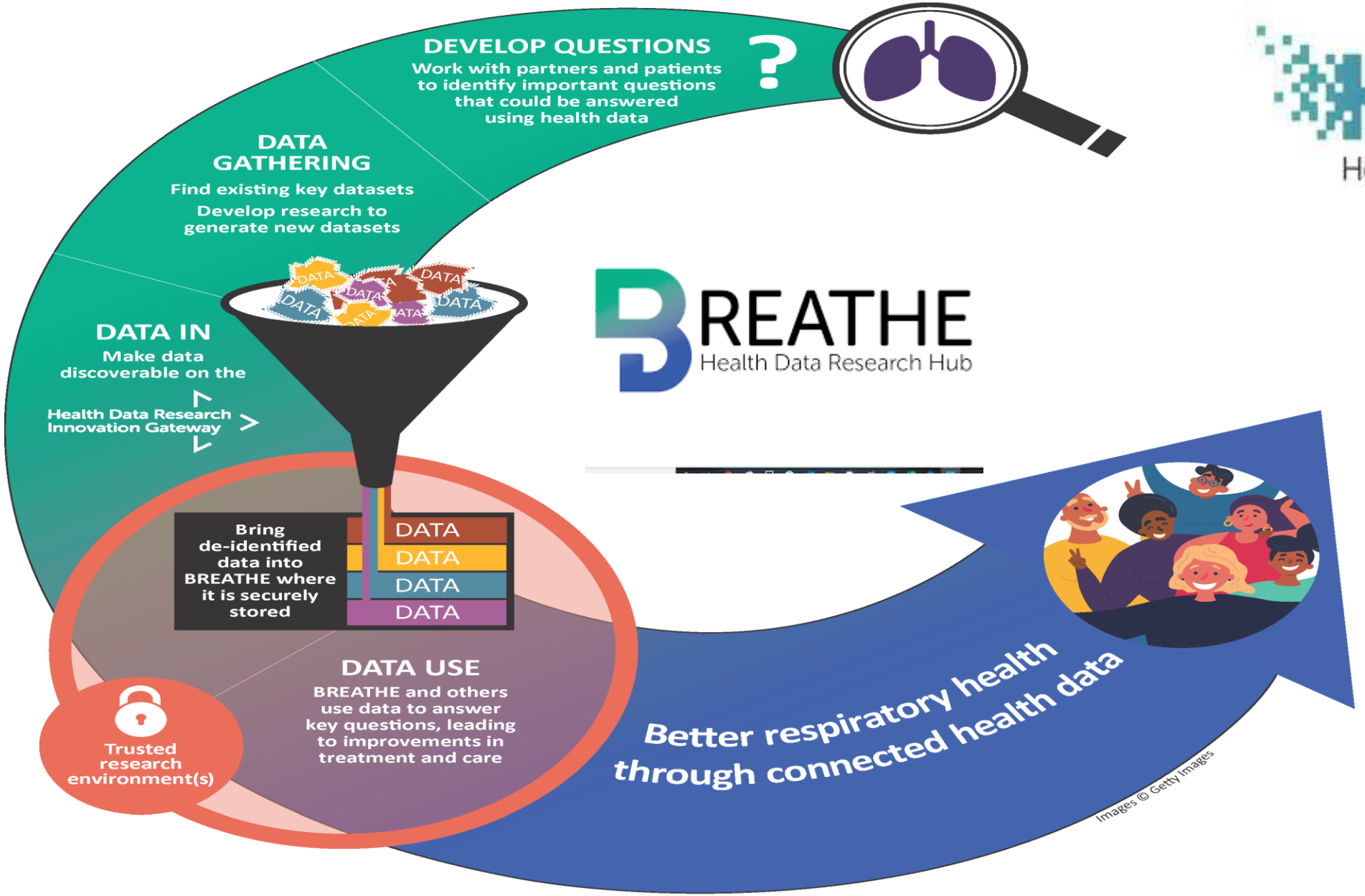
Enabling near real-time evaluations of the UK's mass vaccination programme at scale

Aziz Sheikh on behalf of the EAVE II and DaC-VaP investigators
Director, Usher Institute, University of Edinburgh and
Director, HDR UK BREATHE Hub

Potential conflict of interests

- Member of:
  - Scottish Government's CMO COVID-19 Advisory Group
  - New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) Risk Stratification Subgroup
  - AstraZeneca's Thrombotic Thrombocytopenic Advisory Group.
- All roles are unremunerated.

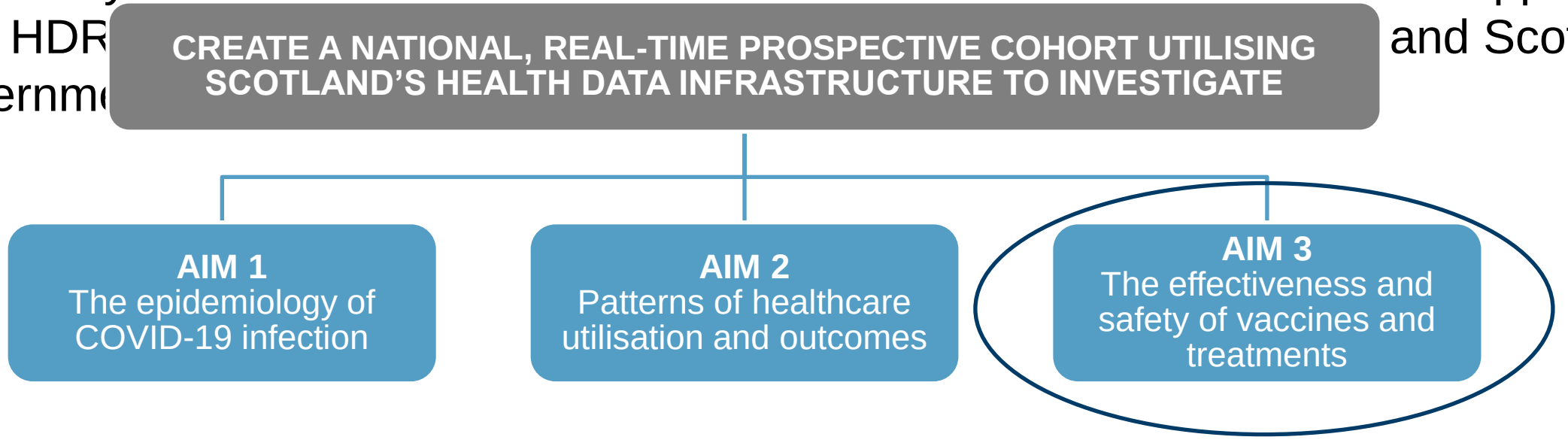


HDRUK
Health Data Research UK

BREATHE
Health Data Research Hub

Background to EAVE II

- Utilising linked data is crucial to monitor, understand and mitigate the effects of pandemics
- EAVE II aims to contribute to this effort for Scotland using a ‘hibernating’ NIHR funded platform originally created to respond to H1N1 pandemic (EAVE: **E**arly assessment of **A**nti-virals and **V**accine **E**ffectiveness)
- Funded by UKRI as part of its initial Rapid Response call with additional support from HDR and Scottish Governm



Effectiveness of H1N1 vaccine for the prevention of pandemic influenza in Scotland, UK: a retrospective observational cohort study

Colin R Simpson, Lewis D Ritchie, Chris Robertson, Aziz Sheikh, Jim McMenamin

Summary

Background A targeted vaccination programme for pandemic H1N1 2009 influenza was introduced in Scotland, UK, in October, 2009. We sought to assess the effectiveness of this vaccine in a sample of the Scottish population during the 2009–10 pandemic.

Methods We assessed the effectiveness of the Scottish pandemic H1N1 2009 influenza vaccination with a retrospective cohort design. We linked data of patient-level primary care, hospital records, death certification, and virological swabs to construct our cohort. We estimated vaccine effectiveness in a nationally representative sample of the Scottish population by establishing the risk of hospital admission and death (adjusted for potential confounders) resulting from influenza-related morbidity in vaccinated and unvaccinated patients and laboratory-confirmed cases of influenza H1N1 2009 in a subset of patients.

Findings Pandemic H1N1 2009 influenza vaccination began in week 43 of 2009 (Oct 21, 2009) and was given to 38 296 (15·5%, 95% CI 15·4–15·6) of 247 178 people by the end of the study period (Jan 31, 2010). 208 882 (85%) people were unvaccinated. There were 5207 emergency hospital admissions and 579 deaths in the unvaccinated population and 924 hospital admissions and 71 deaths in the vaccinated population during 23 893 359 person-days of observation. The effectiveness of H1N1 vaccination for prevention of emergency hospital admissions from influenza-related disorders was 19·5% (95% CI 0·8–34·7). The vaccine's effectiveness in preventing laboratory-confirmed influenza was 77·0% (95% CI 2·0–95·0).

