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Impact of Delta and calendar time on vaccine effectiveness (VE) against new SARS-CoV-2 infection and Ct/viral burden in infections post-vaccination: preliminary analysis on data to 12 July 2021

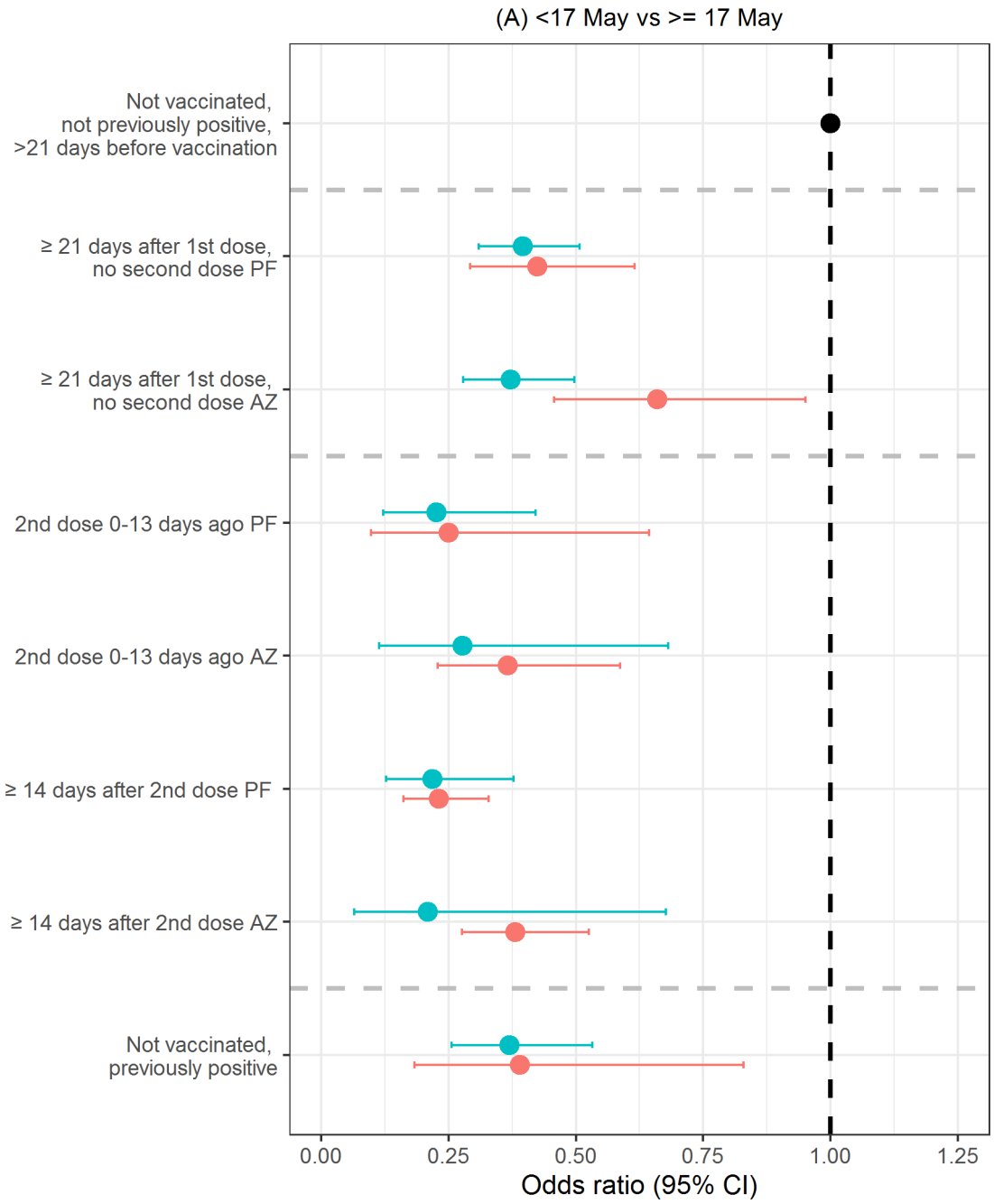
Koen B. Pouwels, Emma Pritchard, Philippa C. Matthews, Nicole Stoesser, David W. Eyre, Owen Gethings, Karina-Doris Vihta, Joel Jones, Thomas House, Jodie Hay, Iain Bell, John I Bell, John N Newton, Jeremy Farrar, Derrick Crook, Tim Peto, Duncan Cooke, Emma Rourke, Ruth Studley, Ian Diamond, A. Sarah Walker and the COVID-19 Infection Survey team

