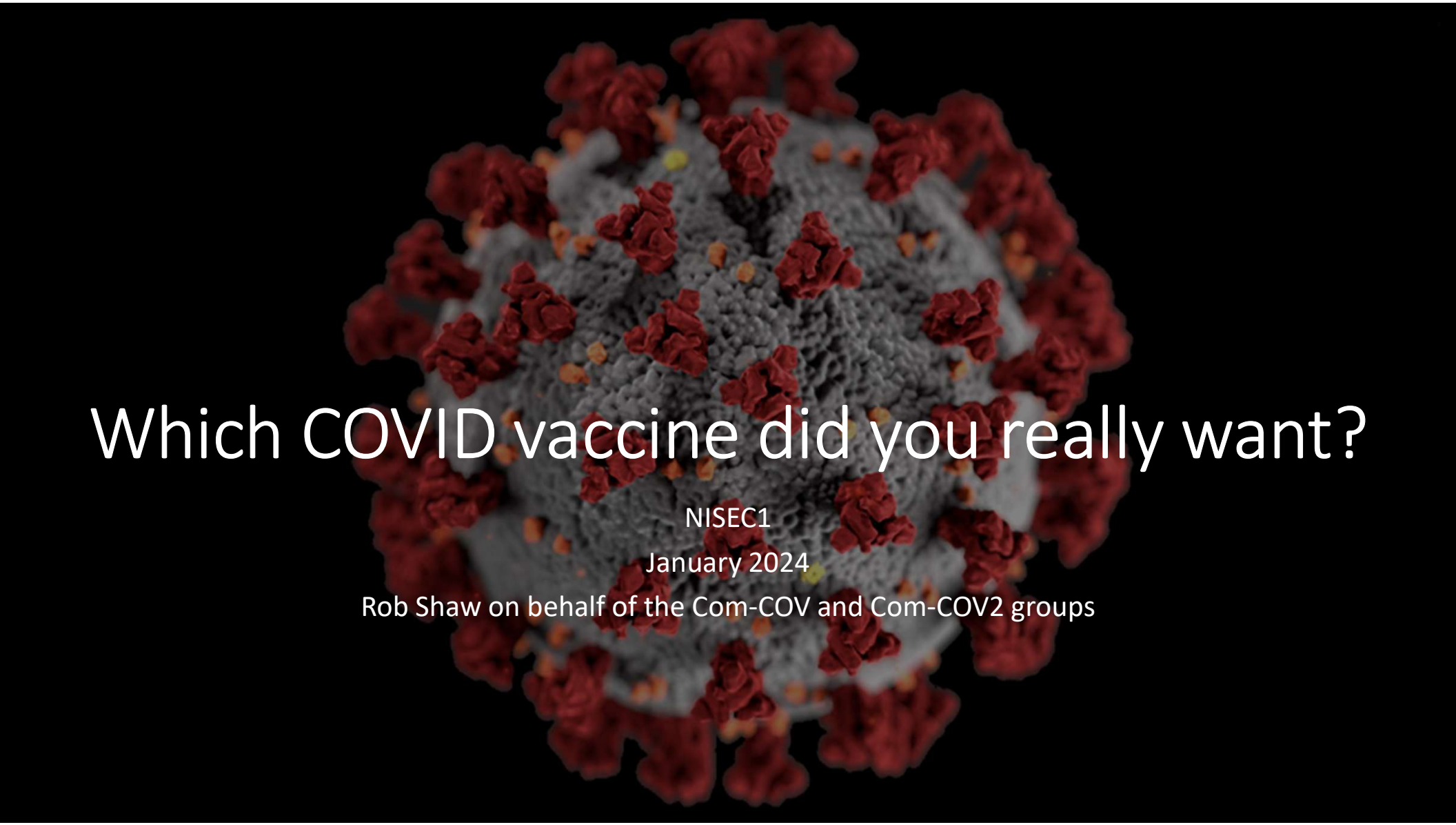
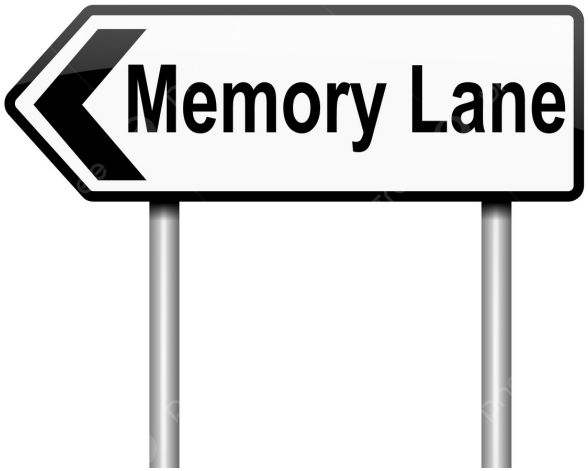


Which COVID vaccine did you really want?

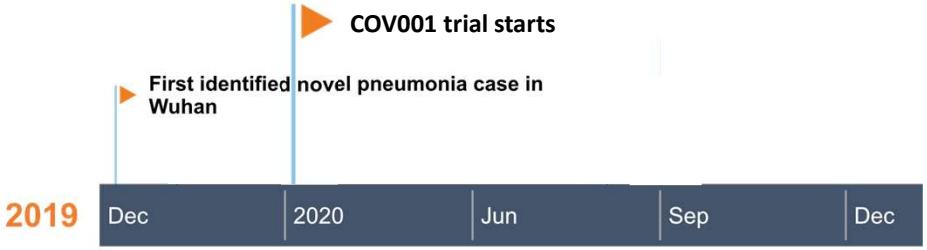
NISEC1

January 2024

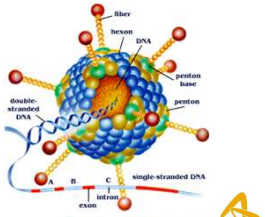
Rob Shaw on behalf of the Com-COV and Com-COV2 groups



