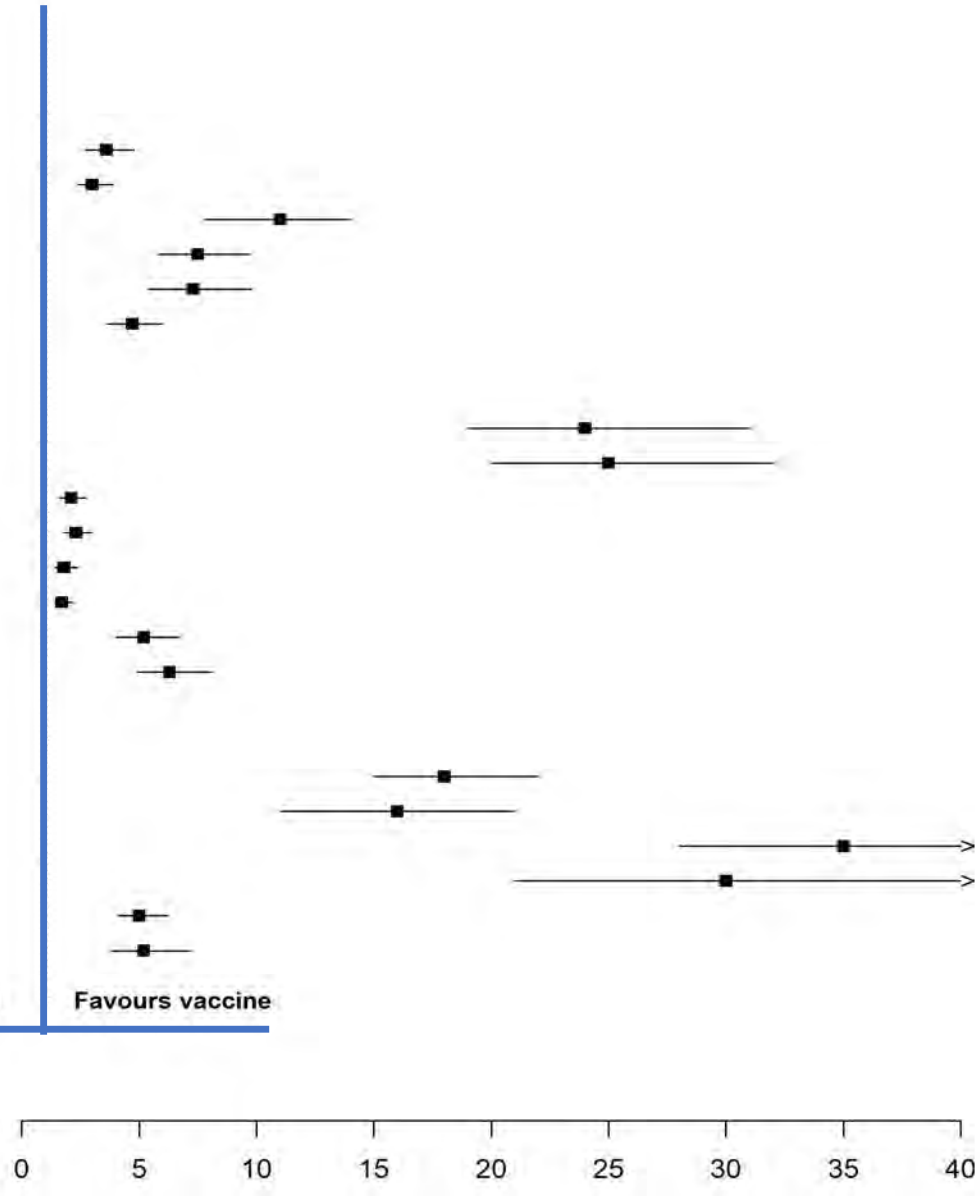
ChAd/ChAd + dose 3 GMR d28 - Anti Spike IgG

		GM (95%CI)	GMR (95%CI)
Anti-spike IgG, ELU/ml			
Control-A	<70	800(629-1016) [n=45]	Ref
	70+	774(579-1034) [n=45]	Ref
ChAd	<70	2828(2246-3560) [n=48]	3.6(95%CI: 2.7,4.8)
	70+	2152(1653-2802) [n=51]	3(95%CI: 2.4,3.9)
NVX	<70	8389(6599-10665) [n=47]	11(95%CI: 7.8,14)
	70+	5822(4495-7541) [n=48]	7.5(95%CI: 5.8,9.7)
NVX-half	<70	6222(4660-8309) [n=50]	7.3(95%CI: 5.4,9.8)
	70+	3387(2643-4341) [n=47]	4.7(95%CI: 3.6,6)
Control-B	<70	815(638-1041) [n=36]	Ref
	70+	731(555-962) [n=55]	Ref
BNT	<70	22479(18276-27648) [n=41]	24(95%CI: 19,31)
	70+	19091(15554-23432) [n=52]	25(95%CI: 20,32)
VLA	<70	1679(1280-2203) [n=42]	2.1(95%CI: 1.6,2.7)
	70+	1974(1505-2589) [n=51]	2.3(95%CI: 1.8,3)
VLA-half	<70	1702(1337-2166) [n=45]	1.8(95%CI: 1.4,2.4)
	70+	1250(975-1602) [n=58]	1.7(95%CI: 1.4,2.2)
Ad26	<70	5582(4415-7057) [n=44]	5.2(95%CI: 4,6.7)
	70+	5464(4266-6998) [n=54]	6.3(95%CI: 4.9,8.1)
Control-C	<70	853(649-1121) [n=46]	Ref
	70+	851(637-1138) [n=55]	Ref
BNT-half	<70	17228(14300-20755) [n=44]	18(95%CI: 15,22)
	70+	15217(11549-20049) [n=59]	16(95%CI: 11,21)
MOD	<70	35522(29205-43204) [n=45]	35(95%CI: 28,43)
	70+	27702(21337-35966) [n=51]	30(95%CI: 21,41)
CVn	<70	4000(3363-4757) [n=49]	5(95%CI: 4.1,6.2)
	70+	3992(3052-5220) [n=54]	5.2(95%CI: 3.8,7.2)