Summary

- We updated our previous vaccine effectiveness analysis (https://www.nature.com/articles/s41591-021-01410-w) using the same models (details at end), but splitting time from second vaccine dose by 0-13 days vs ≥14 days, and estimating separate effects for the calendar period 1dec2020-16may2021 (when Alpha was dominant) and 17may2021 onwards (when Delta became dominant).
- **[p3, table on p13]** Estimated vaccine effectiveness against all infections during 1dec2020-16may2021 (when Alpha was dominant) was similar to that previously reported on data to 8 May 2021 in https://www.nature.com/articles/s41591-021-01410-w.
- **[p3]** Post 17 May 2021, we found no evidence of significant attenuation of vaccine effectiveness (VE) against all new infections after first and second Pfizer doses versus pre 17 May 2021. However, we did find some evidence of attenuation for AZ, leading to significantly lower VE (higher odds ratios (OR)) for AZ vs Pfizer post 17 May2021.
    - For both vaccines, post 17 May 2021 two doses still provides significantly more protection than one dose.
    - Post 17 May 2021, there was no evidence that the effectiveness of AZ >=14 days post second vaccination differed from protection from prior infection without vaccination (heterogeneity p=1.00).
- **[p4, p5]** Considering new infections with Ct<30 or with symptoms as the outcome, power was much lower. Point estimates suggested numerically similar attenuation post 17 May 2021 vs pre 17 May 2021 with AZ to that observed for all new infections. Point estimates suggested some attenuation post 17 May 2021 vs pre 17 May 2021 with Pfizer, but to a smaller degree than with AZ, meaning that VE remained significantly or was still numerically greater with Pfizer than AZ after 17 May 2021 for infections with Ct<30 or with symptoms.
- **[p11, p12]** In contrast, there was no statistical evidence of differences pre vs post 17 May 2021 in vaccine effectiveness against infections with Ct≥30 or without any symptoms reported at any visit within [0,35] days of the first positive test; and point estimates of effect were similar, and substantially lower than against infections with Ct<30 or symptoms, in both periods.
- **[p6, p8]** With increasing time from first and second vaccination, Ct values increased significantly faster in positive cases pre vs post 17 May 2021 (heterogeneity in trend p=0.01), meaning that the difference in Ct values between positive cases that were unvaccinated vs >=14d post second dose narrower substantially, to only median +1.5 (-0.2,+3.2) in positive cases from 14 June 2021 onwards (median Ct 24.1 in unvaccinated [N=539] vs 25.6 in cases >=14d post second dose [N=490]).
    - **[p7, p9]** Ct values were significantly lower in positive cases occurring >=14d after two AZ doses [N=352] than 2 Pfizer doses [N=133]; the difference was median +2.9 (+0.1,+5.7) from 14 June 2021 onwards (p=0.02).
    - **[p7, p9]** Ct values in positive cases occurring >=14d post second dose were consistently estimated to come from a mixture of two sub-populations, a low Ct subpopulation (~21.5)

and a high Ct subpopulation (~33) (consistent with either mild or late identified infection). The relative percentage of cases falling into these two subpopulations varied over time.
    - **[p10]** Similar differences were seen for self-reported symptoms
- **[p11, p12]** In positive cases occurring >=14d post second dose, associations between Ct values and other factors appeared to varied by type of vaccine, being somewhat stronger with age and prior antibody levels [-70,-28] days previously for AZ, but with time since second vaccination for Pfizer. Associations were modest at best, and in particular, a substantial number of low Ct infections occurred in individuals with levels >100 ng/ml.