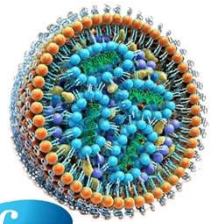
OXFORD
VACCINE GROUP



Vaccines were approaching emergency use authorization under regulation 174



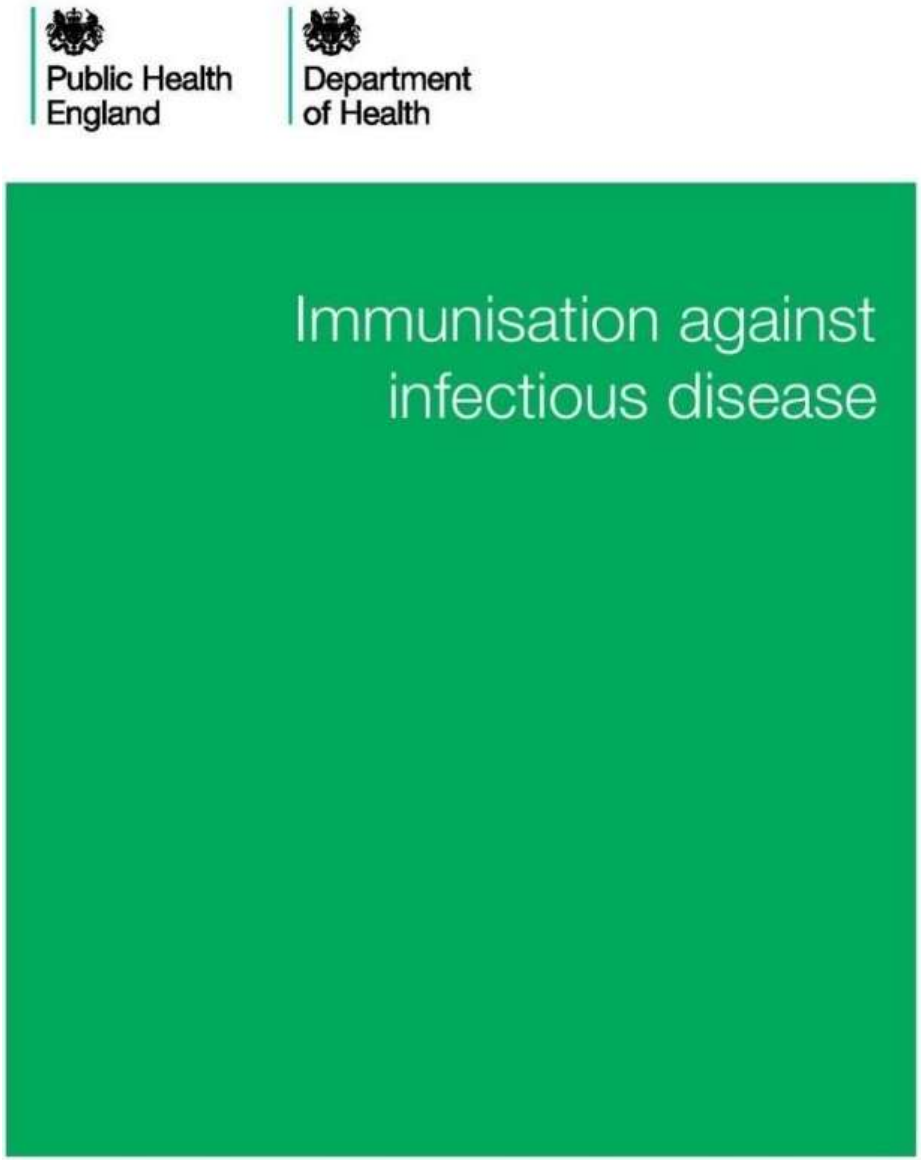
AstraZeneca



Pfizer
BIONTECH

Rationale for another trial

- Almost all vaccines are licensed as homologous schedules (including all COVID vaccines)
- Significant logistical challenges immunising large portions of the population in terms of geo-temporal coordination of vaccine stock
- Policy decisions regarding immunising many with 1 dose vs few with 2 doses in a vaccine-limited setting, by default increasing interval



INDEPENDENT

WhatsApp Alerts › Jet2holidays › ENHANCED BY Go

NEWS SPORT VOICES CULTURE LIFESTYLE TRAVEL PREMIUM MORE INDEPEN

News > World > Europe

France policy on AstraZeneca vaccine 'completely crackers,' says UK government scientific adviser

'It doesn't make any sense. The whole thing looks completely crackers. They are changing the rules almost every week,' says Professor Sir John Bell

Samuel Lovett Science Correspondent • Saturday 20 March 2021 19:03 GMT

• 29 Comments

BBC Sign in Home News Sport Weather iPlayer

NEWS

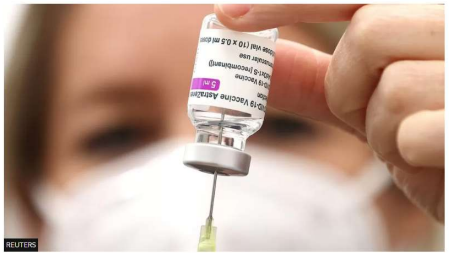
Home | Israel-Gaza war | Cost of Living | War in Ukraine | Climate | UK | World | Business | Politics | Culture

World | Africa | Asia | Australia | Europe | Latin America | Middle East | US & Canada

Covid: Germany limits use of AstraZeneca Covid jab for under-60s

30 March 2021

Coronavirus



BBC Sign in Home News Sport Weather iPlayer

NEWS

Home | Israel-Gaza war | Cost of Living | War in Ukraine | Climate | UK | World | Business | Politics | Culture

Health

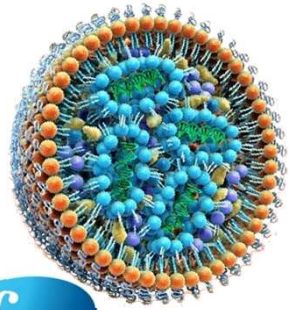
Heart inflammation link to Pfizer and Moderna jabs

9 July 2021

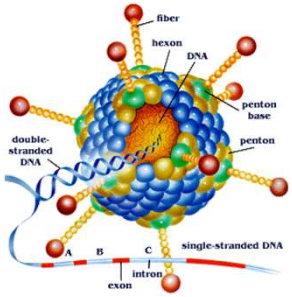
OXFORD VACCINE GROUP

COM COV

Comparing COVID-19 Vaccine Schedule Combinations



Pfizer BIONTECH



AstraZeneca

A single-blind, randomised, phase II UK multi-centre study to determine reactogenicity and immunogenicity of heterologous prime/boost COVID-19 vaccine schedules

Population: 830 participants. Adults aged over 50 with no or mild-moderate well-controlled co-morbidity

8 Arms: Pfizer/Pfizer, Pfizer/AstraZeneca, AstraZeneca/AstraZeneca, AstraZeneca/Pfizer at 28-day and 84-day prime-boost intervals