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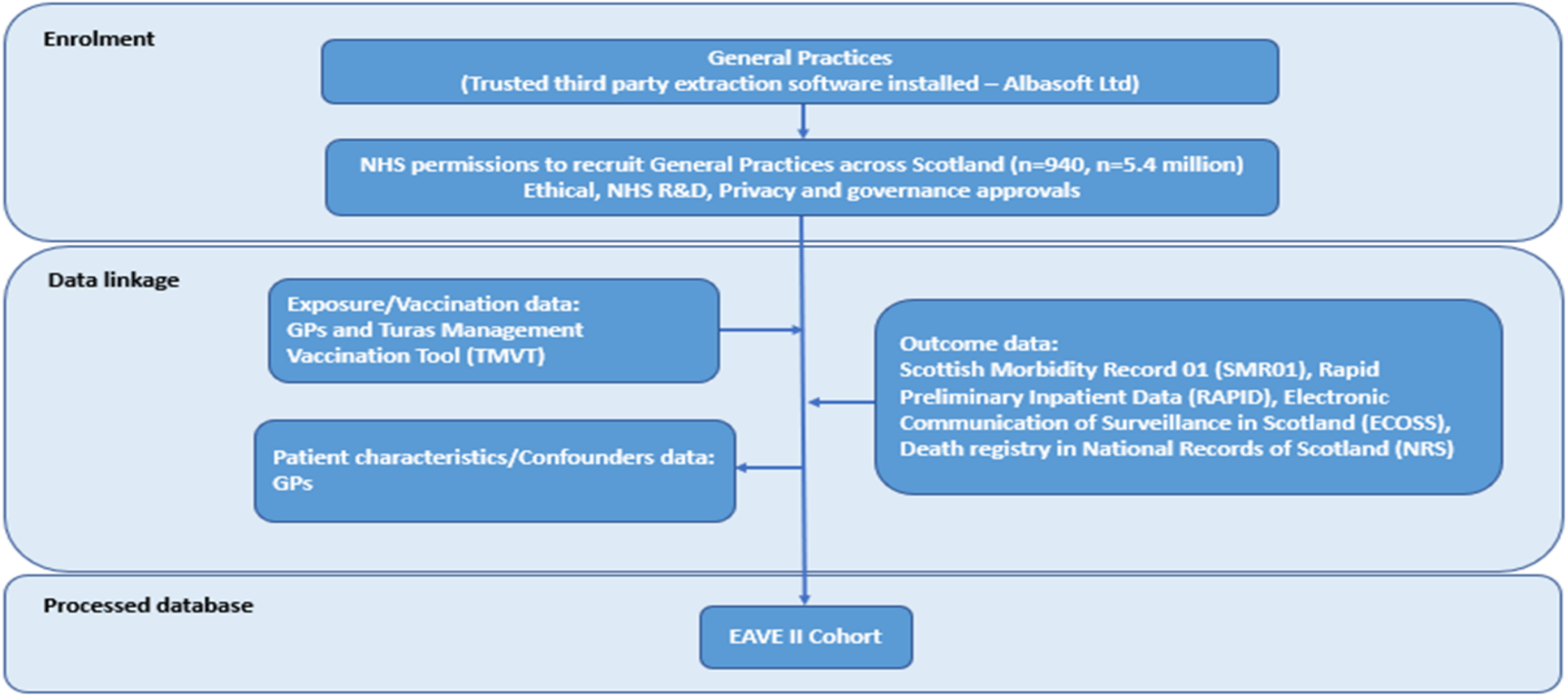
Allergy and Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Edinburgh, UK (C R Simpson PhD, Prof A Sheikh MD); Centre of Academic Primary Care, University of Aberdeen, Aberdeen, UK (Prof Sir L D Ritchie MD); Department of Mathematics and Statistics, University of Strathclyde, Glasgow, UK (Prof C Robertson PhD); Health


Enrolment
General Practices
(Trusted third party extraction software installed – Albasoft Ltd)
NHS permissions to recruit General Practices across Scotland (n=940, n=5.4 million)
Ethical, NHS R&D, Privacy and governance approvals
Data linkage
Exposure/Vaccination data:
GPs and Turas Management
Vaccination Tool (TMVT)
Patient characteristics/Confounders data:
GPs
Outcome data:
Scottish Morbidity Record 01 (SMR01), Rapid
Preliminary Inpatient Data (RAPID), Electronic
Communication of Surveillance in Scotland (ECOSS),
Death registry in National Records of Scotland (NRS)
Processed database
EAVE II Cohort

Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study

Eleftheria Vasileiou, Colin R Simpson*, Ting Shi*, Steven Kerr*, Utkarsh Agrawal, Ashley Akbari, Stuart Bedston, Jillian Beggs, Declan Bradley, Antony Chuter, Simon de Lusignan, Annemarie B Docherty, David Ford, F D Richard Hobbs, Mark Joy, Srinivasa Vittal Katikireddi, James Marple, Colin McCowan, Dylan McGagh, Jim McMenamin, Emily Moore, Josephine L K Murray, Jiafeng Pan, Lewis Ritchie, Syed Ahmar Shah, Sarah Stock, Fatemeh Torabi, Ruby S M Tsang, Rachael Wood, Mark Woolhouse, Chris Robertson†, Aziz Sheikh†*

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See Comment page 1601

*Contributed equally

†Senior authors

Usher Institute (E Vasileiou PhD, Prof C R Simpson PhD, T Shi PhD, S Kerr PhD, A Chuter FRCGP, A B Docherty PhD, S A Shah PhD, S Stock PhD, Prof M Woolhouse PhD, Prof A Sheikh MD) **and Royal**

Summary

Background The BNT162b2 mRNA (Pfizer–BioNTech) and ChAdOx1 nCoV-19 (Oxford–AstraZeneca) COVID-19 vaccines have shown high efficacy against disease in phase 3 clinical trials and are now being used in national vaccination programmes in the UK and several other countries. Studying the real-world effects of these vaccines is an urgent requirement. The aim of our study was to investigate the association between the mass roll-out of the first doses of these COVID-19 vaccines and hospital admissions for COVID-19.

Methods We did a prospective cohort study using the Early Pandemic Evaluation and Enhanced Surveillance of COVID-19—EAVE II—database comprising linked vaccination, primary care, real-time reverse transcription-PCR testing, and hospital admission patient records for 5·4 million people in Scotland (about 99% of the population) registered at 940 general practices. Individuals who had previously tested positive were excluded from the analysis. A time-dependent Cox model and Poisson regression models with inverse propensity weights were fitted to estimate effectiveness against COVID-19 hospital admission (defined as 1–adjusted rate ratio) following the first dose of vaccine.

SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness

On May 19, 2021, the Delta Variant of Concern (VOC), formerly known as the Indian VOC or B 1.617.2, became the dominant strain of SARS-CoV-2 in Scotland. The Alpha VOC (formerly known as the Kent VOC, B.1.1.7, or S gene negative) had been the dominant strain previously, but it has rapidly been replaced (appendix p 1).

Samples were analysed using ThermoFisher's TaqPath RT-PCR, which tests for the presence of three target genes from SARS-CoV-2. S gene-negative samples had a deletion in S gene of B.1.1.7 (Alpha COVID-19, and estimate vaccine effectiveness in preventing COVID-19 hospital admissions in S gene-positive cases. We also employed a test-negative design to estimate vaccine effectiveness against risk of SARS-CoV-2 infection.[5] This analysis was based upon all individuals who have a PCR test for SARS-CoV-2 in the study period, and it compares the proportions positive among individuals vaccinated at the time of the swab test with those unvaccinated when they are tested, adjusting for demographic and temporal covariates.

Building on methods that have previously been described in detail, we defined a COVID-19 hospital admission as being within 14 days of testing positive for SARS-CoV-2.[3,5] Individuals who tested positive within 2 days after a hospital admission were also included. Individuals tested during those S gene-positive aged 5–9 years compared to S gene-negative cases (appendix p 2). There was a slight inverse deprivation gradient with S gene-positive cases disproportionally seen in the most socioeconomically affluent quintile. Most cases (70%) had no underlying relevant comorbidities. 70% of S gene-positive cases had not had any COVID-19 vaccination doses, compared to 75% of S gene-negative cases.

The Cox regression analysis for time to hospital admission found that S gene-positive cases were associated with an increased risk of COVID-19 hospital admission: hazard ratio (HR) 1·85 (95% CI 1·39–2·47) when compared to S gene-negative cases, after adjusting for age, sex, deprivation, temporal trend, and comorbidities. A greater number of COVID-19 relevant comorbidities

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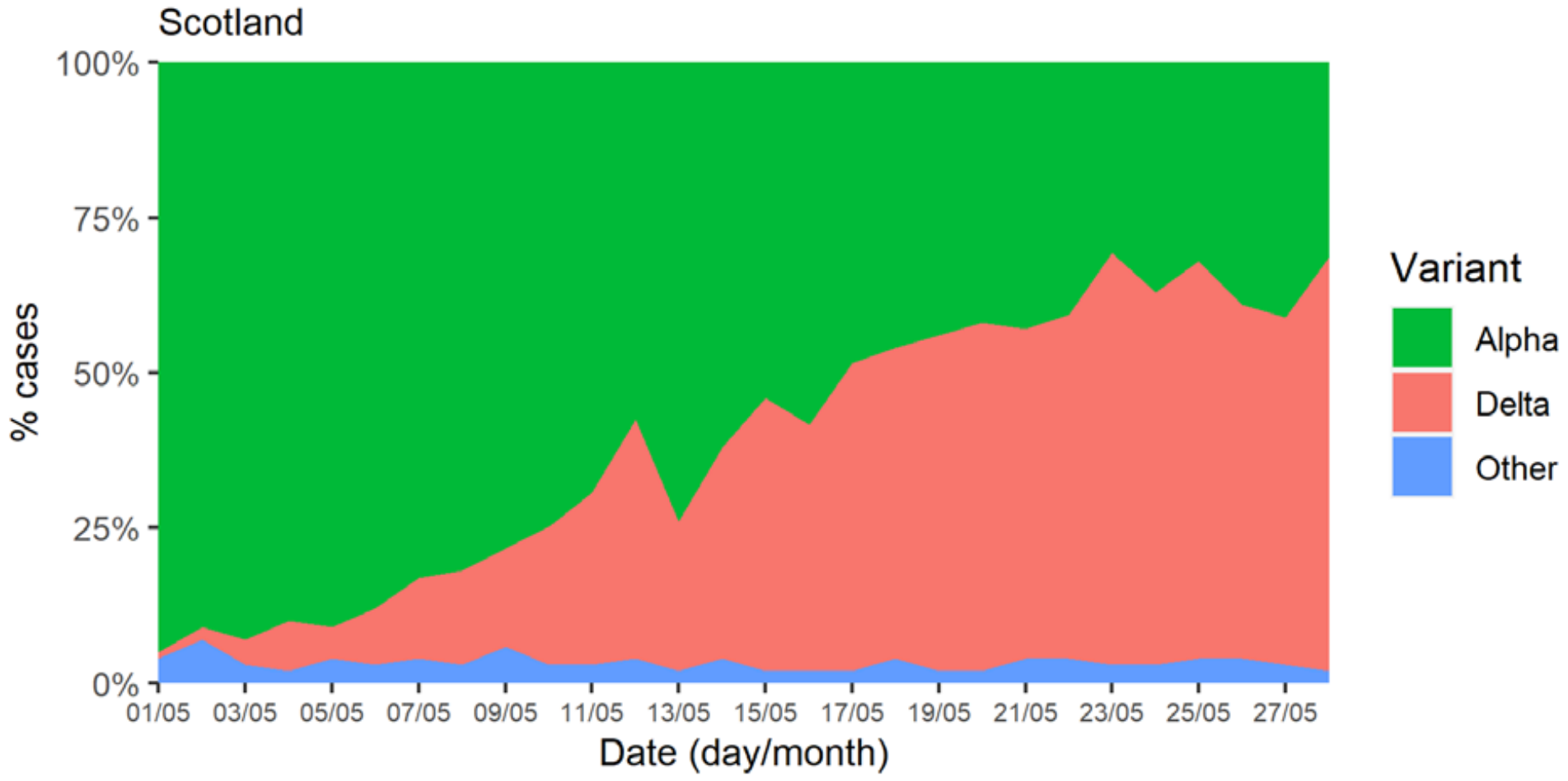
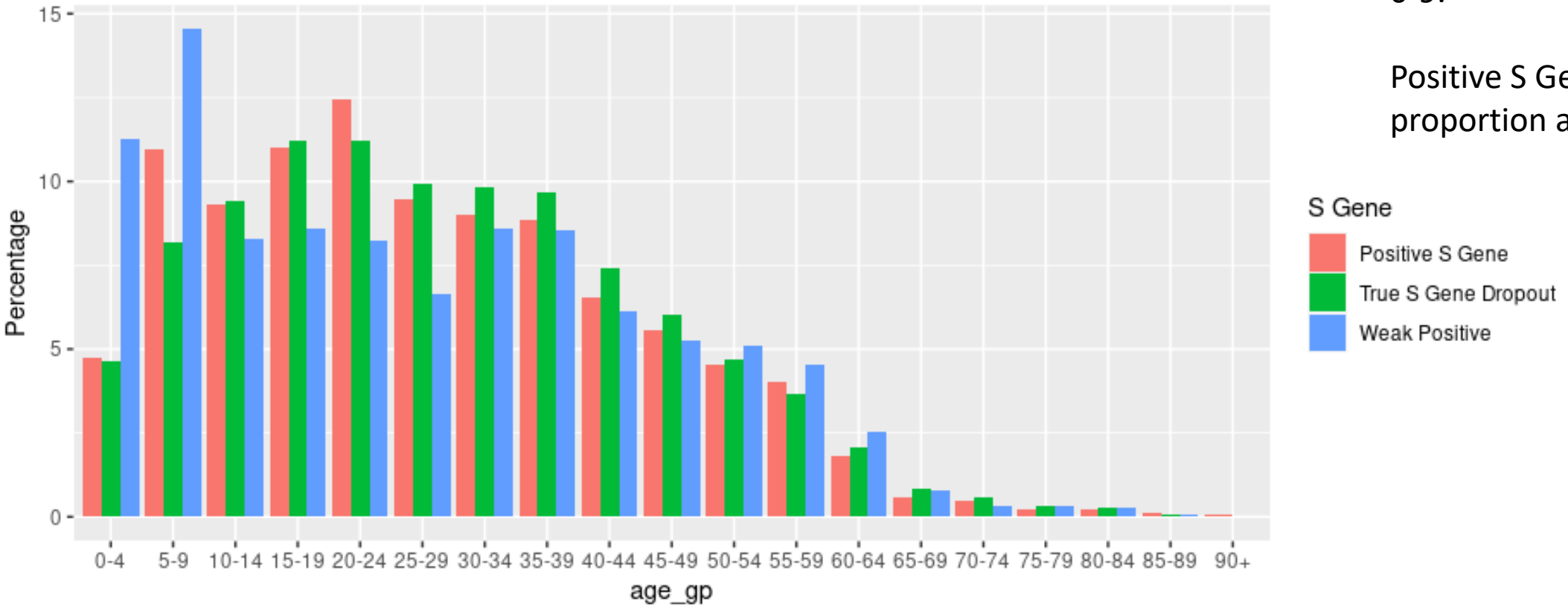
S0140-6736(21)01358-1