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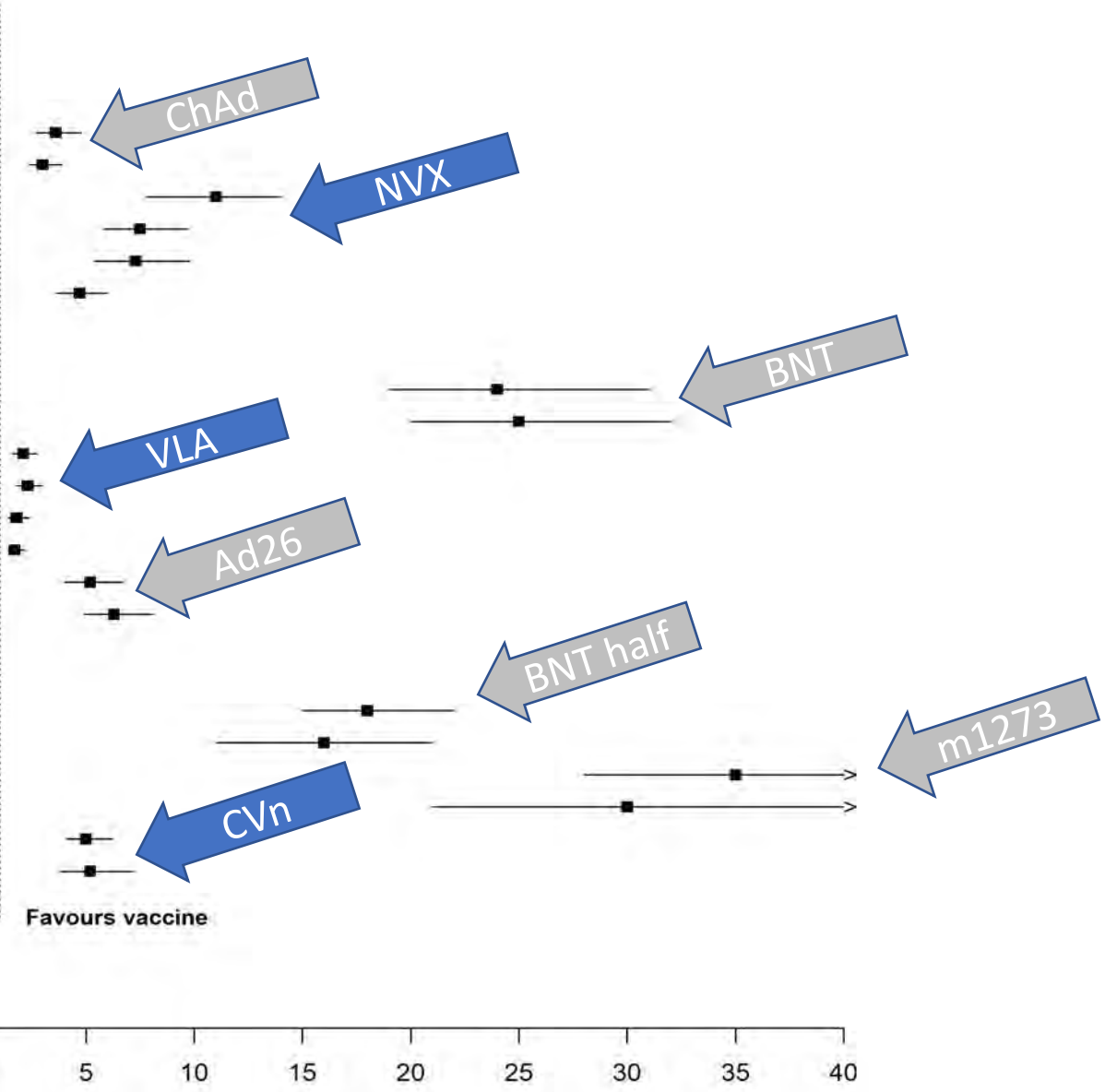
ChAd/ChAd + dose 3 GMR d28 - Anti Spike IgG

		GM (95%CI)	GMR (95%CI)
Anti-spike IgG, ELU/ml			
Control-A	<70	800(629-1016) [n=45]	Ref
	70+	774(579-1034) [n=45]	Ref
ChAd	<70	2828(2246-3560) [n=48]	3.6(95%CI: 2.7,4.8)
	70+	2152(1653-2802) [n=51]	3(95%CI: 2.4,3.9)
NVX	<70	8389(6599-10665) [n=47]	11(95%CI: 7.8,14)
	70+	5822(4495-7541) [n=48]	7.5(95%CI: 5.8,9.7)
NVX-half	<70	6222(4660-8309) [n=50]	7.3(95%CI: 5.4,9.8)
	70+	3387(2643-4341) [n=47]	4.7(95%CI: 3.6,6)
Control-B	<70	815(638-1041) [n=36]	Ref
	70+	731(555-962) [n=55]	Ref
BNT	<70	22479(18276-27648) [n=41]	24(95%CI: 19,31)
	70+	19091(15554-23432) [n=52]	25(95%CI: 20,32)
VLA	<70	1679(1280-2203) [n=42]	2.1(95%CI: 1.6,2.7)
	70+	1974(1505-2589) [n=51]	2.3(95%CI: 1.8,3)
VLA-half	<70	1702(1337-2166) [n=45]	1.8(95%CI: 1.4,2.4)
	70+	1250(975-1602) [n=58]	1.7(95%CI: 1.4,2.2)
Ad26	<70	5582(4415-7057) [n=44]	5.2(95%CI: 4,6.7)
	70+	5464(4266-6998) [n=54]	6.3(95%CI: 4.9,8.1)
Control-C	<70	853(649-1121) [n=46]	Ref
	70+	851(637-1138) [n=55]	Ref
BNT-half	<70	17228(14300-20755) [n=44]	18(95%CI: 15,22)
	70+	15217(11549-20049) [n=59]	16(95%CI: 11,21)
MOD	<70	35522(29205-43204) [n=45]	35(95%CI: 28,43)
	70+	27702(21337-35966) [n=51]	30(95%CI: 21,41)
CVn	<70	4000(3363-4757) [n=49]	5(95%CI: 4.1,6.2)
	70+	3992(3052-5220) [n=54]	5.2(95%CI: 3.8,7.2)



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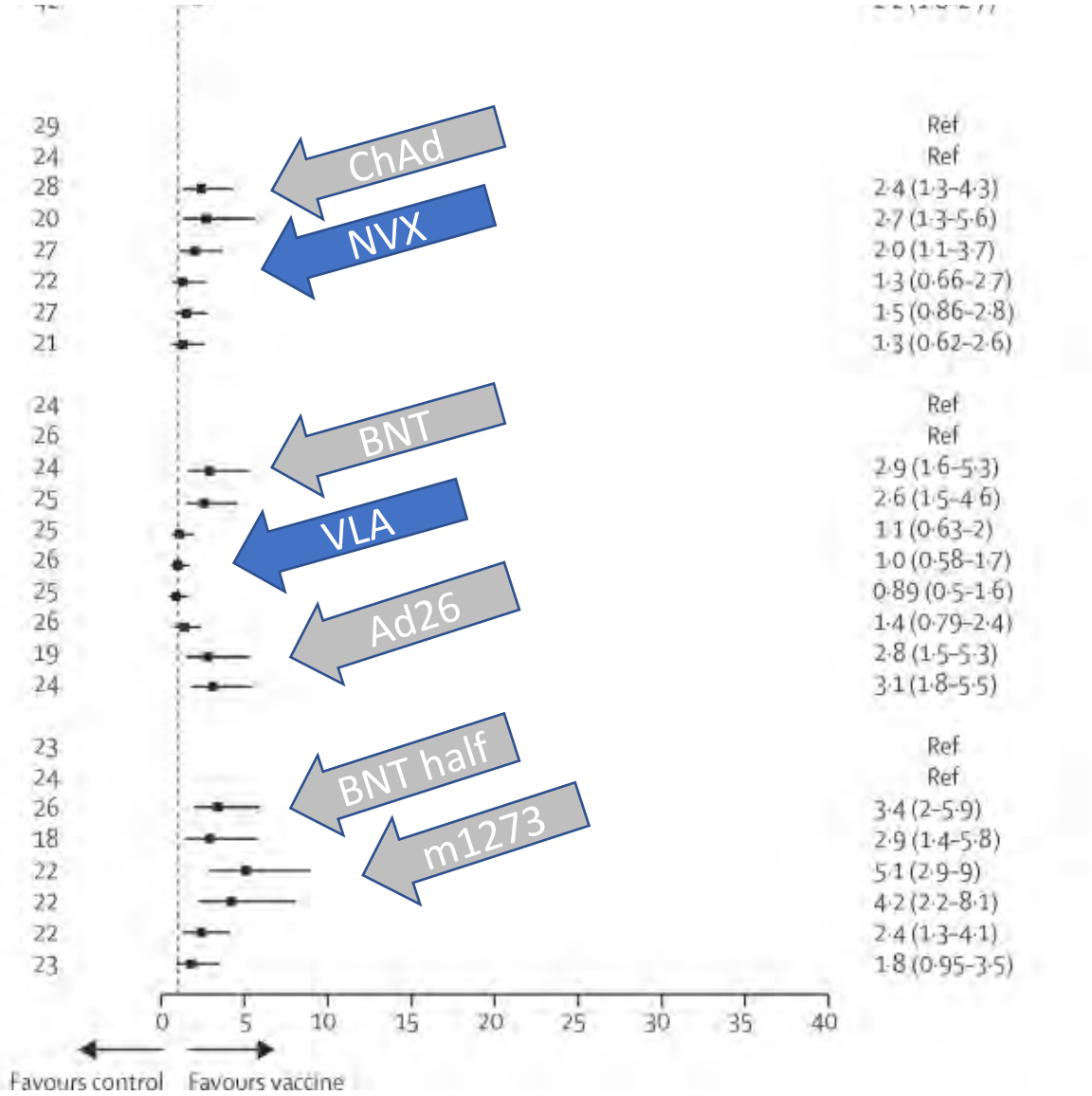
Pfizer primed: cellular response