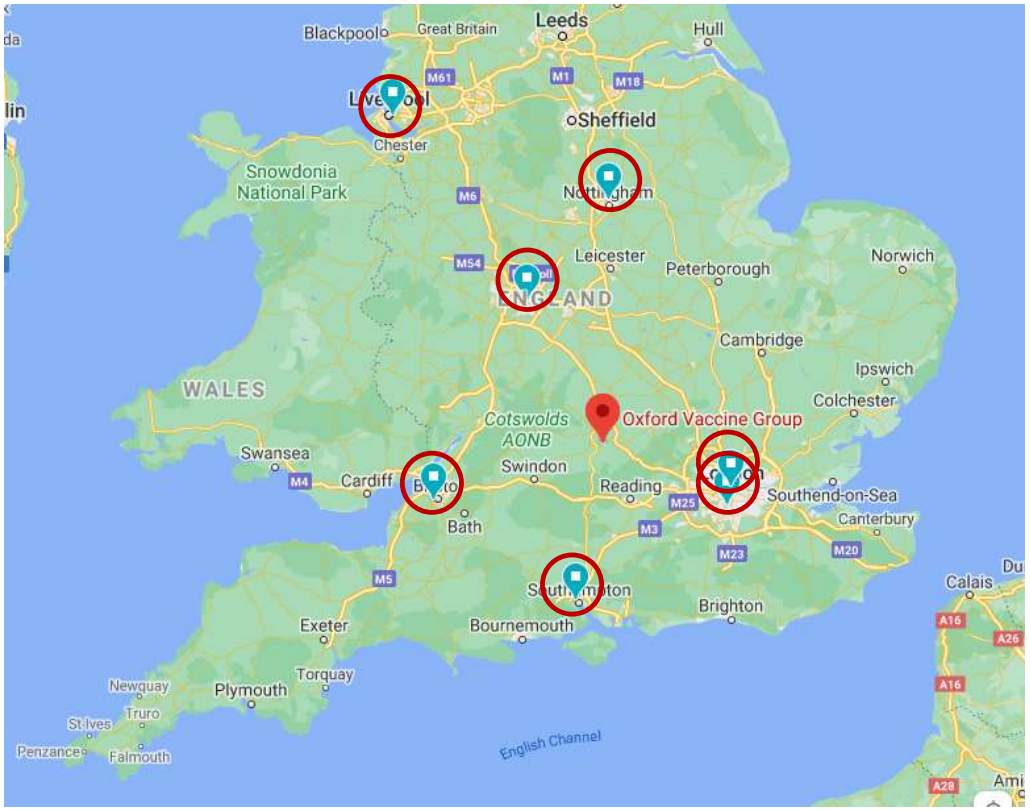
Heterologous & Interval

Study timeline	D0	D7	D14	D28	D35	D42	D56	D84	D112	D182	D364	C19P
4-week vaccination	X			X			V2+28					
4-week Aliquots	Serum PBMCs SAM-strip	Serum SAM-strip	Serum PBMCs SAM-strip	Serum PBMCs SAM-strip	Serum SAM-strip	Serum PBMCs SAM-strip	Serum PBMCs SAM-strip		Serum PBMCs SAM-strip	Serum PBMCs SAM-strip	Serum PBMCs SAM-strip	Serum PBMCs SAM-strip
12-week vaccination	X							X	V2+28			
12-week Aliquots	Serum PBMCs SAM-strip						Serum PBMCs SAM-strip	Serum PBMCs SAM-strip	Serum PBMCs SAM-strip	Serum PBMCs SAM-strip	Serum PBMCs SAM-strip	Serum PBMCs SAM-strip

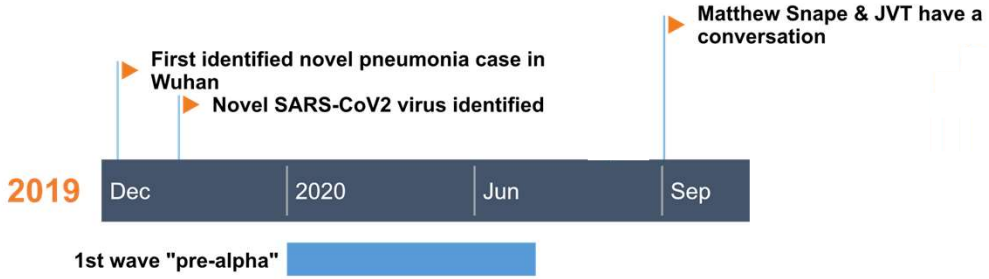
*Protocol amendment: Advice for reactive vs prophylactic paracetamol sub-study for 12-week interval participants at the point of second dose

Com-COV1 Recruiting sites

- Oxford
- Southampton
- Bristol
- St Georges
- UCLH
- Birmingham
- Nottingham
- Liverpool



OXFORD VACCINE GROUP



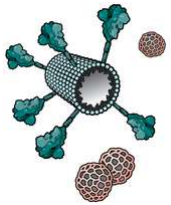
COM COV 2

Comparing COVID-19 Vaccine Schedule Combinations

1077 participants

Community prime (8-12 weeks earlier)	2nd dose
Oxford/AstraZeneca (ChAd)	Oxford/AstraZeneca (ChAd)
	mRNA-1273 (Mod)
	NVX-CoV2372 (NVX)
Pfizer/BioNTech (BNT)	Pfizer/BioNTech (BNT)
	mRNA-1273 (Mod)
	NVX-CoV2372 (NVX)

OXFORD VACCINE GROUP



Study timeline	D0	D7	D14	D28	D56	D294	C19P
Vaccination	X			V2+28			
4-week Aliquots	Serum PBMCs SAM-strip	Serum SAM-strip	Serum PBMCs SAM-strip	Serum PBMCs SAM-strip	Serum PBMCs SAM-strip	Serum PBMCs SAM-strip	Serum PBMCs SAM-strip

*Participants received their 1st dose in the community. There is therefore no pre-prime/baseline sample

**There is a variable (non-randomised) interval of 8-12 weeks

Com-COV2 Recruiting sites

- (Oxford)
- St Georges
- UCLH
- GSTT
- Birmingham
- Nottingham
- Liverpool
- Sheffield
- Hull
- Newcastle

Com-COV Study Team

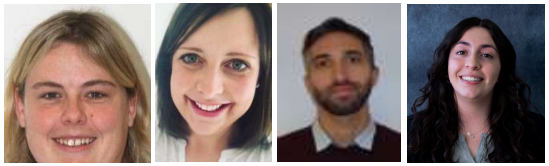
Chief Investigator

Matthew Snape
Maheshi Ramasamy

Lead Fellows

Robert Shaw
Arabella Stuart

Project Managers



Emma Plested
Laura Walker
Iason Vichos
Ella Morey

Sites Coordinator

Nisha Singh
Bryn Horsington
Fei Long

OVG Laboratory Lead

Liz Clutterbuck

OVG Lead RAs

Tanya Dinesh
Samuel Provstgaard-Morys

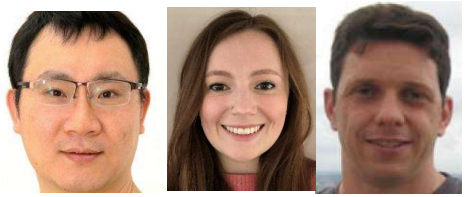
OVG Laboratory PIs

Tess Lambe
Katie Ewer
Bassam Hallis (PHE)

Deputy Chief Medical Officer

Jonathan Nguyen-Van Tam

Statisticians

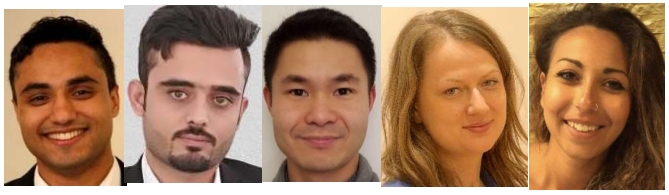


Xinxue Liu
Mel Greenland
Nick Andrews (PHE)

Clinical Operations Director

Hannah Robinson

Data Managers

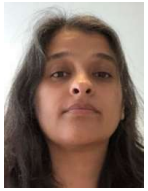


Yama Mujadidi
Samiullah Seddiqi
Andy Yao
Olga Mazur
Hanane Trari Belhadef
10

Senior Research Nurse

Rachel White

Director of Operations



Parv Aley

Com-COV1 & Com-COV2 PIs

Site PIs:

- Maheshi Ramasamy
- Saul Faust
- Adam Finn
- Rajeka Lazarus
- Paul Heath
- Chris Green
- David Turner
- Andrea Collins
- Vincenzo Libri

Site PIs:

- Maheshi Ramasamy
- Paul Heath
- Chris Green
- David Turner
- Andrea Collins
- Vincenzo Libri
- Ruth Payne
- Patrick Lillie
- Anna Goodman
- Chris Duncan

Challenges

Changing social distancing measures

Changing vaccination policies

Changing travel requirements (UK-based and abroad)