See Online for appendix

Changing proportion of infections due to Alpha and Delta VOCs in Scotland over time

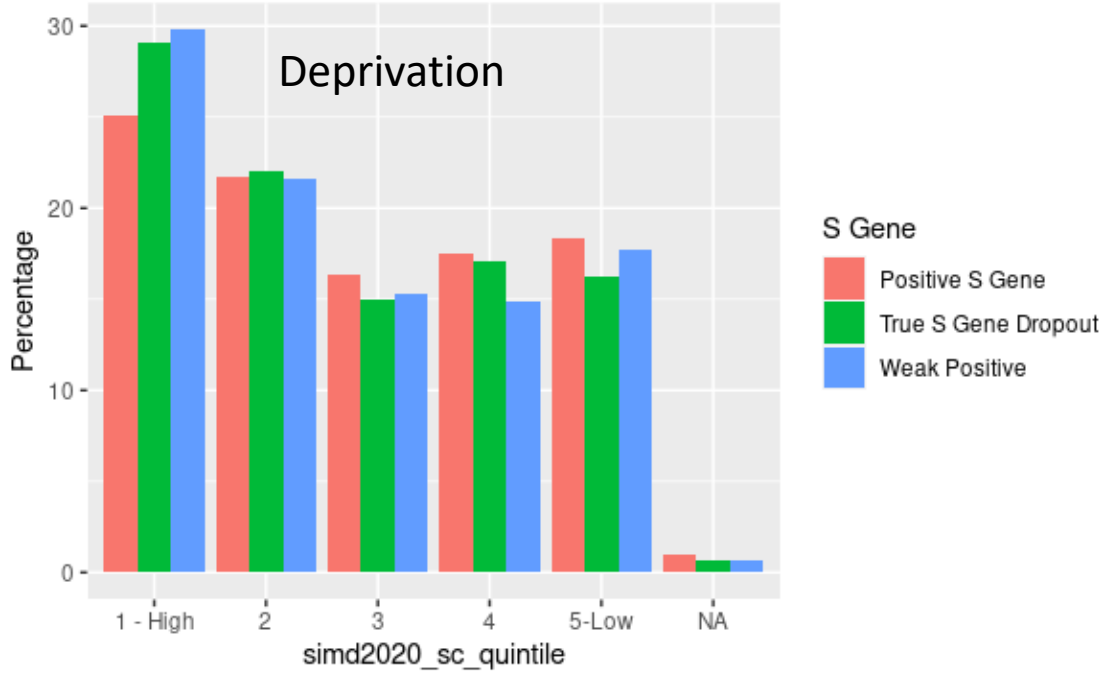


Age Distribution of Cases (1 April – 6 June, 2021)



Weak positive on the S Gene have a greater proportion aged 0-9.

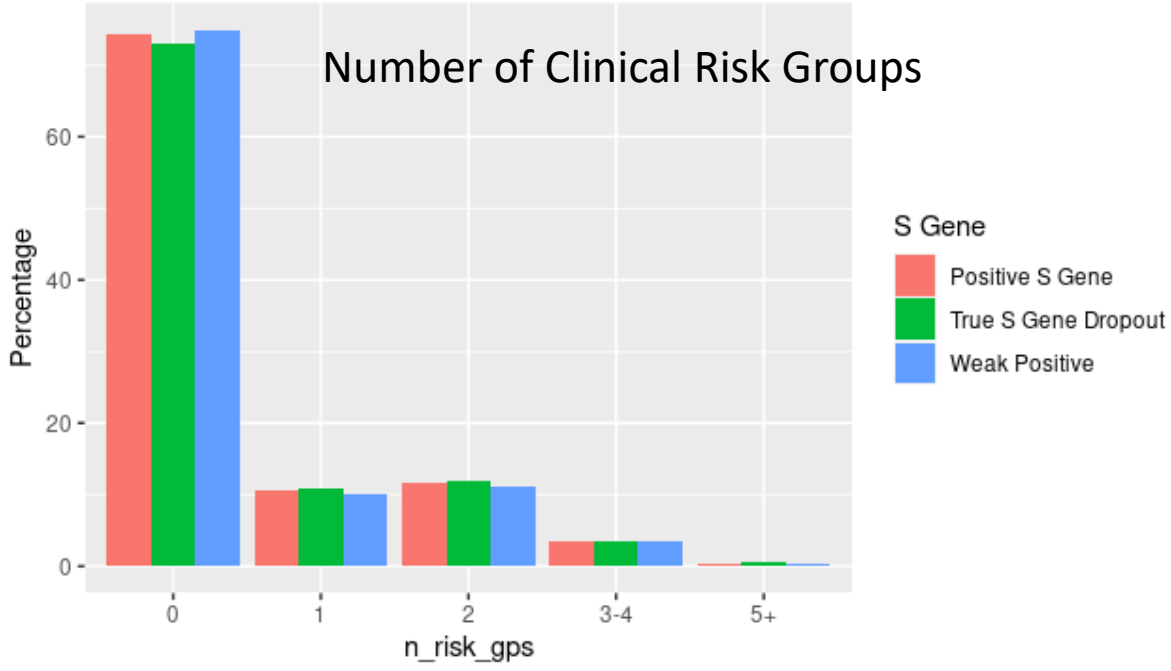
Positive S Gene a greater proportion aged 5-9; 20-24