Cellular response (wild-type), spot forming cells per 10^6 peripheral blood mononuclear cells				
Group A				
Control	<70	38 (25–59)	29	Ref
	≥70	30 (16–57)	24	Ref
ChAd	<70	105 (67–164)	28	2·4 (1·3–4·3)
	≥70	84 (45–156)	20	2·7 (1·3–5·6)
NVX	<70	69 (42–111)	27	2·0 (1·1–3·7)
	≥70	45 (22–92)	22	1·3 (0·66–2·7)
NVX half	<70	46 (27–78)	27	1·5 (0·86–2·8)
	≥70	25 (14–46)	21	1·3 (0·62–2·6)
Group B				
Control	<70	39 (25–59)	24	Ref
	≥70	23 (14–38)	26	Ref
BNT	<70	92 (67–127)	24	2·9 (1·6–5·3)
	≥70	76 (53–111)	25	2·6 (1·5–4·6)
VLA	<70	47 (31–72)	25	1·1 (0·63–2)
	≥70	24 (16–36)	26	1·0 (0·58–1·7)
VLA half	<70	37 (22–64)	25	0·89 (0·5–1·6)
	≥70	39 (23–66)	26	1·4 (0·79–2·4)
Ad26	<70	114 (55–236)	19	2·8 (1·5–5·3)
	≥70	109 (64–187)	24	3·1 (1·8–5·5)
Group C				
Control	<70	25 (13–47)	23	Ref
	≥70	19 (12–31)	24	Ref
BNT half	<70	101 (70–146)	26	3·4 (2–5·9)
	≥70	54 (28–105)	18	2·9 (1·4–5·8)
m1273	<70	143 (82–250)	22	5·1 (2·9–9)
	≥70	88 (46–168)	22	4·2 (2·2–8·1)
CVn	<70	67 (45–101)	22	2·4 (1·3–4·1)
	≥70	33 (19–58)	23	1·8 (0·95–3·5)



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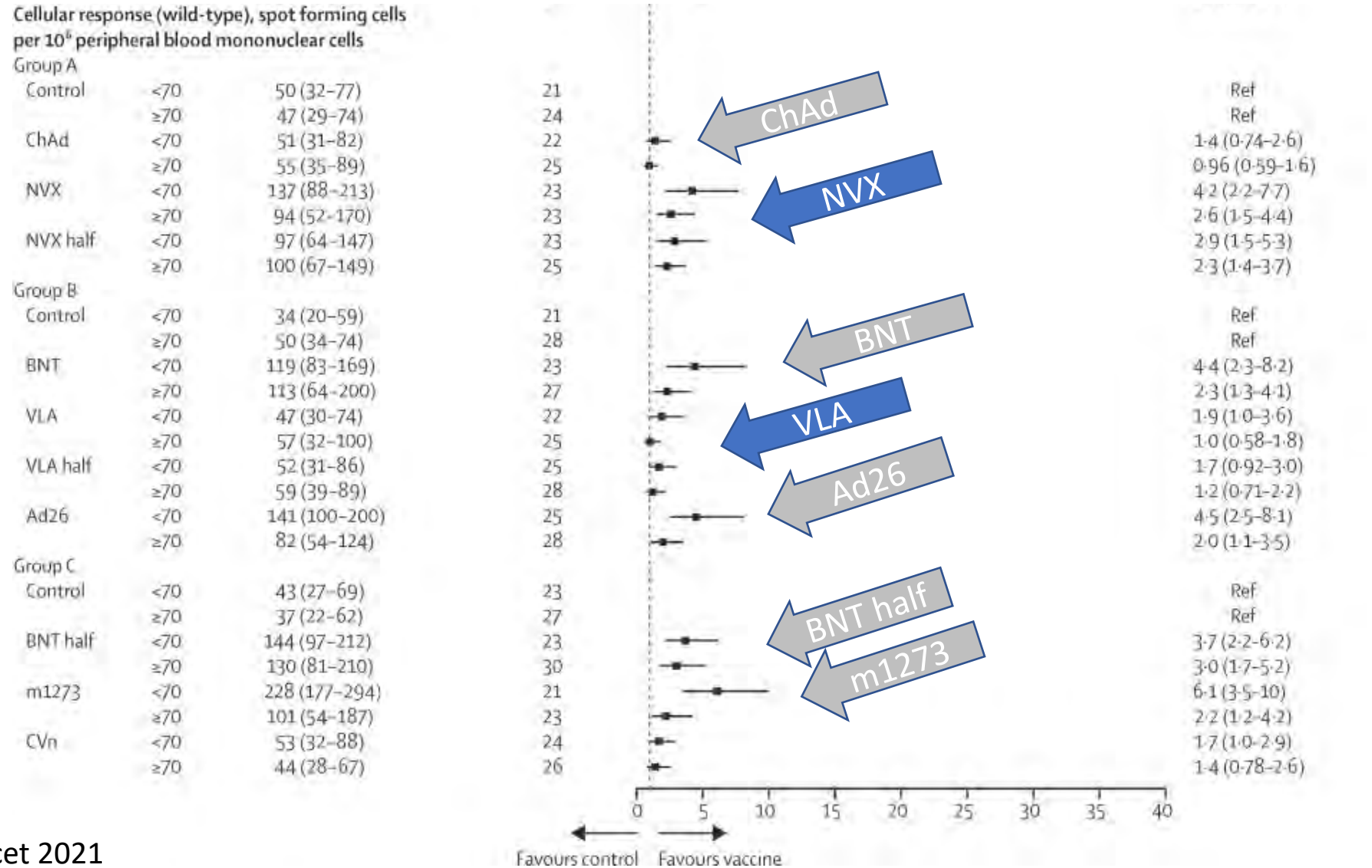
AZ primed: cellular response