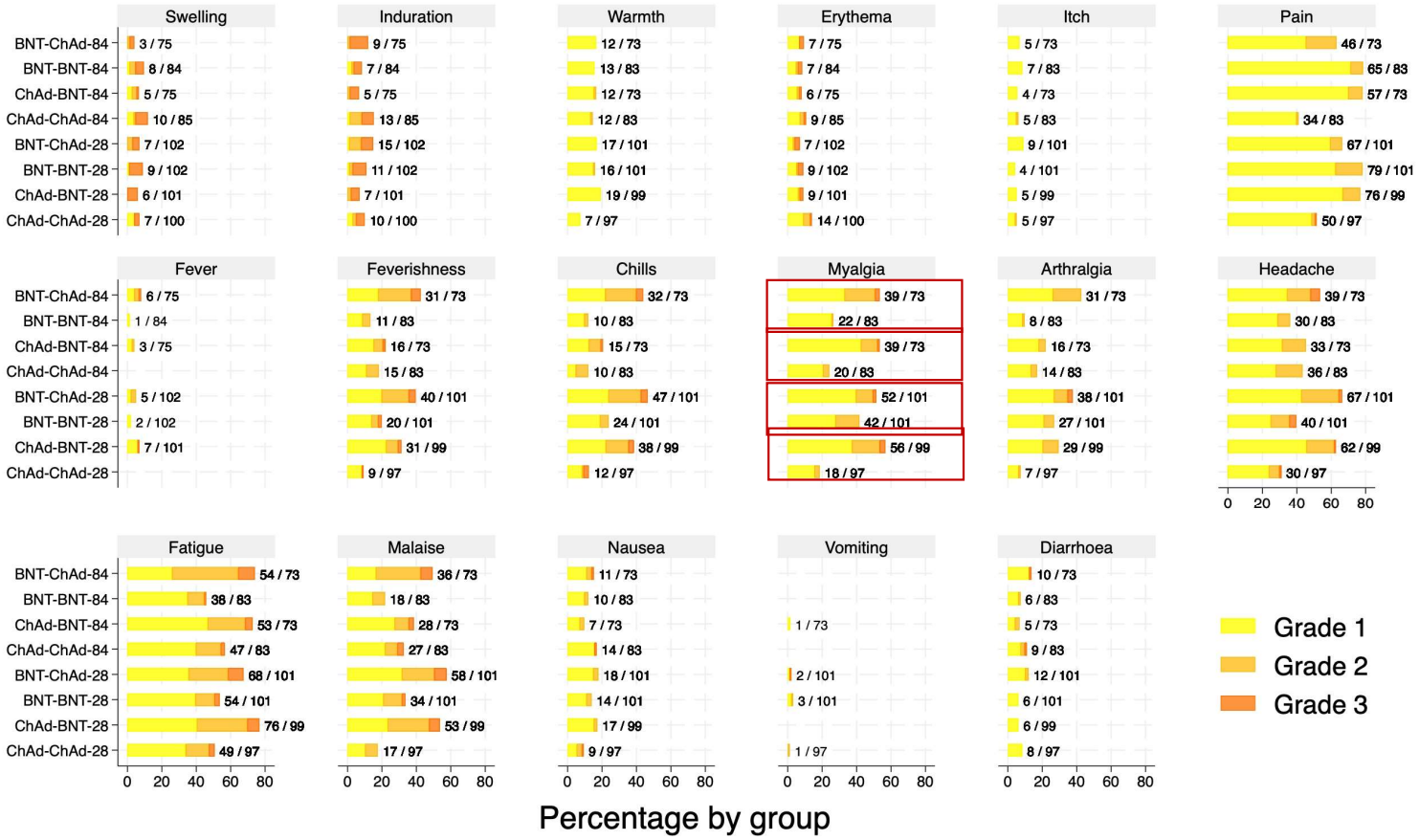
Variations in which country accepted which vaccine

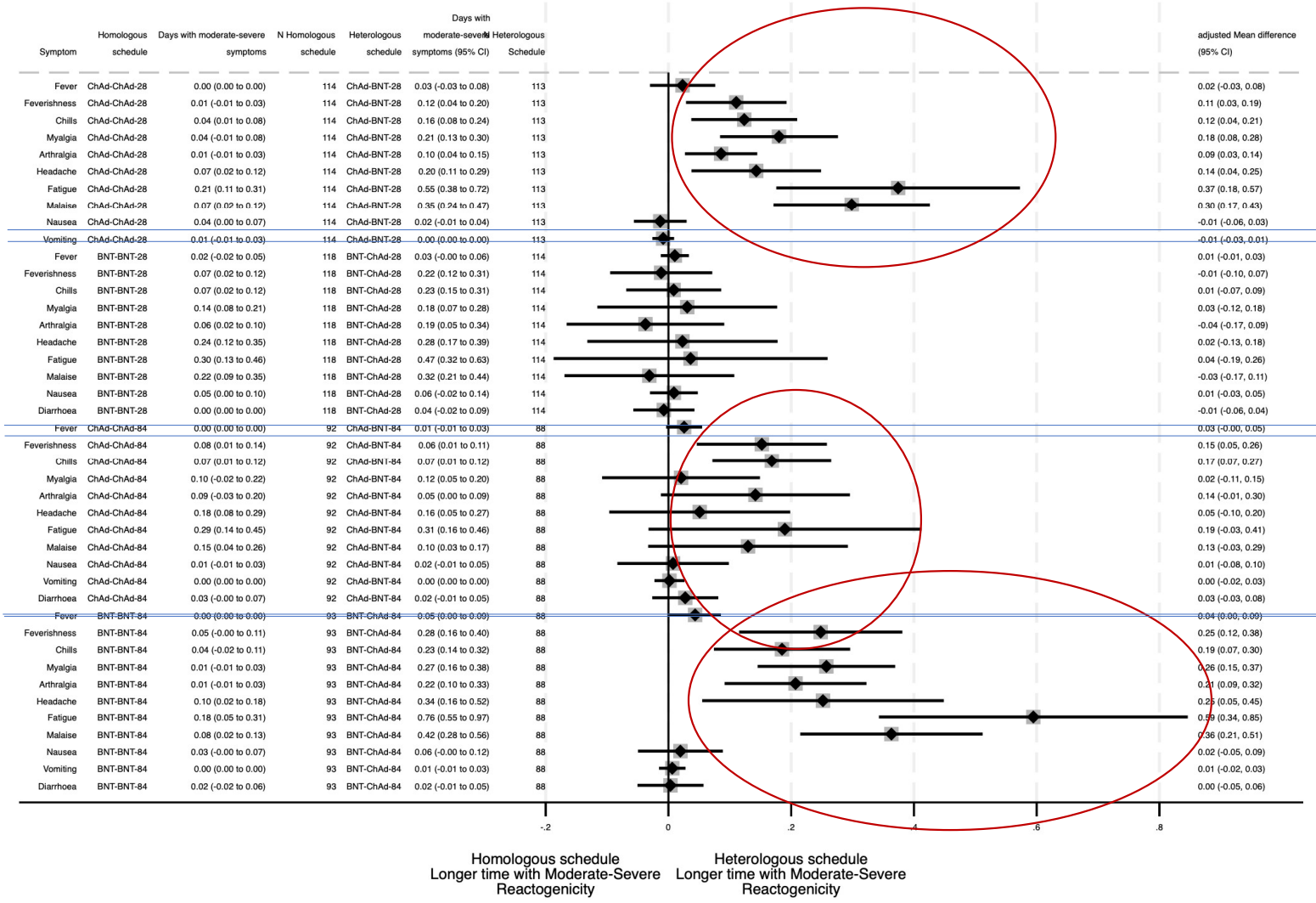
Notably not recruitment!