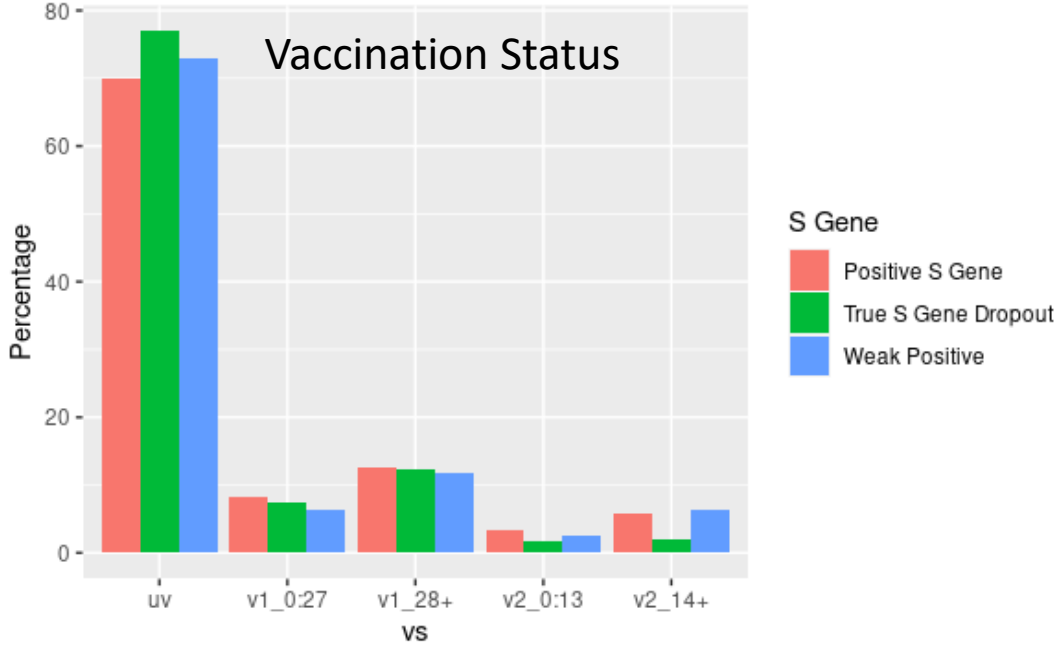


Positive S Gene a slightly greater proportion from low deprivation groups

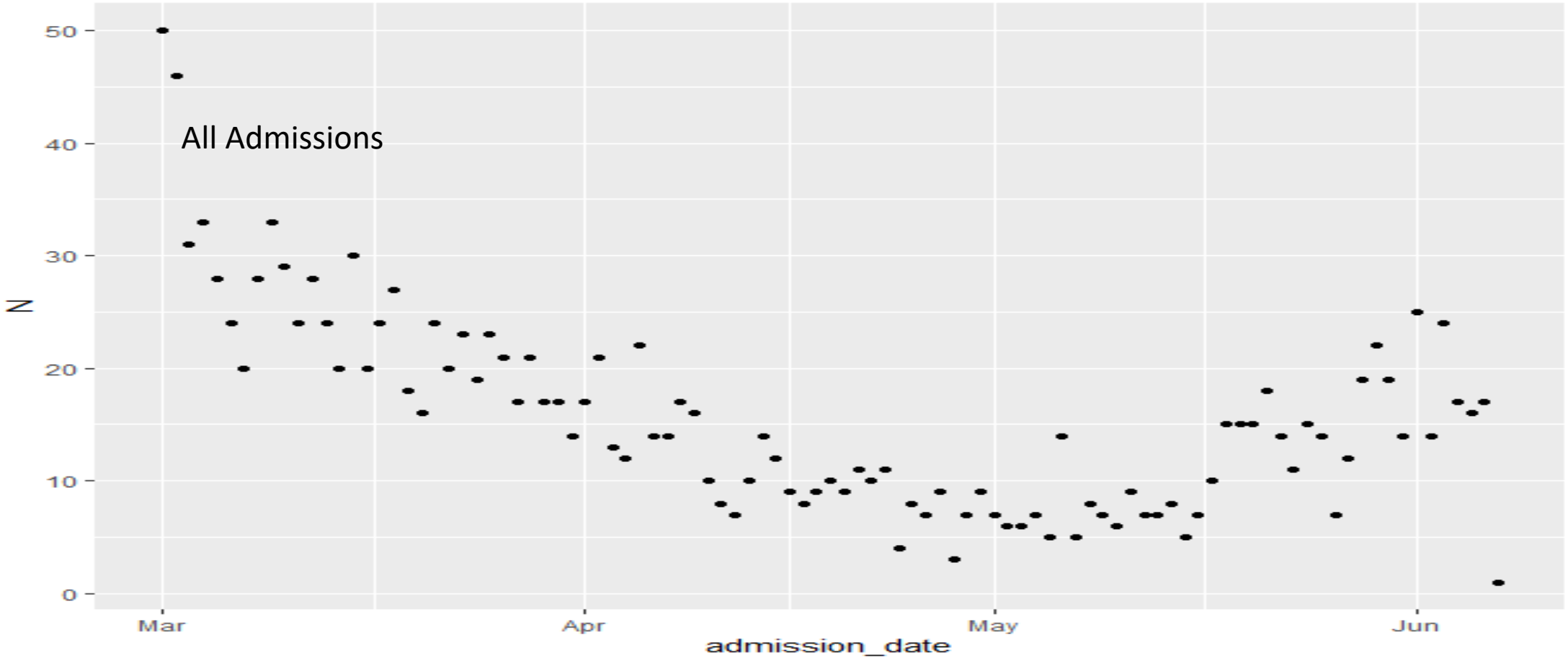
70% of cases have no clinical risk groups – similar pattern in all S Gene groups

70% are unvaccinated – lower than for other S Gene Groups





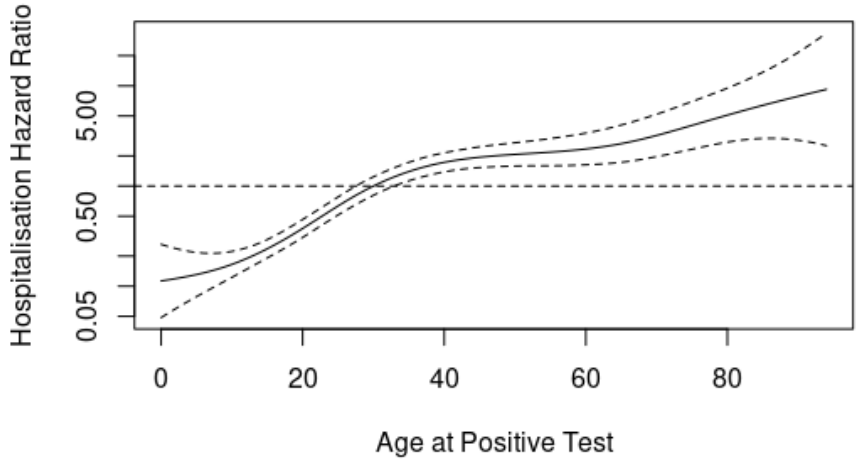
Daily Emergency Admissions to Hospital with a Positive Test



Date of positive test within 14 days prior to admission date and up to 2 days after
Reason for admission is unknown other than an emergency admission following community testing.

Risk of hospitalisation

		HR	LCL	UCL
S Gene Status	**S Gene Negative**	1.00		
	S Gene Positive	1.85	1.39	2.47
	Weak S Positive	0.51	0.30	0.87
Number of clinical	**0**	1.00		
Risk Groups	**1**	1.64	1.22	2.20
	2	1.77	1.31	2.38
	3-4	3.18	2.18	4.62
	5+	6.51	3.52	12.01
Vaccination Status	**Unvaccinated**	1.00		
	v1_0:27	0.65	0.45	0.93
	v1_28+	0.32	0.22	0.46
	v2_0:13	0.34	0.18	0.64
	v2_14+	0.30	0.16	0.54
Gender	**Female**	1.00		
	Male	0.98	0.80	1.21
Deprivation	**SIMD_Q1**	1.00		
	SIMD_Q2	1.07	0.81	1.42
	SIMD_Q3	0.94	0.68	1.29
	SIMD_Q4	0.78	0.56	1.08
	SIMD_Q5	0.73	0.52	1.04
	SIMD_Unknown	0.86	0.21	3.49



While hazard ratio of hospital admission increases with Age this is not nearly as steep as before vaccination

Positive S gene hazard ratio of hospitalisation for COVID-19 is 1.9 (95% CI 1.4, 2.5)

Increased hazard with increased co morbidities

Vaccinated 28+ or 2 doses less likely to be admitted

No temporal trend since April 01.

Vaccine effect against infection – Test Negative Design

06-Jun-21	All Tested	S Gene Positive					S Gene Negative				
Vaccine	Vaccine Status	N	R	VE	LCL	UCL	N	R	VE	LCL	UCL
	Unvaccinated	117263	3672	0	0	0	119419	5828	0	0	0
Pfizer-BioNTech	V1_0-27	6986	317	12	0	22	6857	188	31	20	41
	V1_28+	14214	163	30	17	41	14324	273	38	29	45
	V2_0-13	7233	15	66	43	80	7277	59	73	64	79
	V2_14+	53679	208	79	75	82	53575	104	92	90	93
	Unvaccinated	117263	3672	0	0	0	119419	5828	0	0	0
Oxford-AstraZeneca	V1_0-27	14863	293	7	-7	19	15137	567	9	-1	17
	V1_28+	51392	776	18	9	25	51572	956	37	32	42
	V2_0-13	13984	265	25	14	35	13818	99	64	56	71
	V2_14+	32719	231	60	53	66	32588	100	73	66	78

Vaccine effect is lower in the S Gene positive cases compared to the S Gene negative for 14+ days post dose 2 for both AZ and Pfizer.

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01408-4

Check for updates

OPEN

First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland

C. R. Simpson[1,2], T. Shi[2], E. Vasileiou[2], S. V. Katikireddi[3], S. Kerr[2], E. Moore[4], C. McCowan[5], U. Agrawal[5], S. A. Shah[2], L. D. Ritchie[6], J. Murray[4], J. Pan[7], D. T. Bradley[8,9], S. J. Stock[2], R. Wood[2,4], A. Chuter[10], J. Beggs[10], H. R. Stagg[2], M. Joy[11], R. S. M. Tsang[11], S. de Lusignan[11], R. Hobbs[11], R. A. Lyons[12], F. Torabi[12], S. Bedston[12], M. O'Leary[4], A. Akbari[12], J. McMenamin[4], C. Robertson[4,7] and A. Sheikh[2,10] ✉