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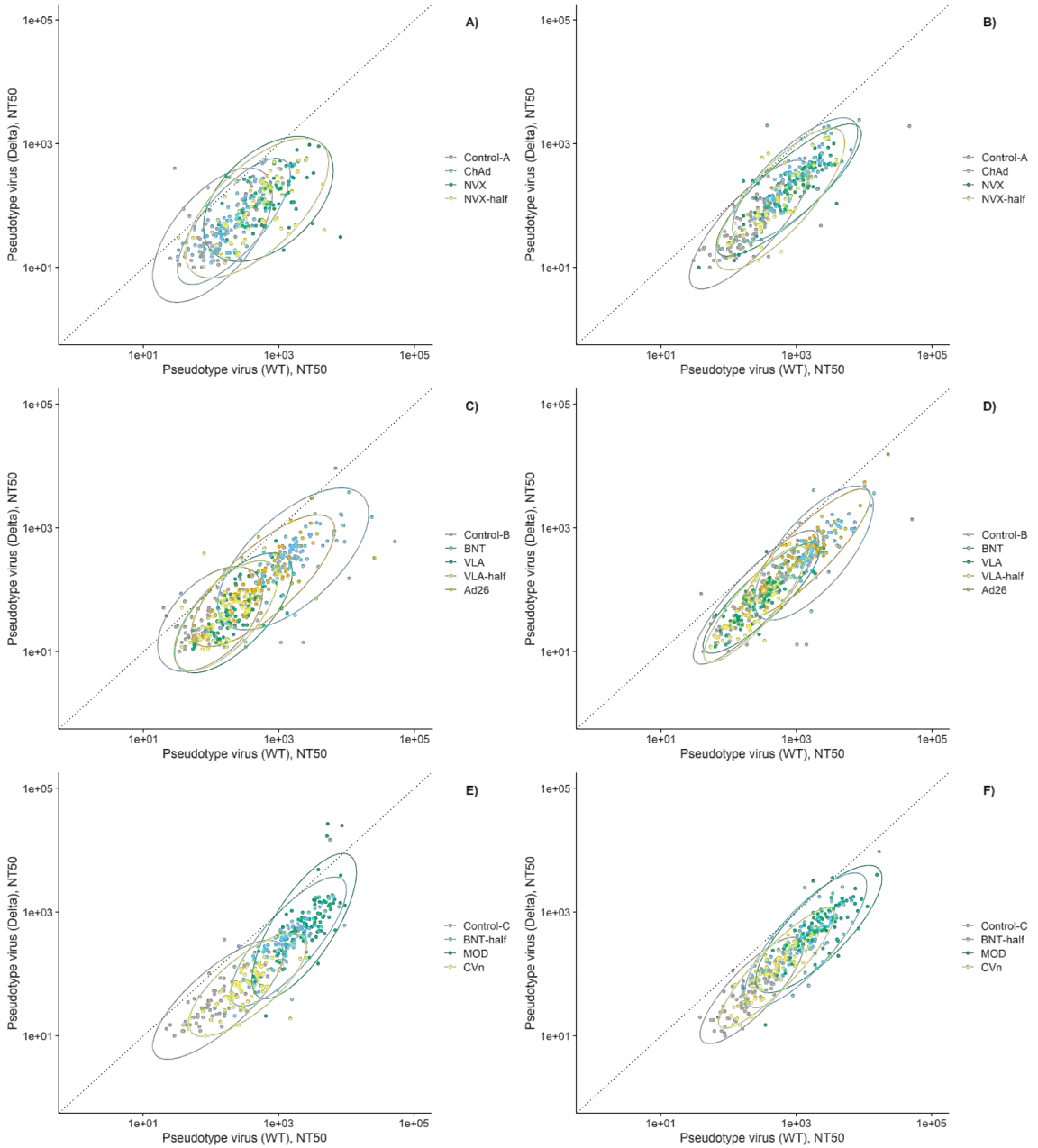
What about variants of concern?

Pseudo-neutralization against wild-type and Delta variants

Delta



Wild type

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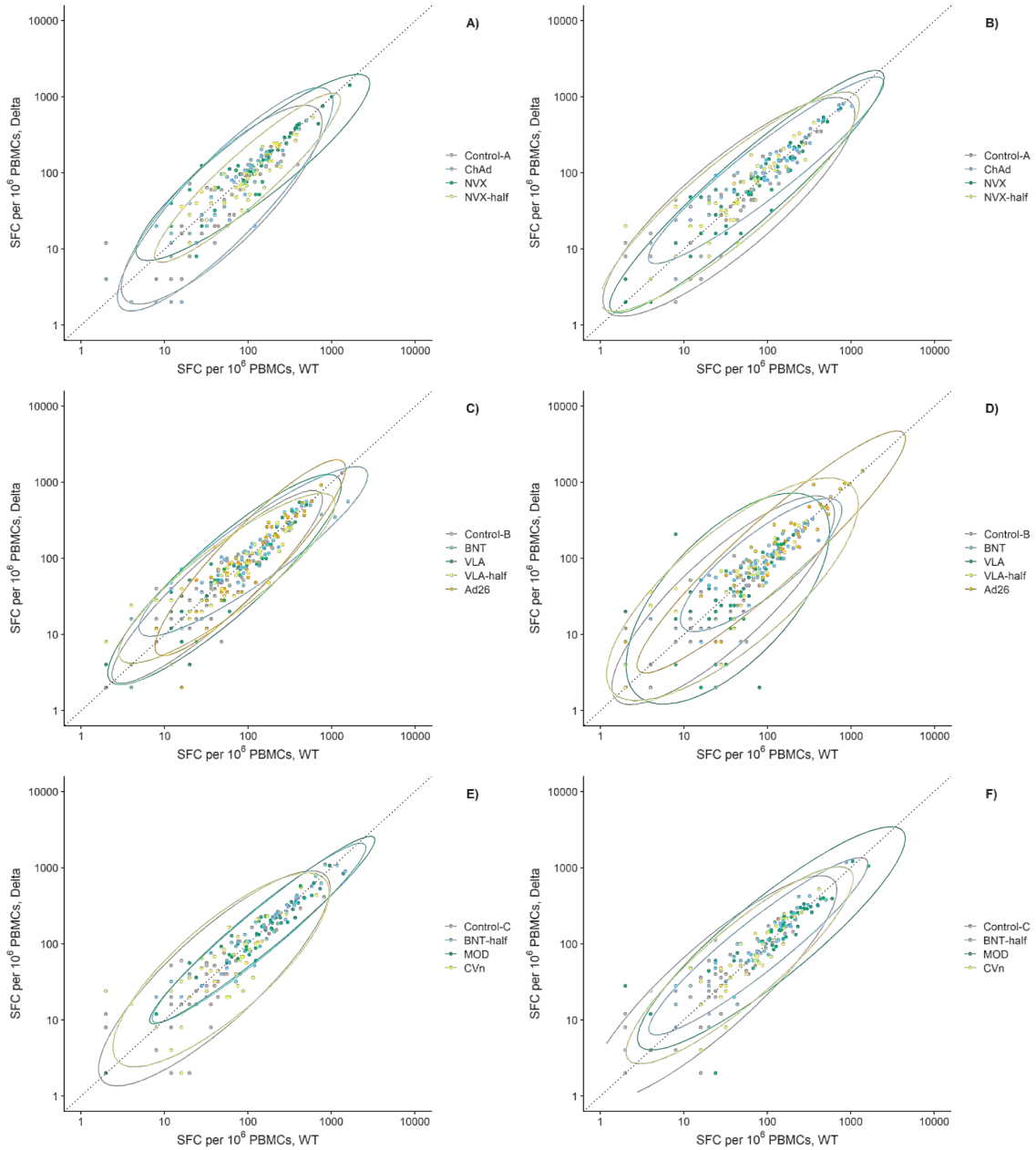
Cellular Immunity against wild-type and Delta variants (Interferon-gamma secreting T cells, detected by ELISPOT)

Delta



Wild type

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COV-BOOST
Evaluating COVID-19 vaccine boosters

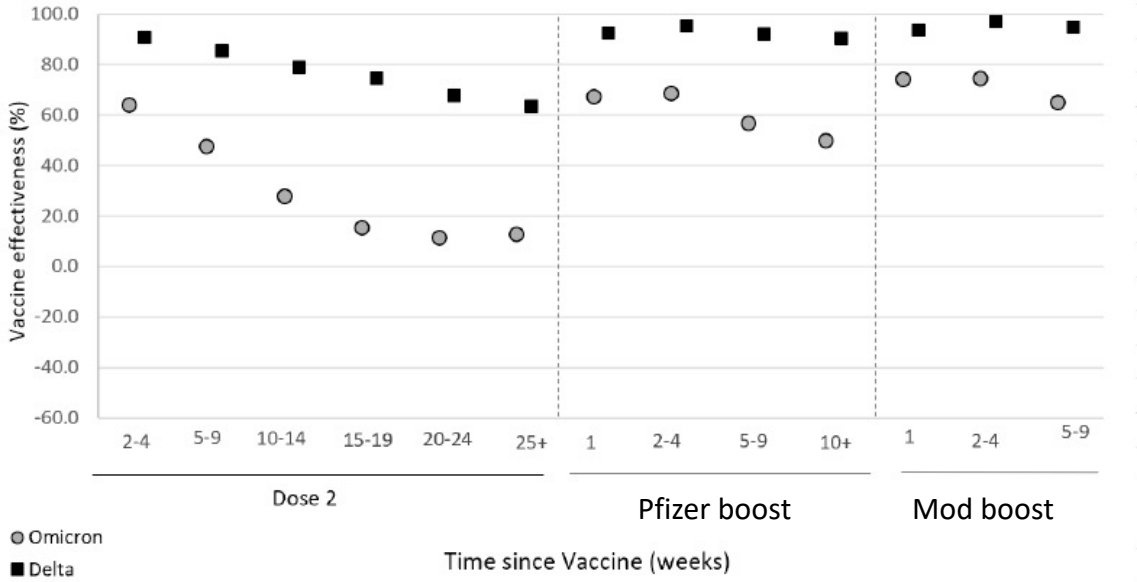
Summary

- Great flexibility in use of mixed schedules
- For Pfizer primed
  - All but Valneeva (whole virus) and Curevac (low dose RNA) generate humoral immune boost
- For AZ primed
  - Humoral boost greatest with Pfizer, Moderna, Ad26, Novavax