Result Highlights

OXFORD
VACCINE GROUP

Reactogenicity



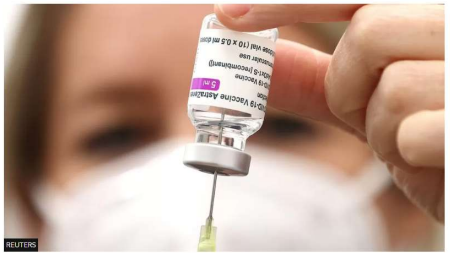


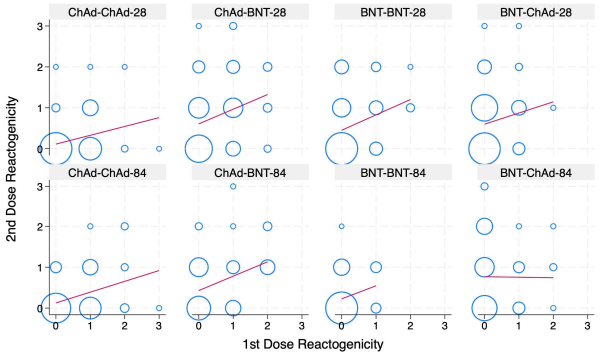
OXFORD
VACCINE GROUP

Summary Reactogenicity Results

- Heterologous schedules produce more symptoms, more severely and they last a little longer (May 2021)
- P… b… The individu… least as important as… schedule in… l and severity of reactogenic…
- Se… …icipants
- First exposu… …ogenic
- If you have sy… …times as likely to have symptoms at boost
- No clear corre… …city and immunogenicity
- All regimens were well-tolerated and no safety issues raised

Immunological musings





Immunogenicity

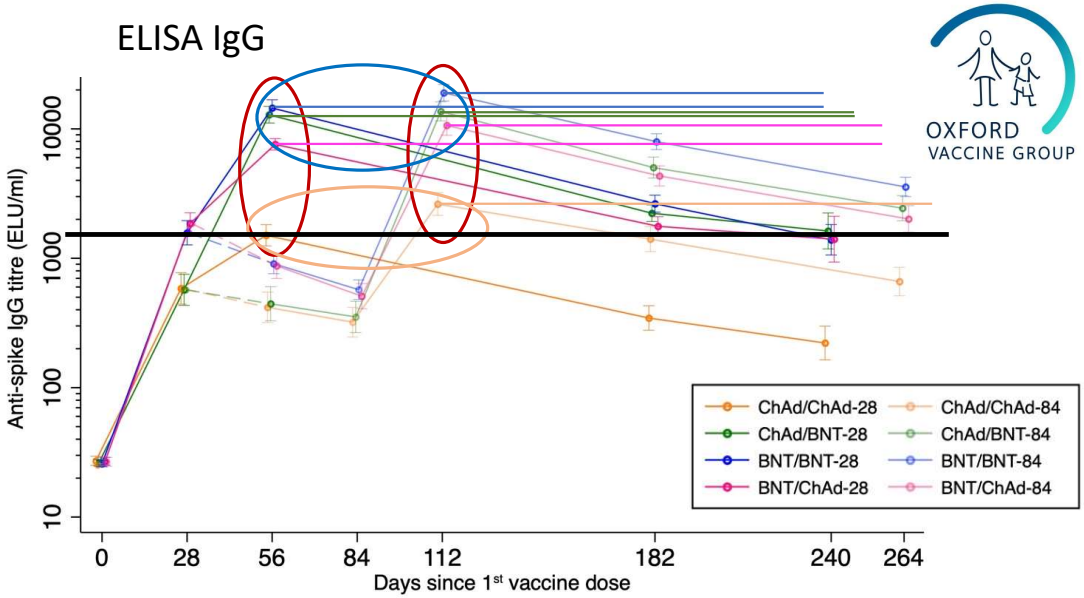
	ChAdOx1 nCoV-19 arms					
	4-week interval			**12-week interval**		
	ChAd/ChAd N=83	ChAd/BNT N=83	GMR	ChAd/ChAd N=89	ChAd/BNT N=77	GMR§
SARS-CoV-2 anti-spike IgG, ELU/ml	1444 (1205-1732) [n=81]	12979 (11217-15018) [n=83]	9.0 (7.1,11.3)	2622 (2152-3195) [n=88]	13465 (11391-15917) [n=76]	5.2 (4.0,6.7)
Pseudotyped virus neutralising antibody, NT_{50}	74 (63-89) [n=77]	529 (450-622) [n=82]	7.2 (5.7,9.1)	188 (153-231) [n=86]	781 (646-946) [n=75]	4.2 (3.1,5.6)
Cellular response – Fresh (WT), SFC/10^6 PBMCs	48 (38-62) [n=79]	186 (148-234) [n=83]	4.0 (2.8,5.5)	35 (27-44) [n=86]	110 (83-145) [n=74]	3.2 (2.2,4.6)
	BNT162b2 arms					
	4-week interval			**12-week interval**		
	BNT/BNT N=84	BNT/ChAd N=83	GMR§	BNT/BNT N=87	BNT/ChAd N=78	GMR§
SARS-CoV-2 anti-spike IgG, ELU/ml	14349 (12470-16511) [n=84]	7530 (6811-8325) [n=83]	0.52 (0.4,0.6)	19011 (16468-21947) [n=85]	10642 (8936-12673) [n=76]	0.57 (0.45,0.71)
Pseudotyped virus neutralising antibody, NT_{50}	585 (500-685) [n=83]	397 (342-460) [n=82]	0.67 (0.5,0.8)	899 (770-1051) [n=81]	645 (529-787) [n=71]	0.72 (0.56,0.92)
Cellular response – Fresh (WT), SFC/10^6 PBMCs	72 (54-95) [n=84]	98 (73-131) [n=83]	1.4 (0.9,2.1)	49 (37-64) [n=82]	37 (28-49) [n=73]	0.80 (0.54,1.2)

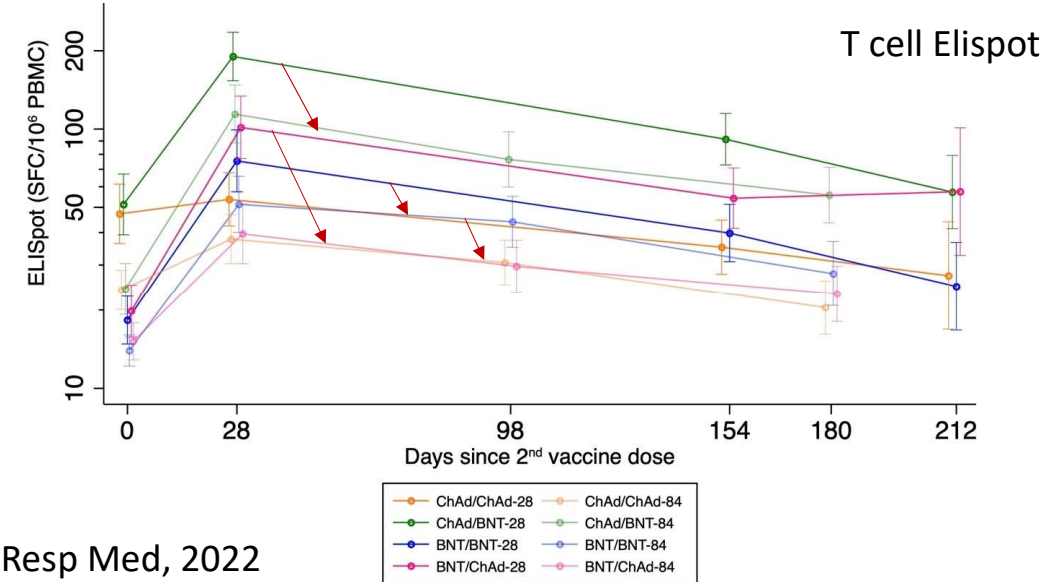
Impact of interval: RCT

At 28 days post second dose

- Pseudotyped virus neutralisation titres were higher in all 12-week vs 4-week groups. GMRs below:
  - **1·4** (1·1-1·8) for BNT / BNT
  - **1·5** (1·2-1·9) for ChAdOx1 / BNT
  - **1·6** (1·3-2·1) for BNT / ChAdOx1
  - **2·4** (1·7-3·2) for ChAdOx1 / ChAdOx1