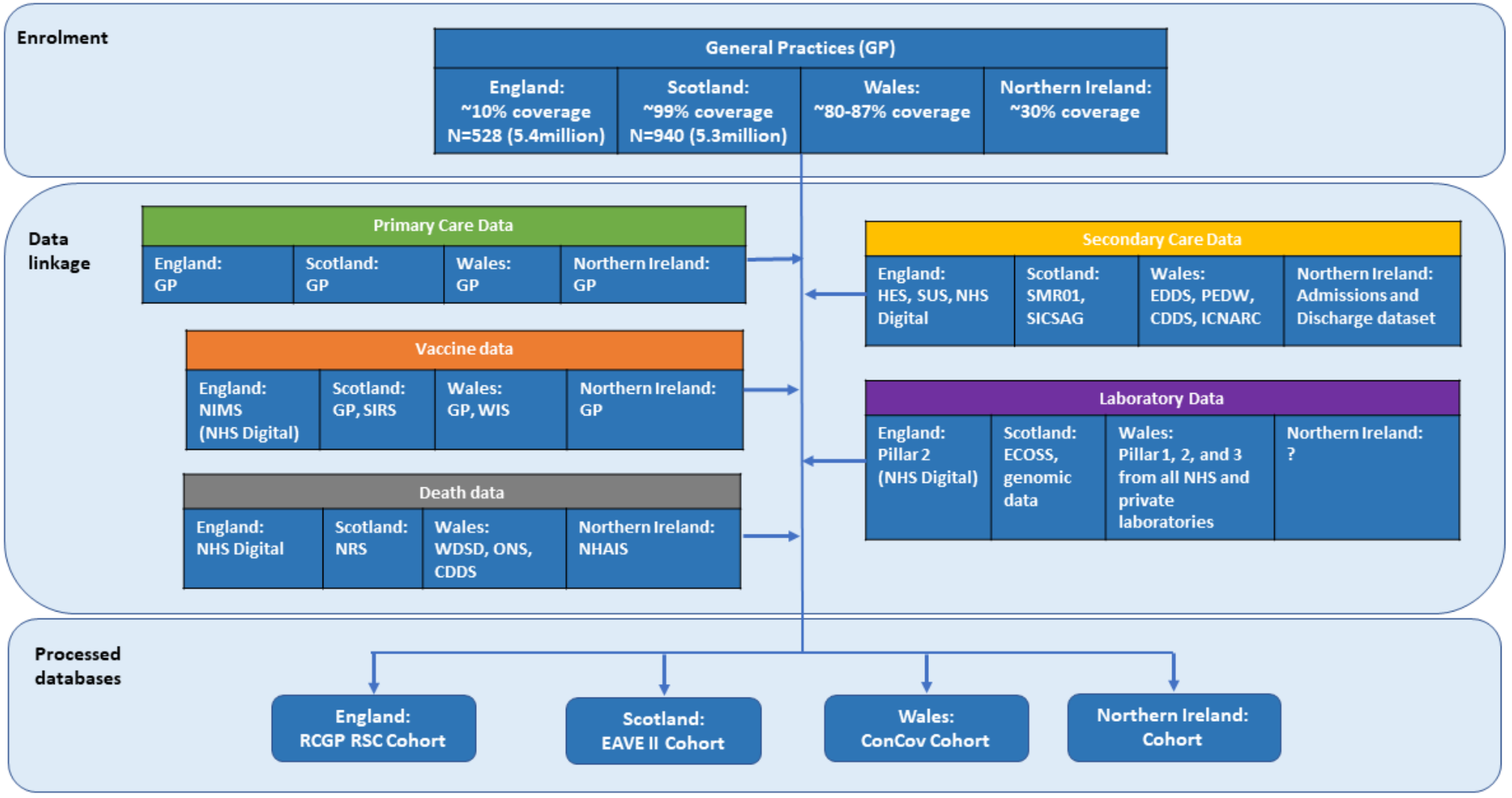
Reports of ChAdOx1 vaccine–associated thrombocytopenia and vascular adverse events have led to some countries restricting its use. Using a national prospective cohort, we estimated associations between exposure to first-dose ChAdOx1 or BNT162b2 vaccination and hematological and vascular adverse events using a nested incident-matched case-control study and a confirmatory self-controlled case series (SCCS) analysis. An association was found between ChAdOx1 vaccination and idiopathic thrombocytopenic purpura (ITP) (0–27 d after vaccination; adjusted rate ratio (aRR) = 5.77, 95% confidence interval (CI), 2.41–13.83), with an estimated incidence of 1.13 (0.62–1.63) cases per 100,000 doses. An SCCS analysis confirmed that this was unlikely due to bias (RR = 1.98 (1.29–3.02)). There was also an increased risk for arterial thromboembolic events (aRR = 1.22, 1.12–1.34) 0–27 d after vaccination, with an SCCS RR of 0.97 (0.93–1.02). For hemorrhagic events 0–27 d after vaccination, the aRR was 1.48 (1.12–1.96), with an SCCS RR of 0.95 (0.82–1.11). A first dose of ChAdOx1 was found to be associated with small increased risks of ITP, with suggestive evidence of an increased risk of arterial thromboembolic and hemorrhagic events. The attenuation of effect found in the SCCS analysis means that there is the potential for overestimation of the reported results, which might indicate the presence of some residual confounding or confounding by indication. Public health authorities should inform their jurisdictions of these relatively small increased risks associated with ChAdOx1. No positive associations were seen between BNT162b2 and thrombocytopenic, thromboembolic and hemorrhagic events.

Dac-VaP: This project enables, for the first time, a common near real-time approach
to studying COVID-19 vaccine uptake, safety and effectiveness, using routinely collected linked national datasets, across the UK.

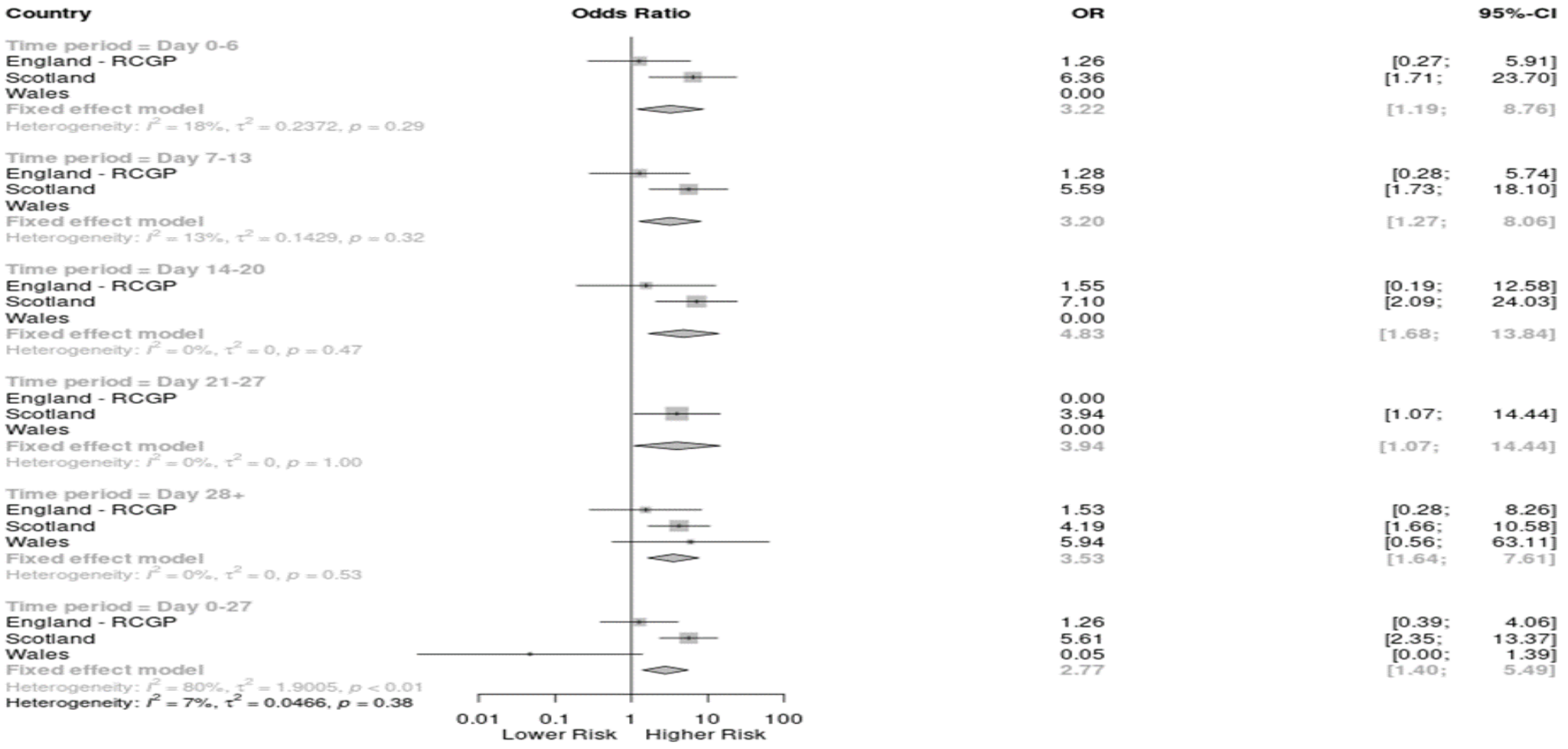
Key Collaborators

Scotland	England	Northern Ireland	Wales
The University of Edinburgh; usher institute; EAVE II; LBASOFT Healthcare Informatics; University of Strathclyde; Public Health Scotland	University of Oxford; Royal College of General Practitioners Research & Surveillance Centre	Queen's University Belfast; HSC Public Health Agency	Swansea University Prifysgol Abertawe; SAIL DATABANK; GIG CYMRU NHS WALES Iechyd Cyhoeddus Cymru Public Health Wales; Population Data Science at Swansea University

Data Linkage



Meta-analysis of association between first dose Oxford-AZ vaccine and ITP across England, Scotland and Wales



Examples of other analyses in progress

Scotland-wide

- Post first and second dose vaccine breakthroughs

Wales-wide

- Vaccine effectiveness in healthcare professionals

Scotland and England

- Post first vaccine dose neurological adverse events

UK-wide

- First and second dose vaccine dose waning

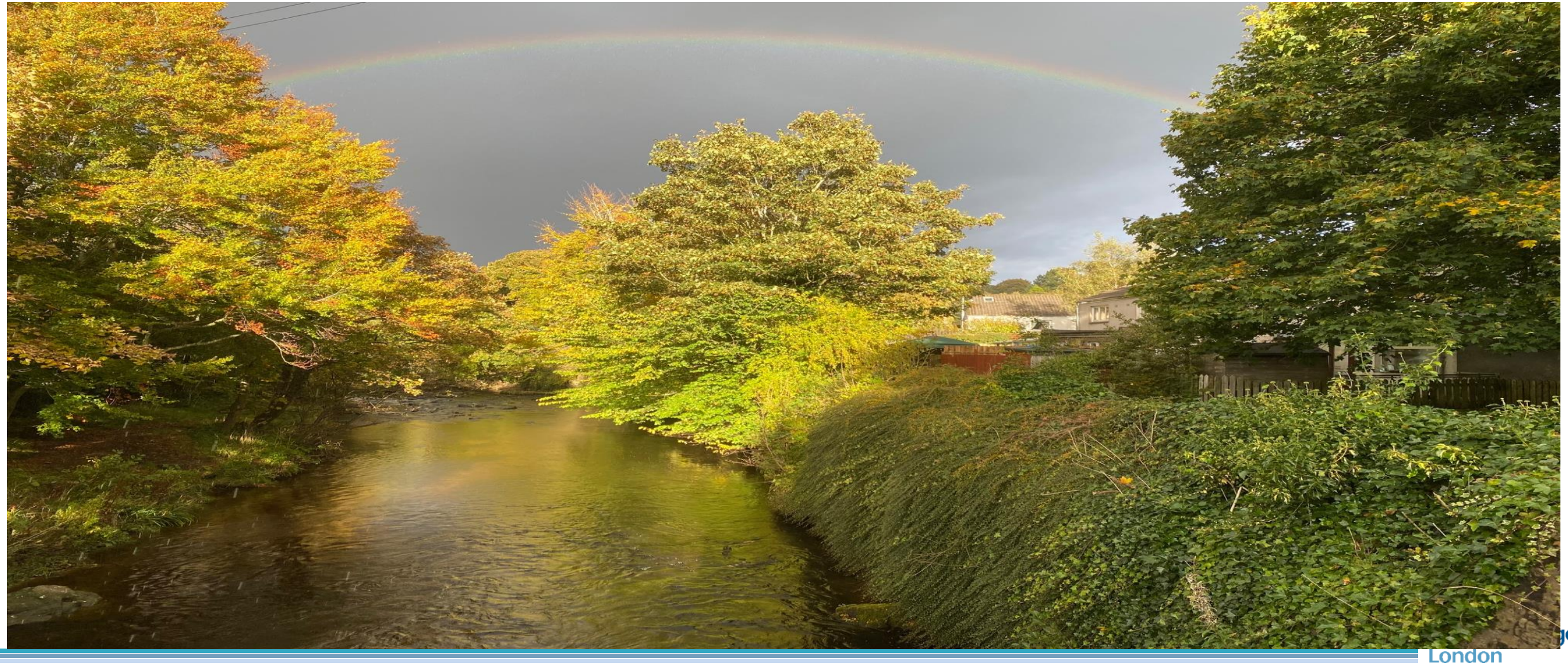
Acknowledgements

- Academic and public health colleagues across the UK
- Professional support staff
- Patient Advisory Group
- Funders

Thank you!