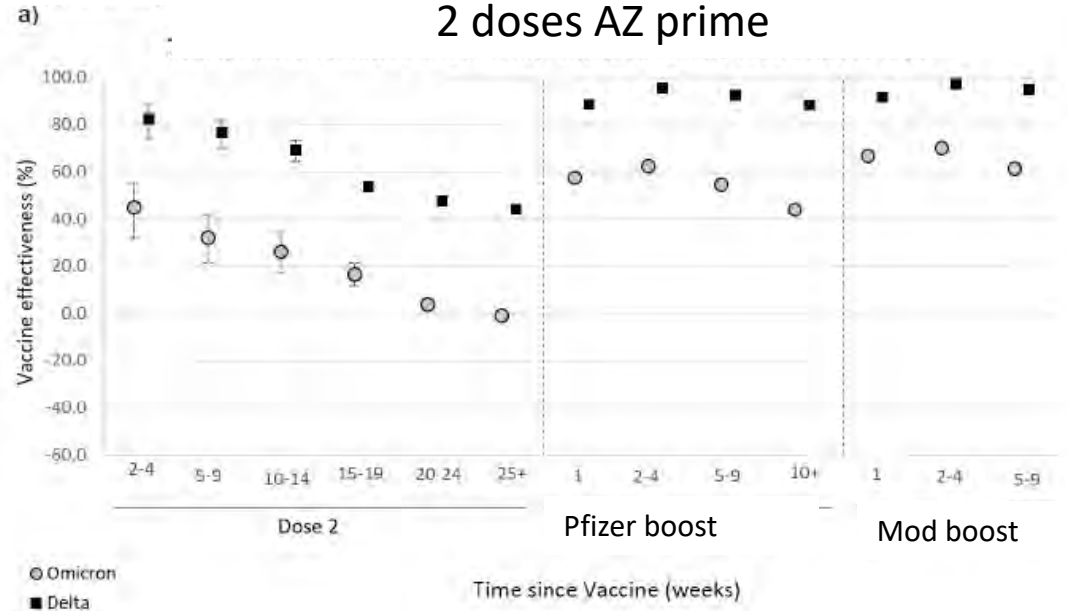
UK HSA data: protection against symptomatic infection

Omicron
Delta

2 doses Pfizer prime



2 doses AZ prime



2 doses Moderna prime

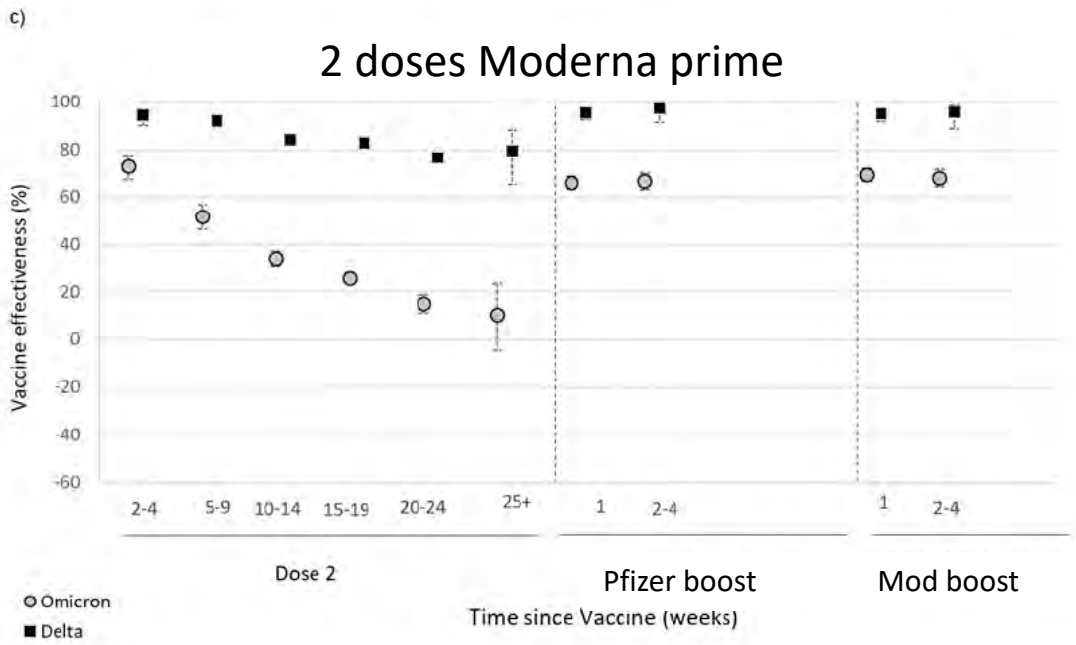
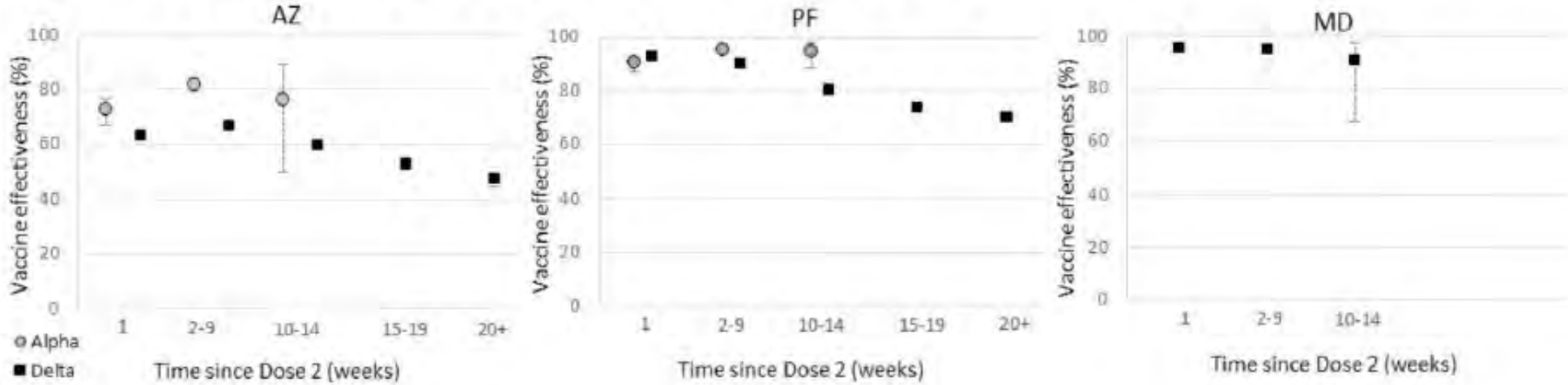
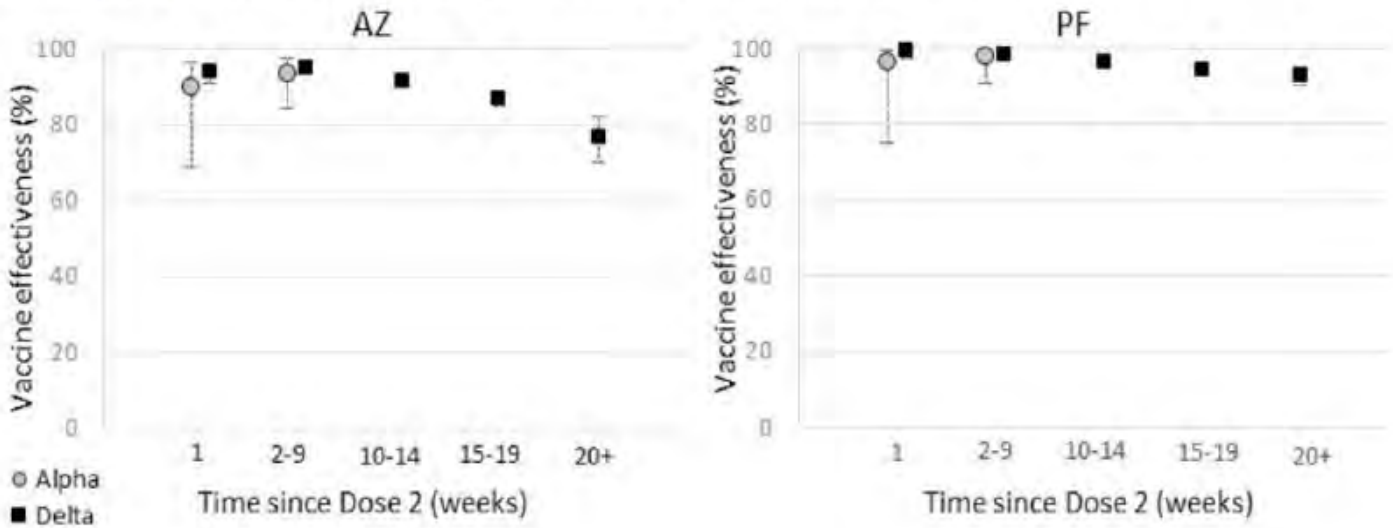