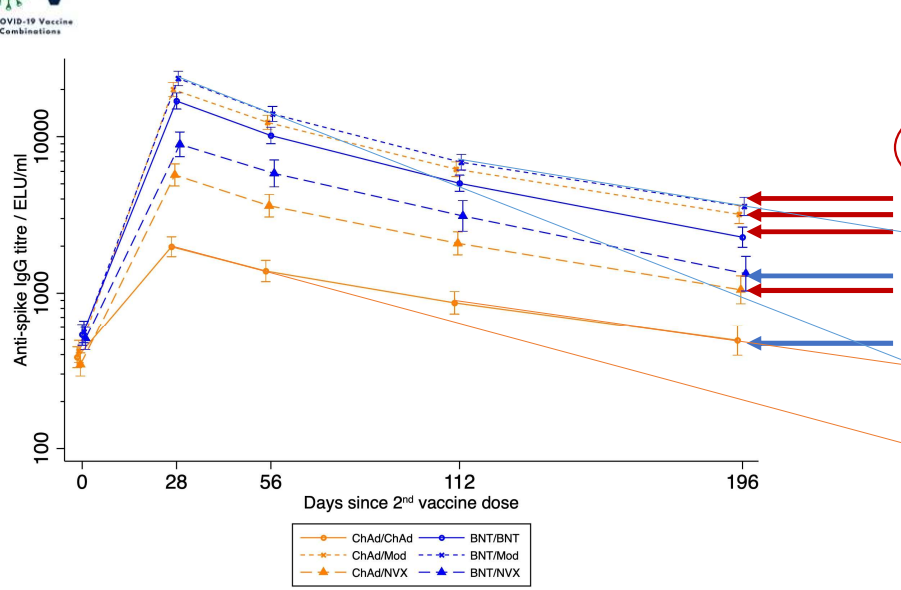
- T cell ELISpot responses were lower in all groups for 12 vs 4 week interval

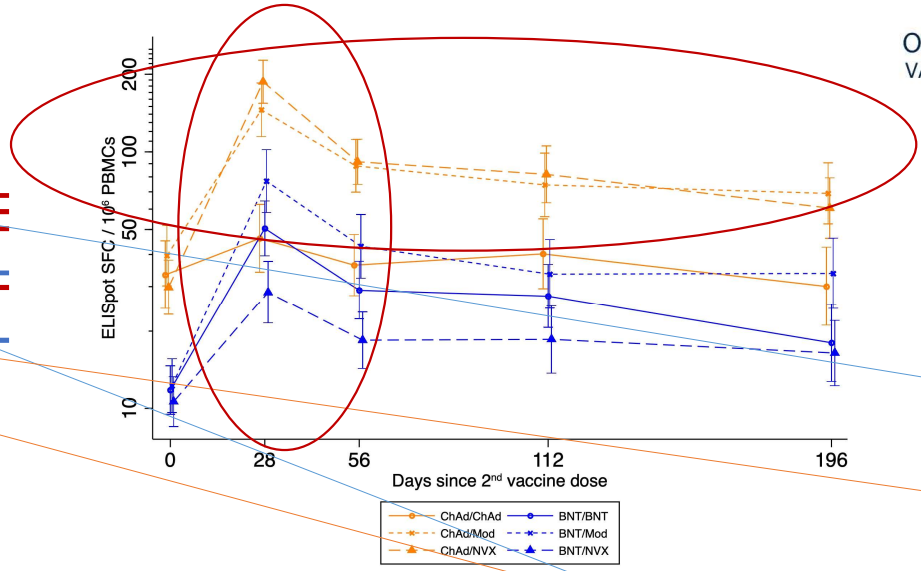




Shaw et al, Lancet Resp Med, 2022

COMCOV2: Persistence of humoral and cellular immune response





- Heterologous ChAd-primed schedules remain more immunogenic vs ChAd/ChAd
- BNT-primed schedules with a second doses of mRNA are more immunogenic vs BNT/NVX
- Schedules with higher peak Ab had a more rapid initial wane – proportional difference between schedules reduces over time
- No indication that heterologous priming schedules *per se* have improved persistence

- T-cell decay differed with plateauing from D56
- Heterologous ChAd-primed schedules gave the largest responses

Heterologous priming schedules might be considered as a viable option sooner in future pandemics

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

COMCOV and COMCOV2

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

COMCOV (12 week, 58 years)	COMCOV (4 week, 58 years)	Anti-spike IgG	95% C.I.
BNT/BNT (12)		19011	(16488-21947)
	BNT/BNT(4)	14349	(12470-16511)
ChAd/BNT (12)		13465	(11391-15917)
	ChAd/BNT (4)	12979	(11217-15018)
BNT/ChAd (12)		10642	(8936-12673)
	BNT/ChAd (4)	7530	(6811-8325)
ChAd/ChAd (12)		2622	(2152-3195)
	ChAd/ChAd (4)	1444	(1205-1732)

Stuart et al, Lancet, 2021

Liu 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
- All combinations above ChAd/ChAd threshold
- Prolonging interval increases immune response almost universally

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

COMCOV and COMCOV2

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

COMCOV (12 week)	COMCOV (4 week)	T cell response	95% C.I.
	ChAd/BNT (4)	186	(148-234)
ChAd/BNT (12)		110	(83-145)
	BNT/ChAd (4)	98	(73-131)
	BNT/BNT (4)	72	(54-95)
BNT/BNT (12)		49	(37-64)
	ChAd/ChAd (4)	48	(38-62)
BNT/ChAd (12)		37	(28-49)
ChAd/ChAd (12)		35	(27-46)