Email: aziz.sheikh@ed.ac.uk

@DrAzizSheikh



This research is part of the Data and Connectivity National Core Study, led by Health Data Research UK in partnership with the Office for National Statistics and funded by UK Research and Innovation.

For further project information please contact: mariagiorgiou@ed.ac.uk press.office@ed.ac.uk

HDR UK Scientific Conference
Data Insights in a Pandemic 23 June 2021

How has data enabled vaccine research?

REal-time Assessment of Community Transmission Study: REACT and Vaccine Data

Professor Paul Elliott
Imperial College London

Imperial College London
Ipsos MORI
NIHR | National Institute for Health Research
Department of Health & Social Care

REACT 1

Running monthly to monitor how the COVID-19 epidemic is progressing over time in the community in England

- 2-week+ ‘snapshot’ of prevalence and spread of COVID-19 across England
- Repeated cross-sections of the population, randomly selecting a new group of participants each round across all 315 lower tier local authorities
- 100,000 to 180,000 people take part in England each month
- Swabs carried from households in cold chain to lab for RT-PCR
- Estimation of R within our 2-week ‘snapshot’
- Prevalence and odds of infection for different socio-demographic characteristics by age, gender, region, key worker status, ethnicity, household size
- Self-report (and data linkage) on vaccine status
- Over 1.8 million people tested to date over 12 rounds

Imperial College London

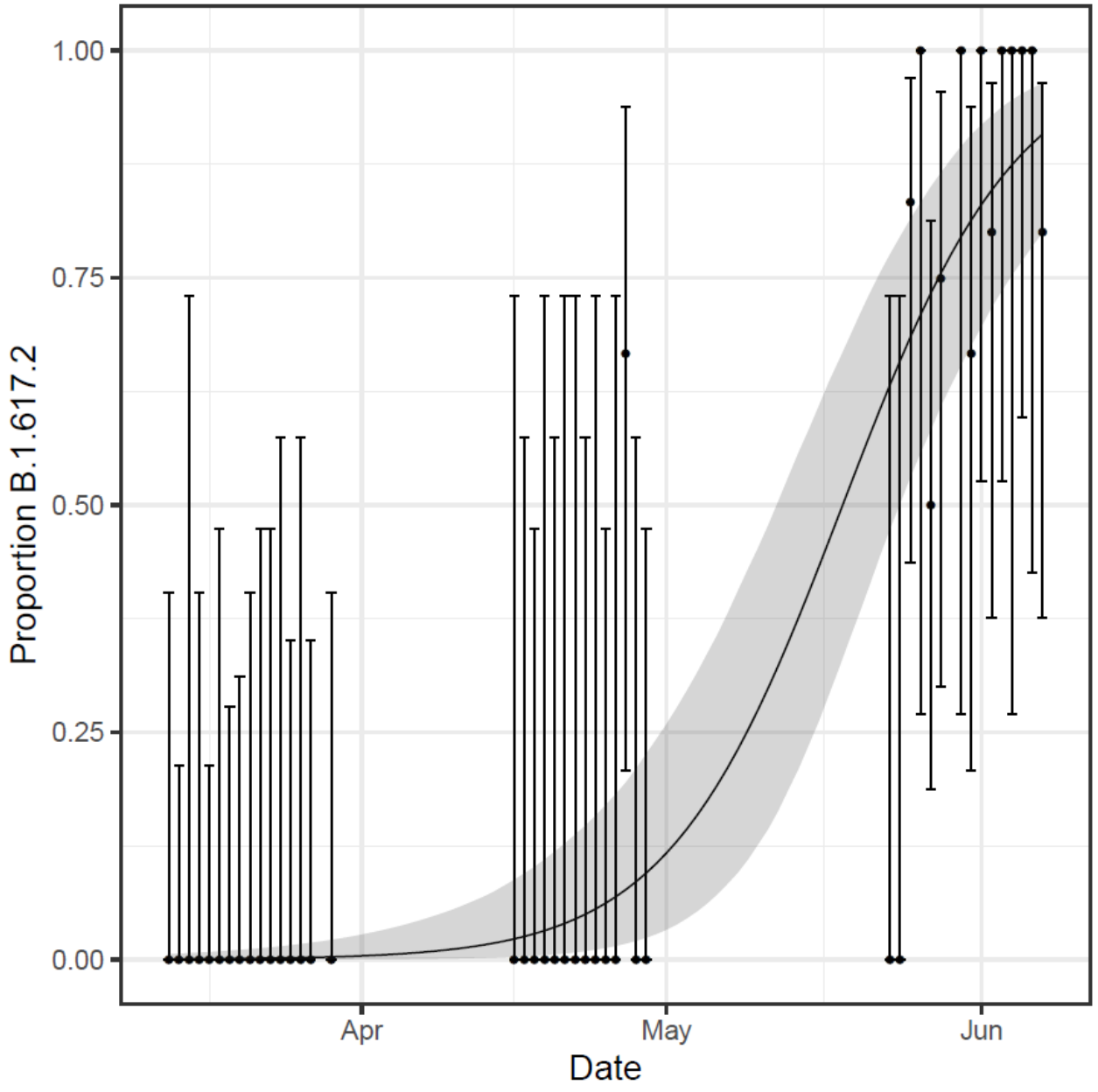
REACT-1: Viral sequencing

From round 11 (15 April to 3 May 2021) to round 12 (20 May to 7 June 2021):

- Near replacement of the Alpha variant with the Delta variant

During round 12

- Delta variant rose from ~60% to ~90% of all determined variants



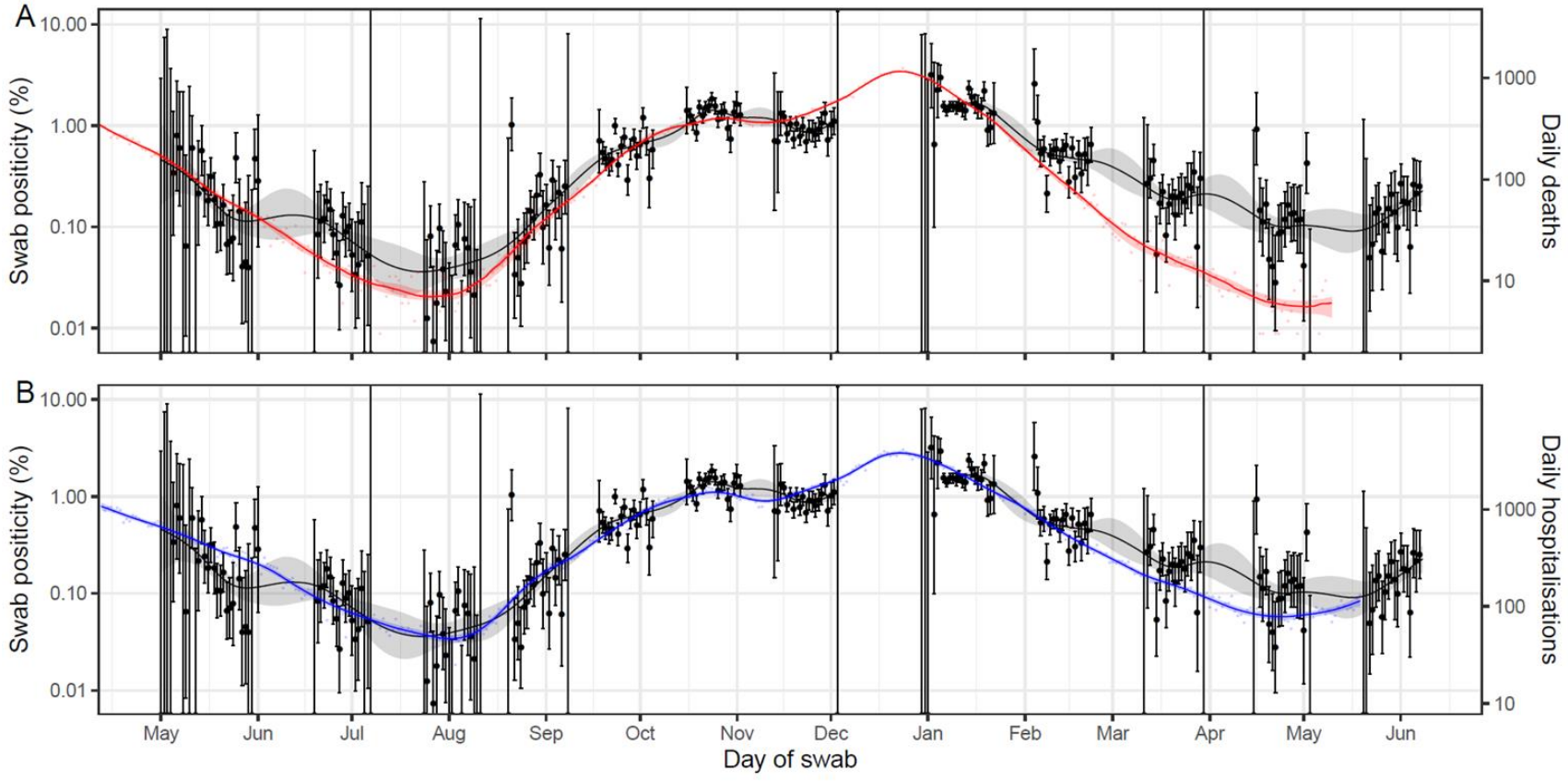
Prevalence compared to hospitalisations and deaths, all ages: May 2020 to June 2021

In early rounds of REACT close approximation of prevalence to:

- Deaths (lagged by 26 days)
- Hospital admissions (lagged by 19 days)