All infections: <17 May (cyan) vs >=17 May (coral)



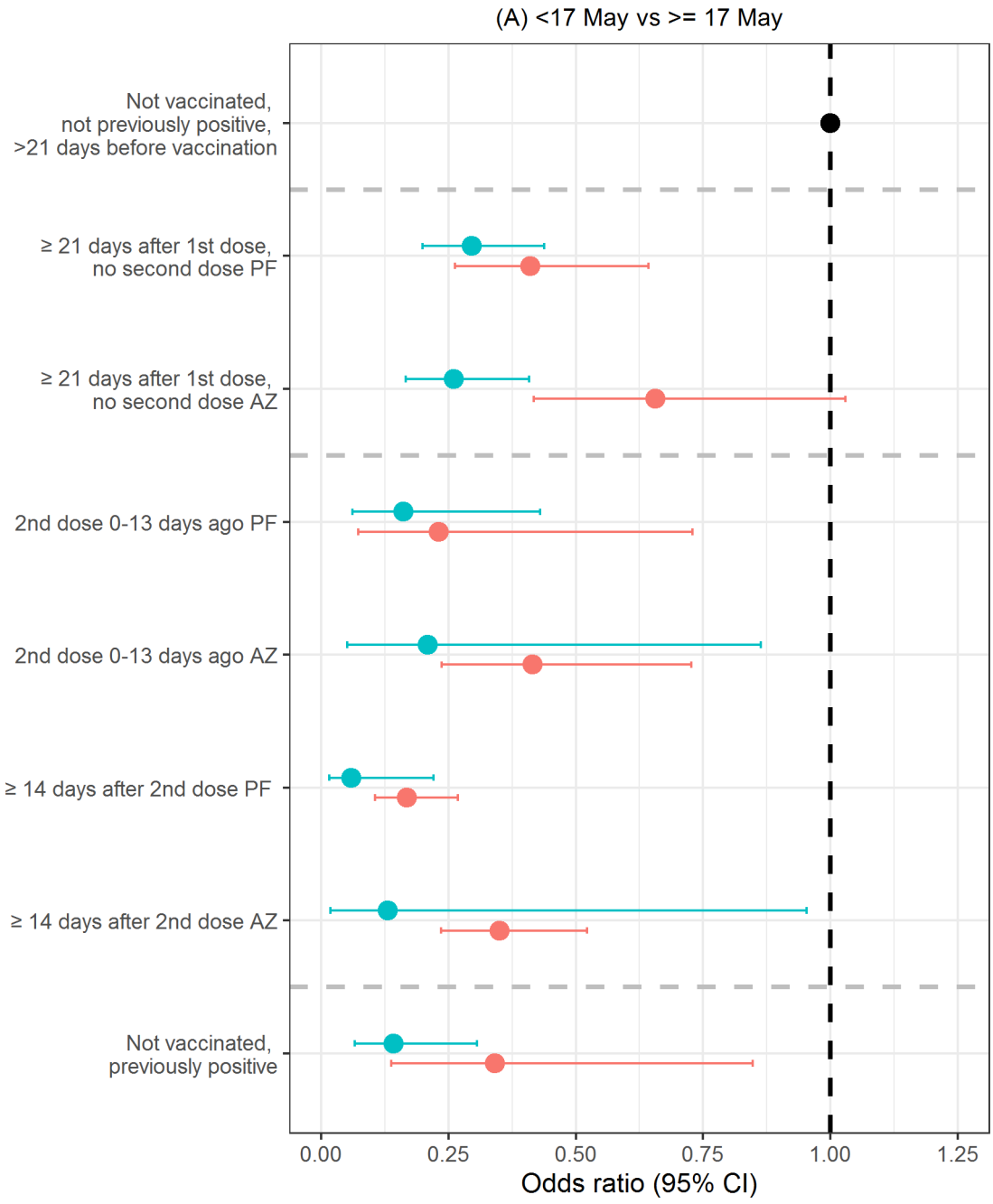
Note: see table on last page for VE estimates (=100%*(1-OR)). Unadjusted heterogeneity p-values:

	One dose ≥21 days	Second dose 0-13 days ago	Second dose ≥14 days
Pf: pre vs post 17may21	0.76	0.99	0.86
AZ: pre vs post 17may21	0.001	0.74	0.22
Pre 17may21: Pf vs AZ	1.00	1.00	1.00
Post 17may21: Pf vs AZ	0.02	0.99	<0.0001

Note: re-infection pre vs post 17may21 p=0.98

	Second dose ≥14 days vs one dose ≥21 days pre may 2021	Second dose ≥14 days vs one dose ≥21 days post may 2021	Second dose ≥14 days vs reinfection post may 2021
Pf	0.02	<0.0001	0.58
AZ	0.93	<0.0001	1.00

Infections with Ct<30: <17 May (cyan) vs >=17 May (coral)



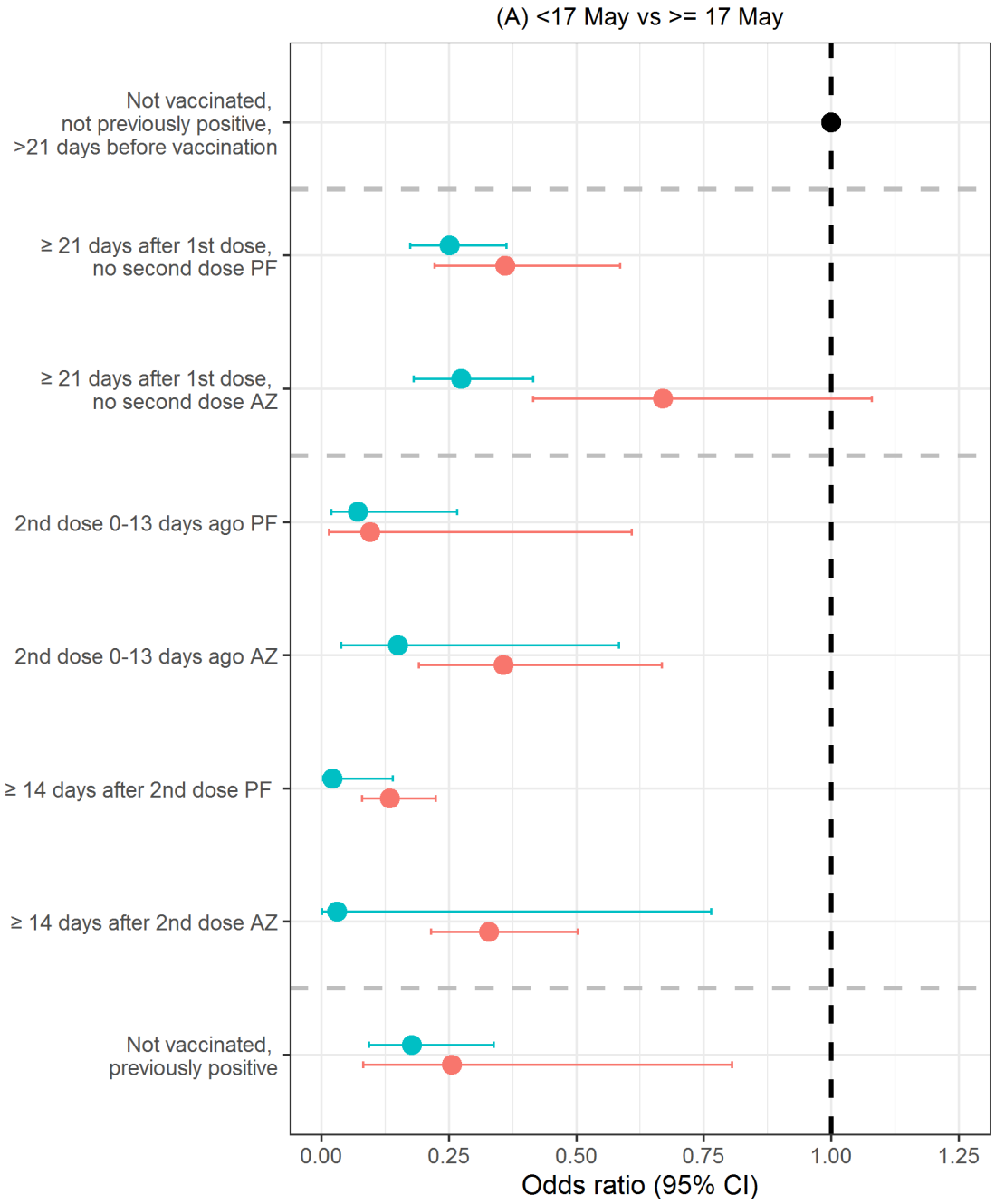
Note: see table on last page for VE estimates (=100%*(1-OR)). Unadjusted heterogeneity p-values:

	One dose ≥21 days	Second dose 0-13 days ago	Second dose ≥14 days
Pf: pre vs post 17may21	1.00	1.00	0.83
AZ: pre vs post 17may21	0.43	1.00	0.99
Pre 17may21: Pf vs AZ	1.00	1.00	1.00
Post 17may21: Pf vs AZ	0.07	0.94	<0.0001

Note: re-infection pre vs post 17may21 p=0.96

	Second dose ≥14 days vs one dose ≥21 days pre may 2021	Second dose ≥14 days vs one dose ≥21 days post may 2021	Second dose ≥14 days vs reinfection post may 2021
Pf	0.006	<0.0001	0.43
AZ	1.00	<0.0001	1.00

Infections with self-reported symptoms within [0,35] days of first positive test: <17 May (cyan) vs >=17 May (coral)



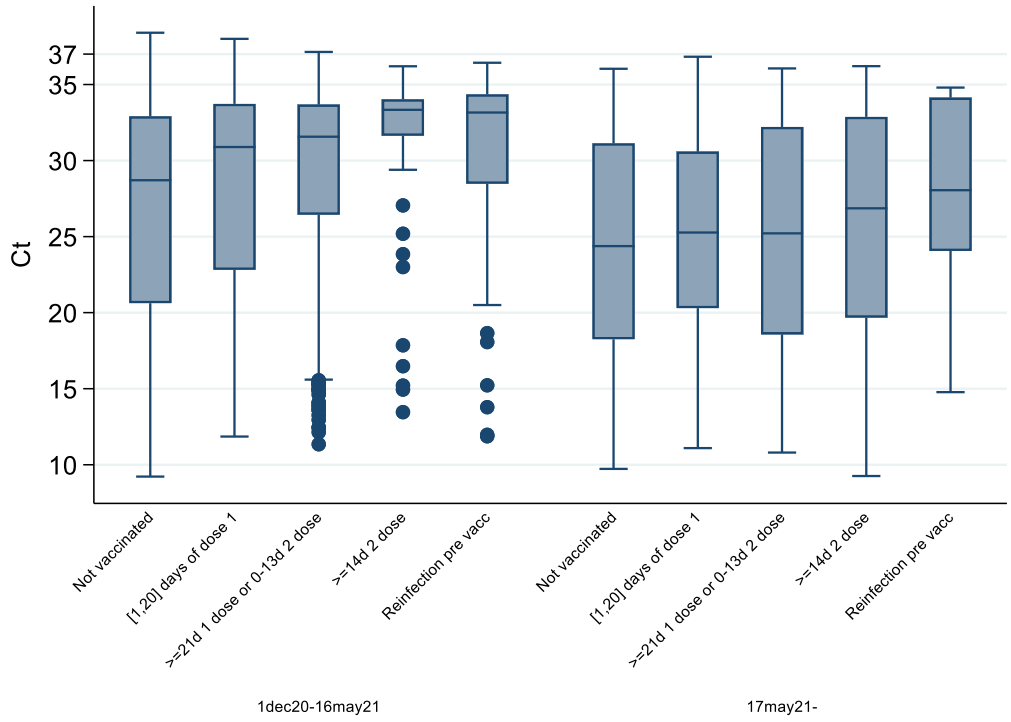
Note: see table on last page for VE estimates (=100%*(1-OR)). Unadjusted heterogeneity p-values:

	One dose ≥21 days	Second dose 0-13 days ago	Second dose ≥14 days
Pf: pre vs post 17may21	0.99	1.00	0.08
AZ: pre vs post 17may21	0.06	0.81	0.38
Pre 17may21: Pf vs AZ	1.00	0.99	1.00
Post 17may21: Pf vs AZ	0.008	0.50	<0.0001

Note: re-infection pre vs post 17may21 p=1.00

	Second dose ≥14 days vs one dose ≥21 days pre may 2021	Second dose ≥14 days vs one dose ≥21 days post may 2021	Second dose ≥14 days vs reinfection post may 2021
Pf	0.001	<0.0001	0.86
AZ	0.53	<0.0001	1.00

Ct values in new positive cases by vaccination/reinfection status 1dec20-16may21 (Alpha-compatible dominant) vs 17may21- (Delta-compatible dominant)



Note: boxes indicate median (IQR).

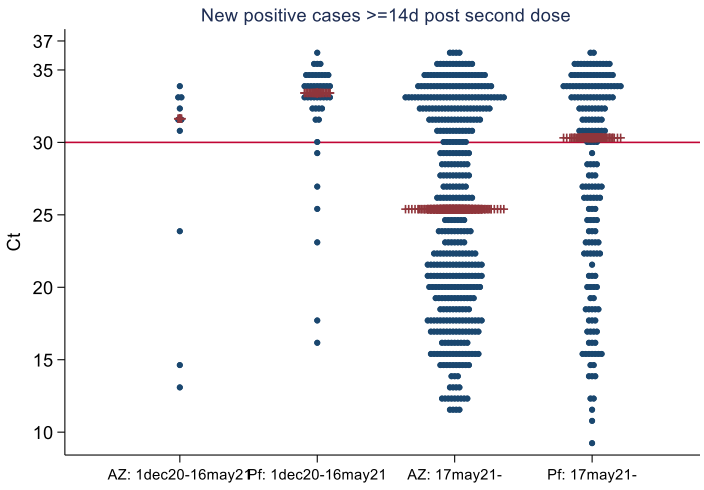
Across vaccination groups (excluding re-infections):

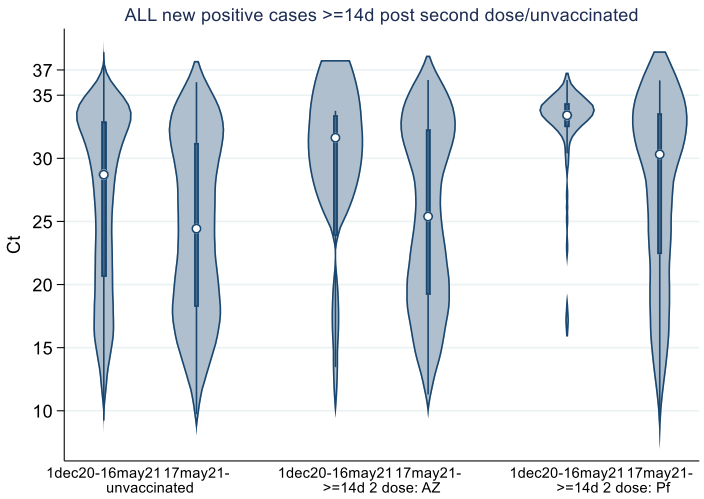
	Median (IQR) in unvaccinated [N]	Median (IQR) in >=14d post second dose [N]	p (ranksum)	Median (95% CI) Ct difference >=14d post second dose vs unvaccinated	Change in median Ct per additional vaccination group* (95% CI)	p (trend)
1dec20-16may21 (Alpha-dominant)	28.7 (20.6-32.9 [N=13520]	33.3 (31.6-34.0) [N=56]	<0.0001	+4.6 (+1.3,+8.0)	+1.5 (+1.1,+2.0)	<0.0001
17may21- (Delta-dominant)	24.4 (18.2-31.1) [N=717]	26.9 (19.7-32.9) [N=592]	0.0001	+2.5 (+0.8,+4.2)	+0.7 (+0.3,+1.2)	0.002
Heterogeneity	-	-	-	p=0.25	p=0.01	-