Stuart et al, Lancet, 2021

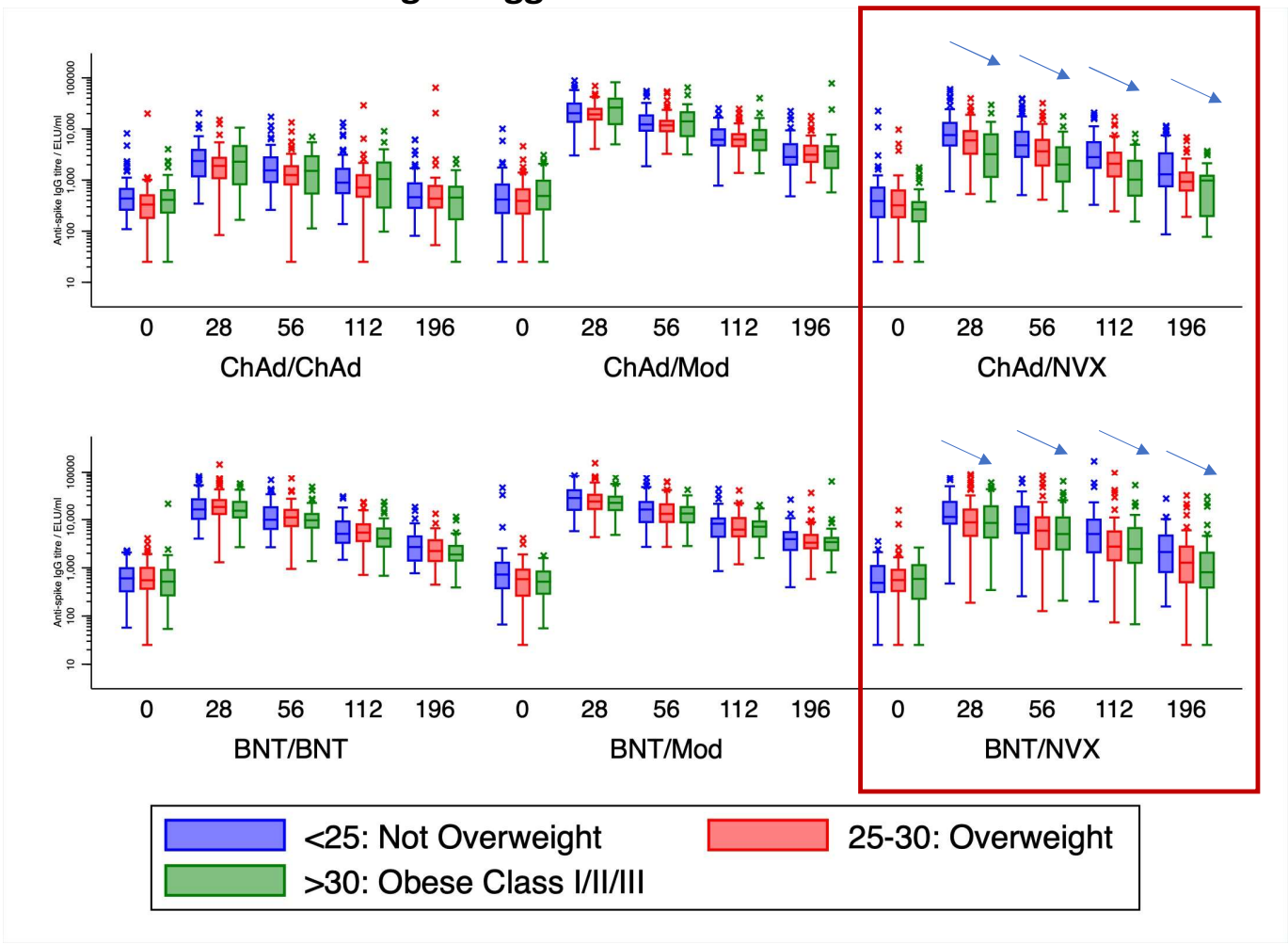
Liu et al, Lancet, 2021

OXFORD VACCINE GROUP

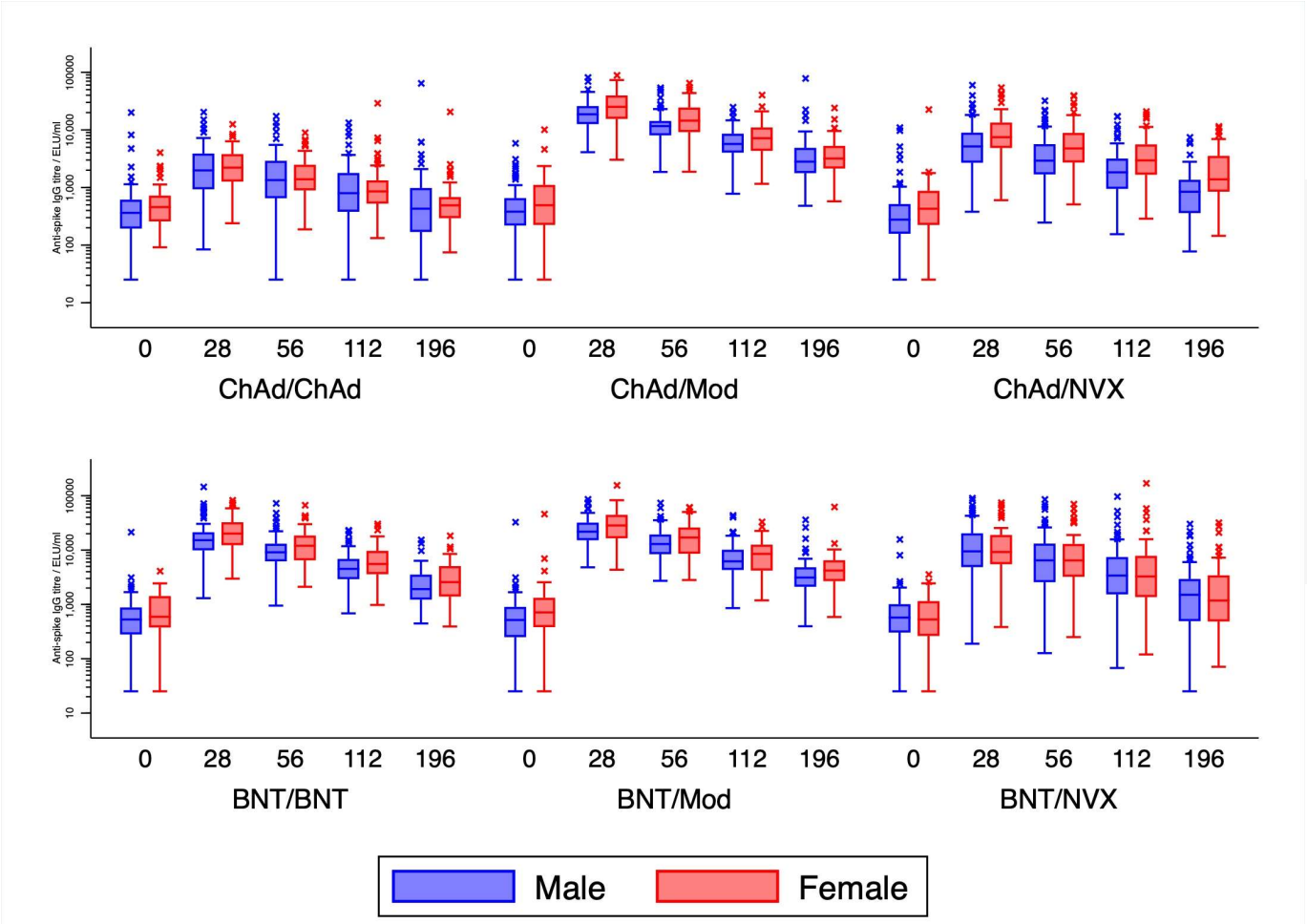
<u>Cellular immunity</u> (IFN-gamma secreting T cells, measured by ELISPOT)

- **ChAd prime, followed by heterologous boost highly immunogenic**
- mRNA/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
- Interval associated with a lower cellular response

Reduced immunogenicity of adjuvanted protein-boosted schedules in those with higher BMI, might suggest that this is dose-related



Almost universal improved immunological response in female participants
Previously demonstrated in homologous ChAd (COV001, COV002)



COMCOV (12 week, 58 years)	COMCOV (4 week, 58 years)	Anti-spike IgG	95% C.I.
BNT/BNT (12)		19011	(16488-21947)
	BNT/BNT(4)	14349	(12470-16511)
ChAd/BNT (12)		13465	(11391-15917)
	ChAd/BNT (4)	12979	(11217-15018)
BNT/ChAd (12)		10642	(8936-12673)
	BNT/ChAd (4)	7530	(6811-8325)
ChAd/ChAd (12)		2622	(2152-3195)
	ChAd/ChAd (4)	1444	(1205-1732)