Figure 1. Vaccine effectiveness against Delta symptomatic disease among individuals aged over 16, with 2 doses of Vaxzevria (AZ), Comirnaty (PF) or Spikevax (MD) in England and 95% confidence intervals



Symptomatic disease

Figure 3. Vaccine effectiveness against Delta hospitalisation among individuals aged over 16, with 2 doses of Vaxzevria (AZ), Comirnaty (PF) or Spikevax (MD) in England and 95% confidence intervals



Hospitalisation

UK HSA

Ongoing work

- 3 month anti-Spike IgG being analysed now – will give indication of how fast peak antibody declines
- “Late boost” arms mirror deployment in general population:
  - Randomised people in control groups in A, B and C to receive
    - Pfizer
    - half Pfizer
    - Half Moderna 7-9 months after the 2nd dose
- Fourth dose studies underway

Summary

- There is great flexibility in use of mixed schedules
- There is a transient increased reactogenicity with mixed adenoviral vectored and mRNA vaccines
- Schedules with mRNA generate highest antibody titres
- Adenoviral vectored vaccine followed by different boost generates highest T cells
- An inactivated whole virus vaccine generated minimal boost after two doses of mRNA

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  - Peter Lockey
- CEPI
  - Jakob Kramer
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  - Nick Andrews
- Laboratories
  - Nexelis
  - Oxford Immunotech
  - Public Health England
    - Bassam Hallis
    - Sue Charlton
  - Screaton Laboratory
    - Gavin Screaton
    - Juthathip Mongkolsapaya
    - Wanwisa Dejnirattisai
- Novavax
  - Seth Toback
  - Lisa Heimbach
- DSMB
- TSC

https://comcovstudy.org.uk/

What side effect gradings mean

COV-BOOST
Evaluating COVID-19 vaccine boosters

Formal reporting of side effect grading is detailed in the study protocol

Overall systemic effects:

MILD	**Transient or mild discomfort (< 48 hours)** **No interference with activity** **No medical intervention/therapy required**
MOD	**Mild to moderate limitation in activity** **Some assistance may be needed** **No or minimal medical intervention/therapy required**
SEVERE	**Marked limitation in activity** **Some assistance usually required** **Medical intervention/therapy required**

What side effect gradings mean

- *Formal reporting of side effect grading is detailed in the study protocol, e.g.*

Pain

- Severe = pain that prevents daily activity
- Moderate = pain that interferes with daily activity

Induration/swelling at injection site

- Severe = >10 cm or that prevents daily activity
- Moderate = 5.1-10 cm or that interferes with daily activity

Fever

- Severe = 39.0 – 40 ^{o}C
- Moderate = 38.5 – 38.9 ^{o}C

COV-BOOST

Evaluating COVID-19 vaccine boosters

University of Southampton | NHS University Hospital Southampton NHS Foundation Trust

Chief Investigator Saul Faust
Munro et al, Lancet Dec 2021

Neutralising antibodies following Pfizer 3rd dose

Wild type

Delta

	Prime with ChAd/ChAd					Prime with BNT/BNT				
	Control (n=93)	BNT (n=95)	VLA (n=95)	VLA half (n=107)	Ad26 (n=101)	Control (n=97)	BNT (n=96)	VLA (n=99)	VLA half (n=98)	Ad26 (n=89)
SARS-CoV-2 anti-spike IgG, ELU/mL										
GMC*	763 (630–924; n=91)	20 517 (17 718–23 757; n=93)	1835 (1514–2224; n=93)	1430 (1198–1707; n=103)	5517 (4647–6548; n=98)	3197 (2714–3767; n=94)	27 242 (24148–30 731; n=96)	4204 (3640–4856; n=98)	3721 (3200–4326; n=98)	17 079 (14 488–20 133; n=87)
GMR†	Ref	24·48 (19·5–30·79)	2·20 (1·75–2·77)	1·81 (1·45–2·27)	5·84 (4·65–7·33)	Ref	8·11 (6·59–9·99)	1·31 (1·07–1·62)	1·25 (1·01–1·54)	5·63 (4·55–6·97)
Pseudotype virus neutralising antibody (wild-type), NT_{50}										
GMT*	69·6 (57·2–84·6; n=91)	1621 (1314–1998; n=93)	202 (166–247; n=89)	147 (124–174; n=95)	563 (454–698; n=95)	205 (167–253; n=93)	1789 (1520–2107; n=95)	289 (244–342; n=91)	234 (200–272; n=87)	1441 (1188–1749; n=75)
GMR†	Ref	21·58 (16·93–27·51)	2·68 (2·10–3·43)	2·01 (1·57–2·55)	6·85 (5·37–8·73)	Ref	8·35 (6·88–10·14)	1·38 (1·14–1·68)	1·22 (1·00–1·49)	7·84 (6·37–9·64)
Pseudotype virus neutralising antibody (delta), NT_{50}										
GMT*	20·4 (16·4–25·5; n=91)	315 (254–391; n=93)	35·2 (28·4–43·7; n=89)	31·1 (25·6–37·7; n=95)	125 (99–159; n=90)	56·5 (43·6–73·3; n=92)	392 (320–479; n=95)	67·1 (55·4–81·2; n=94)	54·7 (45·1–66·4; n=92)	418 (330–530; n=78)
GMR†	Ref	14·43 (10·97–18·98)	1·65 (1·25–2·17)	1·50 (1·14–1·96)	5·33 (4·04–7·03)	Ref	6·60 (5·10–8·53)	1·19 (0·92–1·54)	1·02 (0·79–1·32)	8·02 (6·12–10·50)
Live virus neutralising antibody, normalised NT_{50}										
GMT*	174 (139–218; n=30)	4899 (3955–6069; n=38)	354 (215–584; n=21)	301 (212–427; n=25)	1053 (691–1605; n=23)	756 (568–1007; n=34)	4603 (3685–5749; n=36)	836 (580–1207; n=20)	555 (407–756; n=23)	3535 (2459–5080; n=19)
GMR†	Ref	25·61 (18·07–36·31)	2·04 (1·37–3·05)	1·81 (1·23–2·65)	5·97 (4·03–8·84)	Ref	5·79 (4·25–7·90)	1·42 (0·98–2·06)	0·93 (0·65–1·33)	5·36 (3·67–7·83)