Divergence of deaths and hospitalisations from prevalence since February 2021

Hospitalisations have begun to reconverge since late April 2021



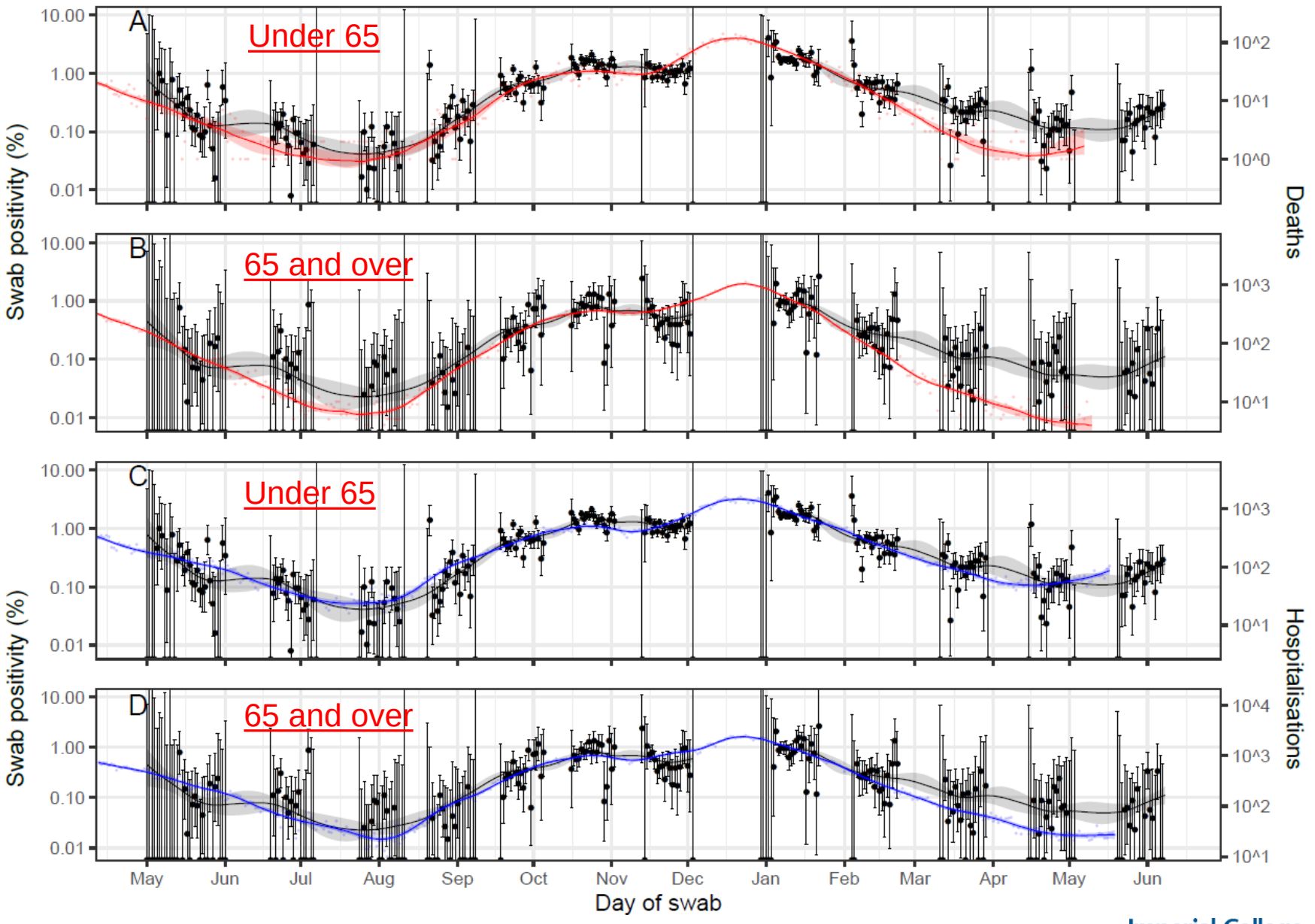
Prevalence compared to hospitalisations and deaths by age: May 2020 to June 2021

In those aged 65 and over (vaccinated population):

- Continued divergence of both deaths and hospitalisations

In those aged less than 65 (largely unvaccinated or single dose):

- Slight reconvergence of deaths
- Rapid reconvergence of hospitalisations



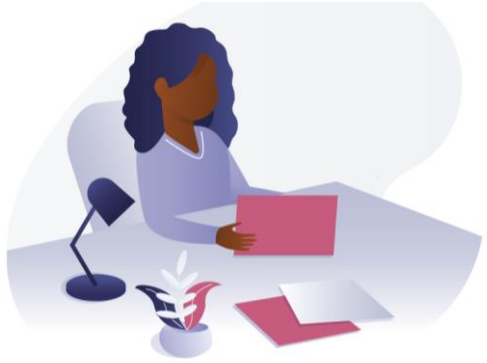
REACT-1 round 12 (20 May to 7 June 2021): Numbers and % PCR positive by vaccination status

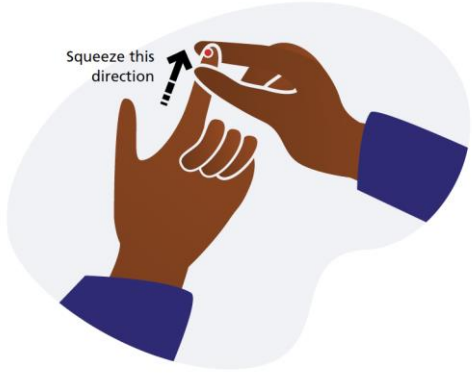
Age Group	Vaccination Status	Negative	Positive	Total	Percentage positive (95% confidence interval)
<65	Status not known	11107	27	11134	0.24% (0.17% , 0.35%)
	Not vaccinated	21854	51	21905	0.23% (0.18% , 0.31%)
	Vaccinated - dose not known	1176	0	1176	0.00% (0.00% , 0.23%)
	Vaccinated - 1 dose	18367	19	18386	0.10% (0.07% , 0.16%)
	Vaccinated - 2 doses *	25301	17	25318	0.07% (0.04% , 0.11%)
65+	Status not known	5034	6	5040	0.12% (0.05% , 0.26%)
	Not vaccinated	855	0	855	0.00% (0.00% , 0.32%)
	Vaccinated - dose not known	1713	1	1714	0.06% (0.01% , 0.33%)
	Vaccinated - 1 dose	287	1	288	0.35% (0.06% , 1.94%)
	Vaccinated - 2 doses *	23082	13	23095	0.06% (0.03% , 0.10%)

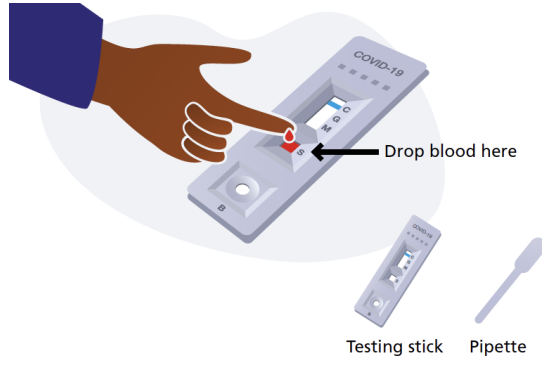
* Small number reporting 3 doses have been included in this group (<10 participants).

REACT-2: estimating community prevalence of SARS-CoV-2 antibody in England

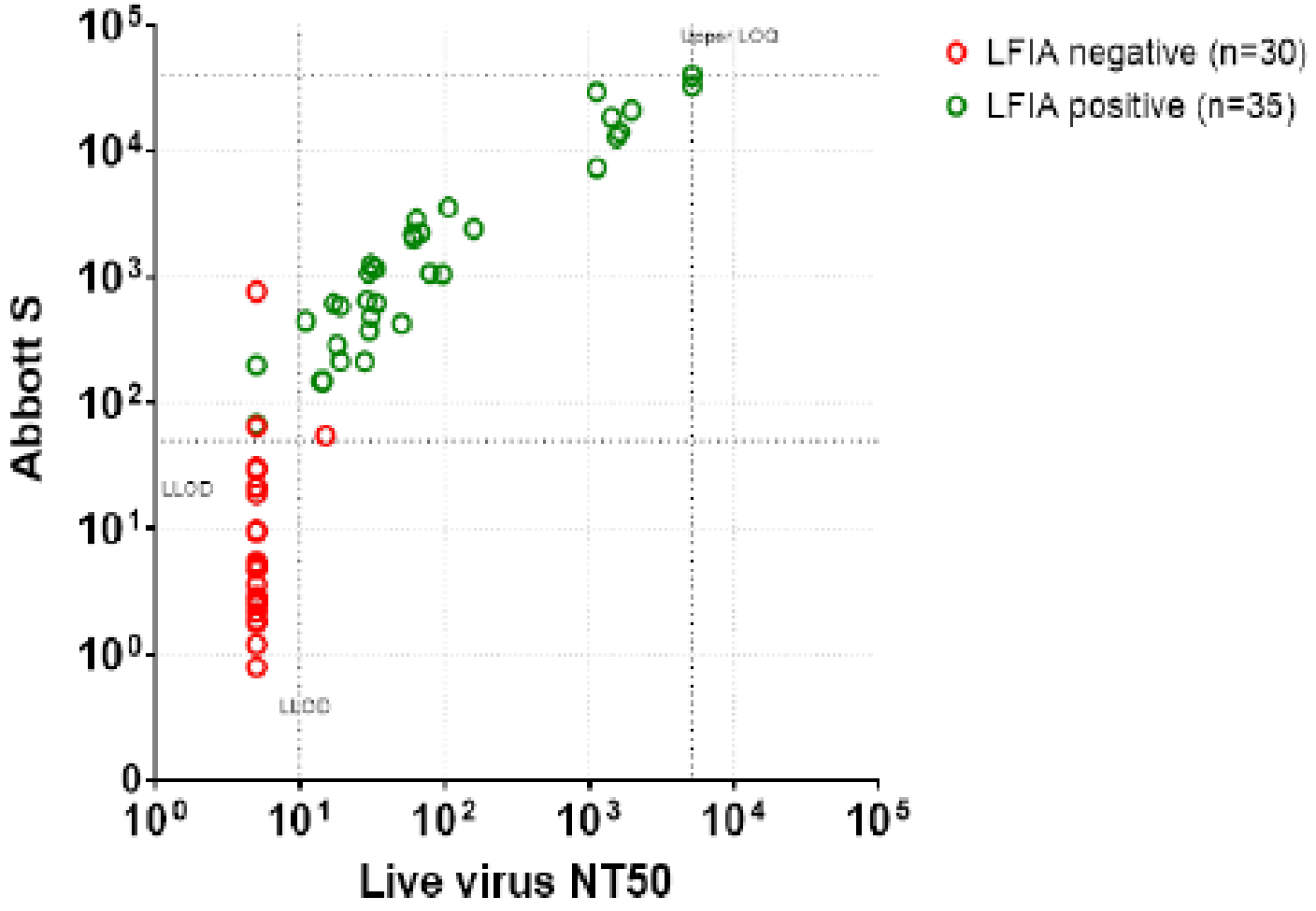
- Random sample of adults in England, 100,000 – 190,000 per round
- Self-sampling and testing at home
- Questionnaire to report result and upload photo of test
- Fortress LFIA
  - Coronavirus structural spike (S) protein as the target antigen
  - Compared to results from in-house ELISAs
    - sensitivity 84.4% (70.5, 93.5)
    - specificity 98.6% (97.1, 99.4)
- Analysis
  - Prevalence by age, sex, region, ethnicity, work
  - Track the epidemic
  - Measure changing antibody prevalence over time
  - Vaccination history