OXFORD VACCINE GROUP

- Homologous Pfizer is 6-10 times humorally more immunogenic than homologous AstraZeneca
- Interval increases humoral response by about 1.5x

- Heterologous AstraZeneca-primed schedules produces the biggest cellular response
- Interval appears to reduce cellular response

- Both homologous schedules provide high level protection against severe SARS-CoV2
  - (and so do the heterologous schedules)

Implications

- Policy
  - Heterologous schedules are a safe and immunogenic option to ease logistical constraints of mass vaccine roll out
    - Since been shown to be effective
    - Particularly helpful in LMIC

- Immunological
  - Interval effect is probably mediated by germinal centre maturation in the lymph nodes. Avidity testing would help confirm this. ?Unlikely to see further benefit beyond 3 months
  - There are fundamental differences in which the immune system is primed by the different vaccine platforms, likely mediated by the location and manner in which antigen is presented
    - Viral vectored and adjuvanted protein vaccines produce proportionally more neutralising responses than mRNA

Outputs Timeline

OXFORD VACCINE GROUP

Com-COV Reactogenicity
Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data.
Lancet
12 May

Com-COV2 Primary Outcome
Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): a single-blind, randomised, phase 2, non-inferiority trial.
Lancet
6 Dec

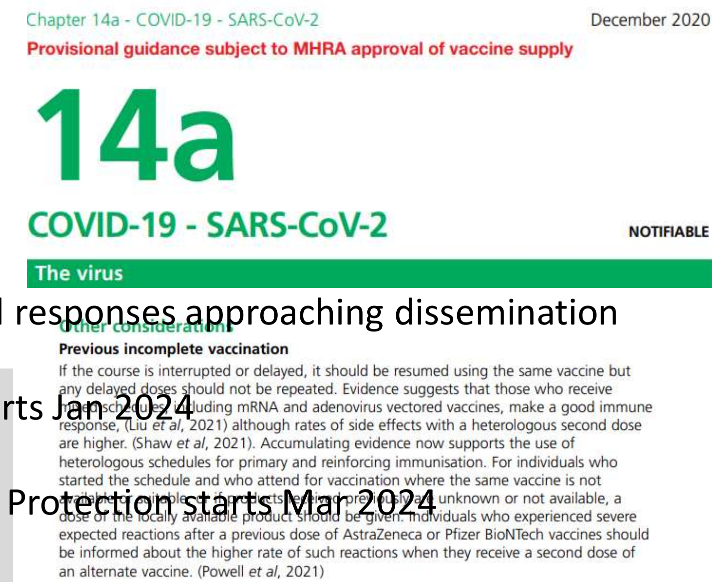
Com-COV Interval
Effect of priming interval on reactogenicity, peak immunological response, and waning after homologous and heterologous COVID-19 vaccine schedules: exploratory analyses of Com-COV, a randomised control trial.
Lancet Respiratory Medicine
8 Jun

Com-CO2 Persistence
Persistence of immune response in heterologous COVID vaccination schedules in the Com-COV2 study – A single-blind, randomised trial incorporating mRNA, viral-vector and protein-adjuvant vaccines.
Journal of Infection
5 Apr

2021 | May | Jul | Sep | Nov | 2022 | Mar | May | Jul | Sep | Nov | 2023 | Mar | 2023

6 Aug
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.
Lancet
Com-COV Primary Outcome

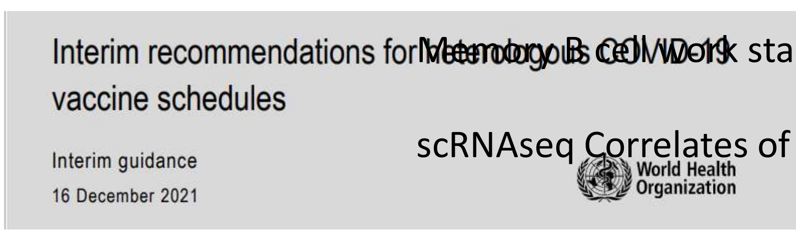
20 Dec
Reduced neutralisation of SARS-CoV-2 omicron B.1.1.529 variant by post-immunisation serum.
Lancet
Com-COV2 Omicron Neutralisation


Chapter 14a - COVID-19 - SARS-CoV-2
December 2020
Provisional guidance subject to MHRA approval of vaccine supply
14a
COVID-19 - SARS-CoV-2
NOTIFIABLE
The virus
Other considerations
Previous incomplete vaccination
If the course is interrupted or delayed, it should be resumed using the same vaccine but any delayed doses should not be repeated. Evidence suggests that those who receive mixed schedules, including mRNA and adenovirus vectored vaccines, make a good immune response, (Liu *et al*, 2021) although rates of side effects with a heterologous second dose are higher. (Shaw *et al*, 2021). Accumulating evidence now supports the use of heterologous schedules for primary and reinforcing immunisation. For individuals who started the schedule and who attend for vaccination where the same vaccine is not available, or if the product used previously is unknown or not available, a dose of the locally available product should be given. Individuals who experienced severe expected reactions after a previous dose of AstraZeneca or Pfizer BioNTech vaccines should be informed about the higher rate of such reactions when they receive a second dose of an alternate vaccine. (Powell *et al*, 2021)

Mucosal immunological responses approaching dissemination

Memory B cell Work starts Jan 2024

scRNAseq Correlates of Protection starts Mar 2024


Interim recommendations for heterologous COVID-19 vaccine schedules
Interim guidance
16 December 2021
World Health Organization


COM-COV
Comparing COVID-19 Vaccine Schedule Combinations


NHS
Health Research Authority


MHRA
Regulating Medicines and Medical Devices


HM Government


UK Health
Security
Agency


NHS
University College
London Hospitals
NHS Foundation Trust


NHS
North Bristol
NHS Trust


University of Nottingham Health Service
NHS


NHS
University Hospitals
Bristol and Weston
NHS Foundation Trust


NHS
Hull University
Teaching Hospitals
NHS Trust


NHS
Sheffield Teaching Hospitals
NHS Foundation Trust


Oxford University Hospitals
NHS
NHS Foundation Trust


NHS
Guy's and St Thomas'
NHS Foundation Trust


NHS
University Hospital Southampton
NHS Foundation Trust


St George's University Hospitals
NHS
NHS Foundation Trust


NHS
University Hospitals
Birmingham
NHS Foundation Trust


NHS
The Newcastle upon Tyne Hospitals
NHS Foundation Trust


University of
BRISTOL


LSTM
LIVERPOOL SCHOOL
OF TROPICAL MEDICINE


UNIVERSITY OF
OXFORD


OXFORD
VACCINE GROUP


NISEC


NIHR | Oxford Biomedical
Research Centre


CEPI


NOVAVAX

Than Great job! done!

Site PIs:

- Maheshi Ramasamy
- Saul Faust
- Adam Finn
- Rajeka Lazarus
- Paul Heath
- Chris Green
- David Turner
- Andrea Collins
- Vincenzo Libri

- Maheshi Ramasamy
- Paul Heath
- Chris Green
- David Turner
- Andrea Collins
- Vincenzo Libri
- Ruth Payne
- Patrick Lillie
- Anna Goodman
- Chris Duncan

OXFORD VACCINE GROUP