Testing against Omicron pending

COV-BOOST

Evaluating COVID-19 vaccine boosters

University of Southampton | NHS University Hospital Southampton NHS Foundation Trust

Chief Investigator Saul Faust
Munro et al, Lancet Dec 2021

Cellular Immune response following Pfizer 3rd dose

Wild type

Delta

	Prime with ChAd/ChAd					Prime with BNT/BNT				
	Control (n=93)	BNT (n=95)	VLA (n=95)	VLA half (n=107)	Ad26 (n=101)	Control (n=97)	BNT (n=96)	VLA (n=99)	VLA half (n=98)	Ad26 (n=89)
Cellular response (wild-type), spot forming cells per 10^6 peripheral blood mononuclear cells										
GM*	42·6 (30·9–58·8; n=49)	115·5 (81·7–163·3; n=50)	52·2 (36·3–75; n=47)	55·5 (40·4–76·3; n=53)	106·0 (80·1–140·4; n=53)	29·4 (21·0–41·2; n=50)	83·8 (65·4–107·2; n=49)	33·5 (24·7–45·4; n=51)	38·1 (26·1–55·5; n=51)	111·0 (71·8–171·6; n=43)
GMR‡	Ref	3·15 (2·08–4·76)	1·39 (0·92–2·11)	1·40 (0·93–2·11)	2·74 (1·82–4·12)	Ref	2·65 (1·78–3·95)	1·04 (0·69–1·55)	1·12 (0·75–1·66)	2·93 (1·93–4·44)
Cellular response (delta), spot forming cells per 10^6 peripheral blood mononuclear cells										
GM*	42·2 (30·5–58·3; n=49)	123·2 (93·0–163·3; n=50)	52·8 (36·9–75·6; n=47)	54·7 (41·5–72·0; n=53)	102·1 (74·4–140·2; n=53)	28·2 (19·9–39·9; n=50)	82·1 (65·7–102·7; n=49)	29·6 (20·9–42·0; n=51)	39·2 (27·2–56·6; n=51)	121·5 (78·9–187·0; n=43)
GMR‡	Ref	3·23 (2·15–4·86)	1·40 (0·93–2·12)	1·39 (0·93–2·08)	2·67 (1·79–4·00)	Ref	2·71 (1·78–4·13)	0·96 (0·63–1·47)	1·22 (0·80–1·85)	3·29 (2·12–5·11)
Cellular response (beta), spot forming cells per 10^6 peripheral blood mononuclear cells										
GM*	47·6 (35·2–64·4; n=49)	120·5 (88·0–165·0; n=50)	52·6 (36·3–76·3; n=47)	56·8 (41·0–78·7; n=53)	99·9 (72·6–137·6; n=53)	27·6 (19·9–38·5; n=50)	85·2 (69·8–103·9; n=49)	31·1 (22·5–42·9; n=51)	40·3 (28·1–57·7; n=51)	118·6 (78·3–179·7; n=43)
GMR‡	Ref	2·88 (1·89–4·38)	1·25 (0·82–1·90)	1·28 (0·85–1·94)	2·30 (1·52–3·48)	Ref	2·86 (1·92–4·28)	1·05 (0·70–1·56)	1·27 (0·85–1·89)	3·36 (2·21–5·10)

ChAd=ChAdOx1 nCoV-19 vaccine, Oxford–AstraZeneca. Control=quadrivalent meningococcal conjugate vaccine. BNT=BNT162b2 vaccine, Pfizer-BioNTech. VLA=VLA2001 vaccine, Valneva. VLA half=half dose of VLA2001 vaccine. Ad26=Ad26.COV2.S vaccine, Janssen. ELU=ELISA laboratory units. GMC=geometric mean concentration. GMR=geometric mean ratio. GM=geometric mean. GMT=geometric mean titre. NT_{50}=50% neutralising antibody titre. NT_{80}=80% neutralising antibody titre. *Data are GM (95% CI; number of samples available). †GMRs of the study vaccines were calculated by comparing to their corresponding controls in group A, B, or C, after adjusting for age group, site, baseline anti-spike IgG, interval between first and second dose, and interval between second and third dose; for primary endpoint of anti-spike IgG, 99% CIs were presented to account for multiple comparisons; for the secondary endpoints, 95% CIs were presented. ‡GMRs of the study vaccines were calculated by comparing to their corresponding controls in group A, B, or C, after adjusting for age group, site, baseline cellular response against wild-type, interval between first and second dose, and interval between second and third dose; 95% CIs were presented.

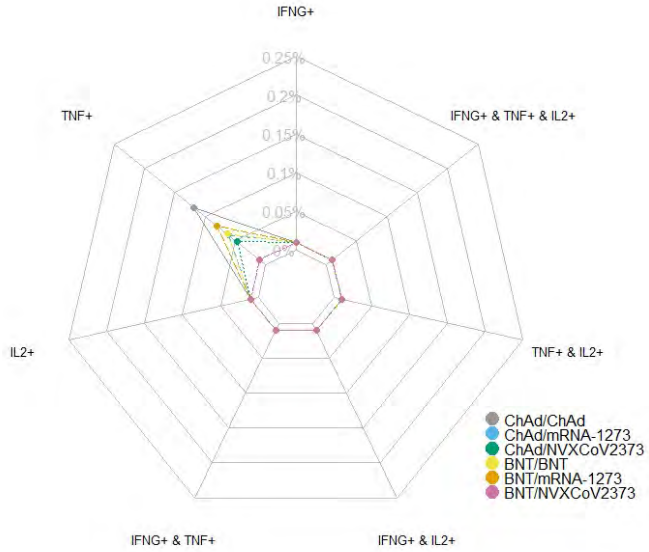
Table 6: **Immune responses by third dose vaccine allocation and priming vaccine schedule at 28 days post boost dose among the COVID-19-naive modified intention-to-treat population, group B**

Neutralising activity against variants of concern (live VNA)

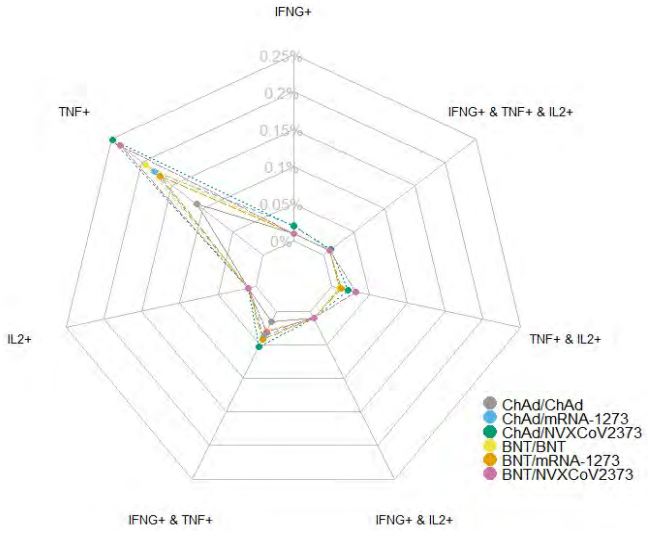
	Prime with ChAd (N= 41 – 52)				Prime with BNT (N=46 – 49)			
	ChAd/ChAd	ChAd/mRNA-1273	ChAd/NVX-CoV2373	P value	BNT/BNT	BNT/mRNA-1273	BNT/NVX-CoV2373	P value
WT	109 (70-168)	1660 (1289-2138)	449 (313-644)		1501(1188-1896)	1883 (1546-2294)	1109 (805-1529)	
Beta	25 (18-34)	368 (253-536)	114 (74-175)		405 (290-565)	603 (442-822)]	451 (305-666)	
Beta to WT ratio	**0.27** (0.18-0.42)	**0.26** (0.21-0.32)	**0.3** (0.24-0.37)	0.27	**0.29** (0.23-0.36)	**0.33** (0.27-0.4)	**0.43** (0.36-0.52)	0.03
Delta	41 (27-64)	661 (496-881)	159 (103-247)		697 (520-933)	873 (688-1107)	629 (444-891)	
Delta to WT ratio	**0.33** (0.27-0.42)	**0.42** (0.34-0.51)	**0.45** (0.38-0.54)	0.87	**0.48** (0.39-0.59)	**0.47** (0.39-0.55)	**0.57** (0.5-0.65)	0.12