* estimating average change in median Ct comparing [1,20] days after 1st dose vs unvaccinated, >=21 days after first dose through to 13 days post second dose vs [1,20] days after 1st dose, >=14 days post second dose vs >=21 days after first dose through to 13 days post second dose – ie trend in Ct across the first 4 categories above (excluding re-infection).

Note: 6 cases 17may21- onwards with specific vaccine type unknown.

Ct values in new cases before [N=56] and after [N=592] 17 May 2021 who were >=14 days post second vaccination





	Median (IQR) in AZ [N]	Median (IQR) in Pf [N]	p (ranksum)	Change in median Ct (95% CI)
1dec20-16may21 (Alpha-dominant)	31.6 (23.8-33.4) [N=10]	33.4 (32.5-34.4) [N=43]	0.008	+1.9 (-0.4,+4.2)
17may21- (Delta-dominant)	25.4 (19.2-32.3) [N=412]	30.3 (22.4-33.5) [N=174]	0.0003	+4.9 (+2.3,+7.6)

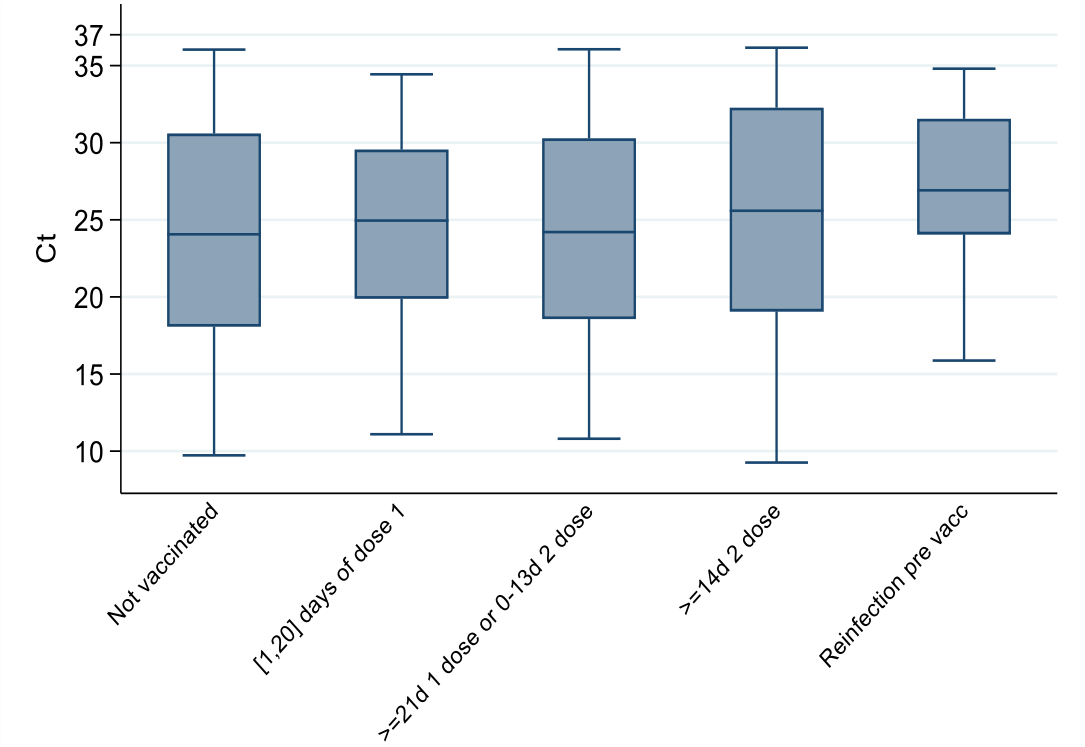
Note: 3 and 6 vaccine types respectively unknown or mixed.