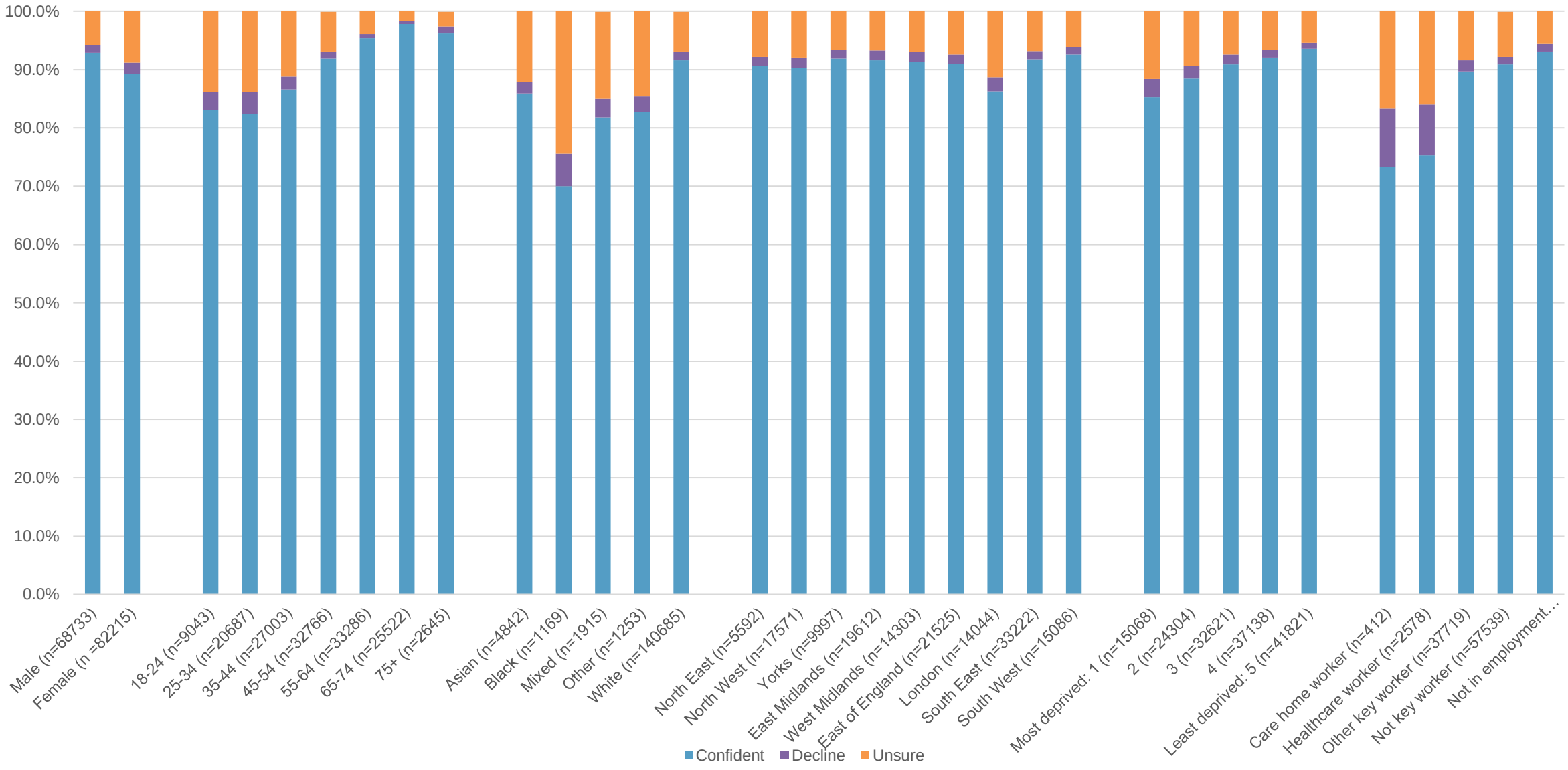


Association of LFIA results with virus micro-neutralisation titre, healthcare worker study

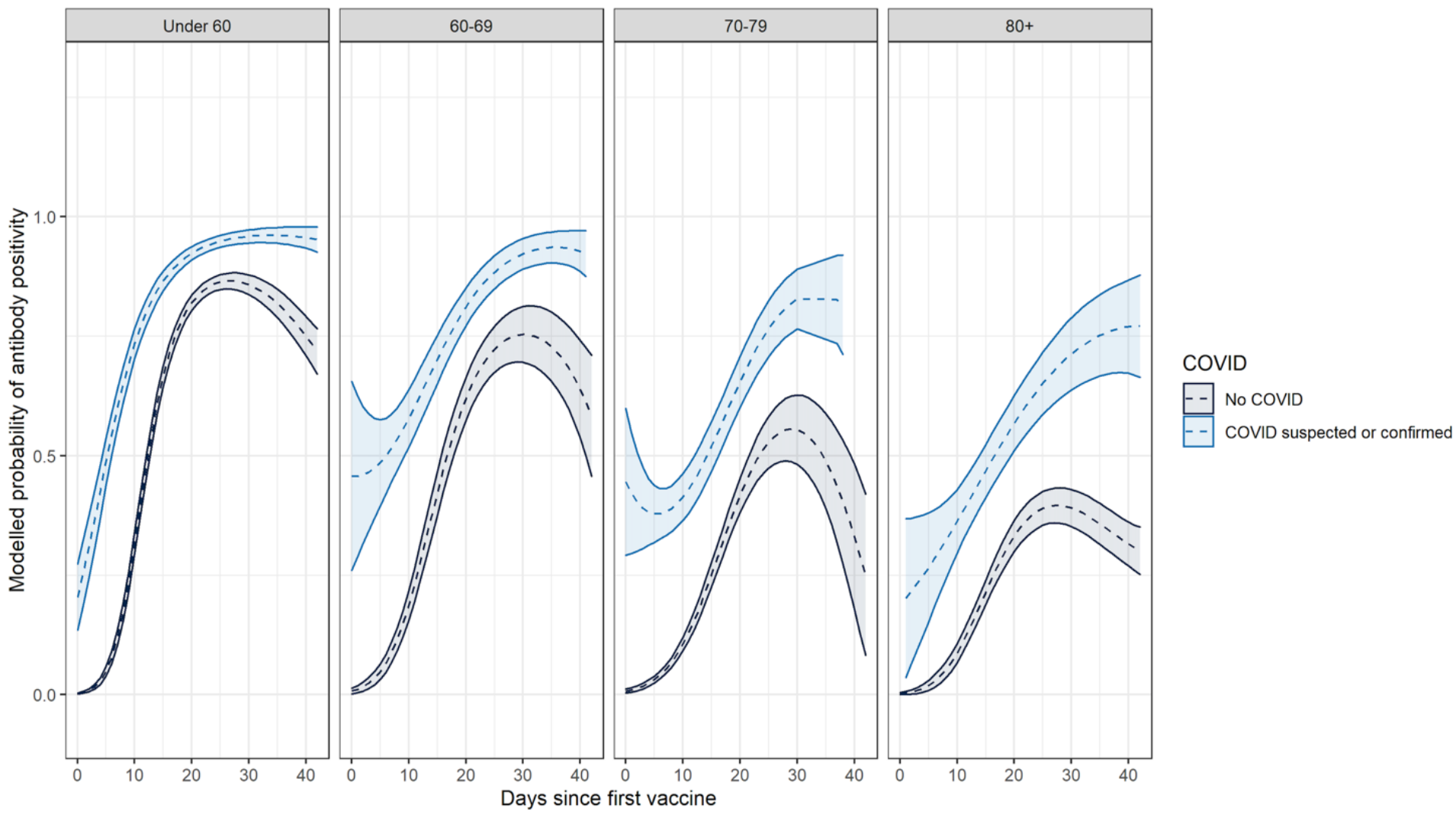


Sera from healthcare workers on day of vaccination or 21 days post vaccination with BNT162b2 first dose. Serum samples were assayed by live virus neutralisation assay using SARS-CoV-2 nucleocapsid staining as a readout for Vero-E6 cells. Serum titres required to neutralise 50% of virus signal were calculated (NT_{50}).

REACT 2: Vaccine confidence, Round 5 (26 January to 8 February 2021)
Proportion accepting or intend to accept vaccine offer (blue bars), n=172,099



REACT-2 Round 5: IgG positivity by age following single vaccination (Pfizer/BioNTech)



Modelled IgG positivity with time since single dose of BNT162b2, third order polynomial model by age group and prior COVID status
Logistic regression model with age and prior COVID infection status as categorical covariates and days since vaccine as a continuous variable with a third order polynomial term. Model includes interaction terms between i) age and days since vaccine, and ii) prior COVID infection status and days since vaccine. Shaded area indicates 95% confidence intervals, calculated from the standard error of the fitted values.

REACT-2 Round 5: IgG positivity
≥21 days after 1 and 2 Pfizer/BioNTech doses by age

	Pfizer single dose, >21 days earlier					Pfizer two doses				
Category	Positive	Total	Prevalence	Lower CI	Upper	Positive	Total	Prevalence	Lower	Upper
18-29	213	225	94.7	90.9	96.9	30	30	100.0	91.7	100.0
30-39	270	300	90.0	86.1	92.9	48	48	100.0	94.7	100.0
40-49	358	425	84.2	80.5	87.4	104	108	96.3	90.9	98.6
50-59	462	599	77.1	73.6	80.3	118	128	92.2	86.2	95.7
60-69	221	313	70.6	65.3	75.4	70	73	95.9	88.6	98.6
70-79	148	304	48.7	43.1	54.3	38	41	92.7	80.6	97.5
80+	293	845	34.7	31.5	37.9	477	543	87.8	84.8	90.3

Ward et al https://www.medrxiv.org/content/10.1101/2021.02.26.21252512v1.full.pdf

Summary

- Delta variant now dominant across England
- Divergence between infection prevalence and deaths and hospitalisations at ages 65+ consistent with two vaccine doses being highly effective
- Reconvergence between pattern of prevalence and pattern of deaths and hospitalisations since late April 2021 for those aged under 65
  - Rapid roll-out of mass vaccination to younger ages should effectively slow growth
- High vaccine confidence in most socio-demographic groups (Jan-Feb 2021)
- Excellent antibody response to prior infection and vaccine and two vaccine doses