Screaton lab

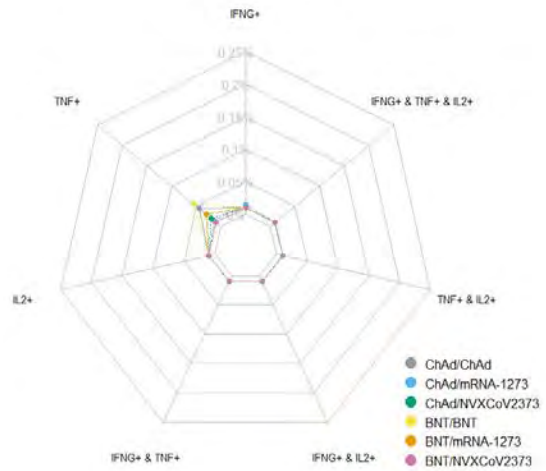
CD4+ at D0 (pre-boost)



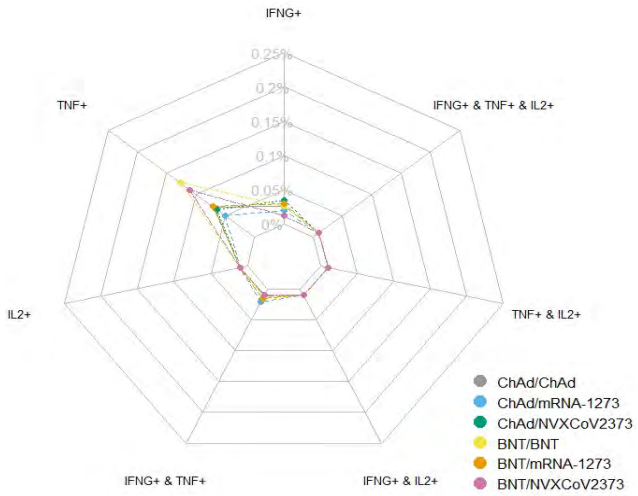
CD4+ at D14 post boost



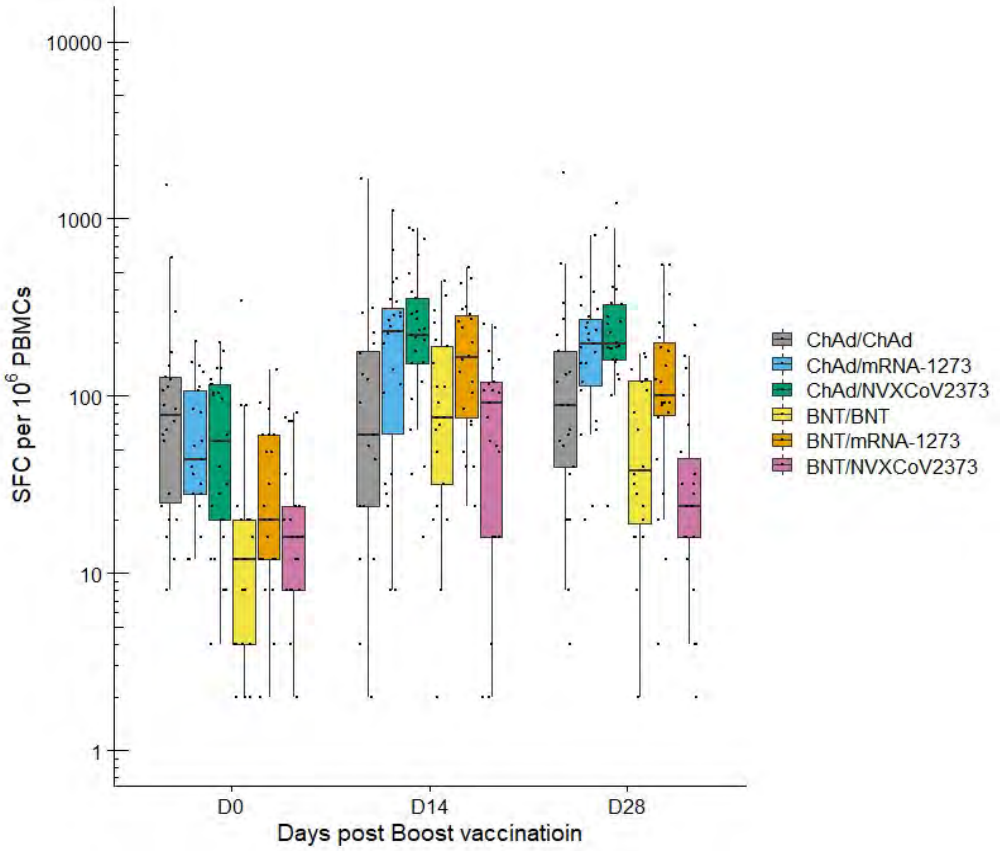
CD8+ at D0 (pre-boost)



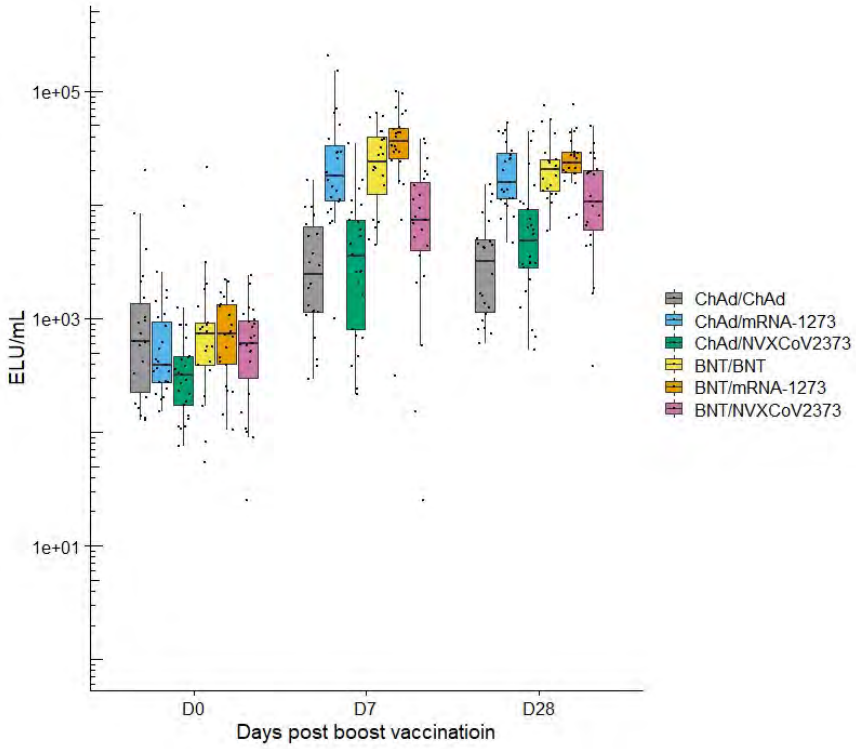
CD8+ at D14 post boost



T cell kinetics: immunology cohort only



IgG kinetics: immunology cohort only



- IgG rise ongoing to day 28 in groups receiving Novavax boost
- Will be evaluated again at 2 months post-boost