Best fitting mixture model (based on BIC) for new positives >=14 days after second vaccine dose had two distributions for both time periods:

>=14days after second dose	1dec20-16may21 (Alpha-dominant) [N=56]		17may21- (Delta-dominant) [N=586]	
	% in class	Mean Ct	% in class	Mean Ct
Higher viral burden	20%	21.7 (16.6-26.9)	62%	21.3 (20.6-22.0)
Lower viral burden	80%	33.5 (33.1-33.9)	38%	33.2 (33.0-33.5)

- In both periods, Ct values in positive cases occurring >14d post vaccination were estimated to come from a mixture distribution of a low Ct subpopulation (~21.5) and a high Ct subpopulation (~33) (consistent with either mild or late identified infection). What differed is the percentage of positive cases falling into the low Ct/higher viral burden subpopulation (20% pre vs 62% post 17 May 2021)

Ct values in new positive cases by vaccination/reinfection status in last 4 weeks (from 14jun2021) when all cases were plausible Delta-compatible, regardless of Ct

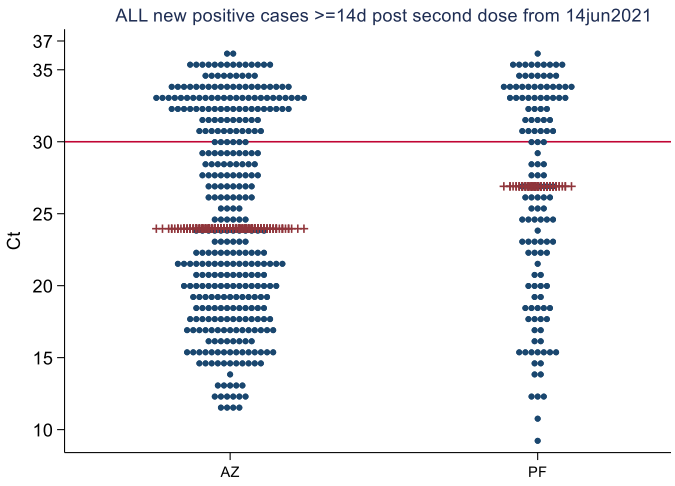


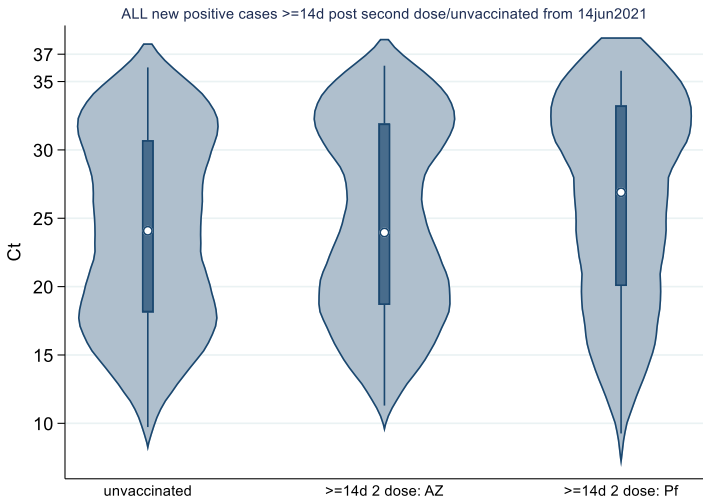
Note: boxes indicate median (IQR).

Across vaccination groups (excluding re-infections):

	Median (IQR) in unvaccinated [N]	Median (IQR) in >=14d post second dose [N]	p (ranksum)	Median (95% CI) Ct difference >=14d post second dose vs unvaccinated	Change in median Ct per additional vaccination group* (95% CI)	p (trend)
14jun21-	24.1 (18.1-30.6) [N=539]	25.6 (19.1-32.3) [N=490]	0.007	+1.5 (-0.2,+3.2)	+0.3 (-0.2,+0.9)	0.24

Ct values in new positive cases after 14 June 2021 who were >=14 days post second vaccination





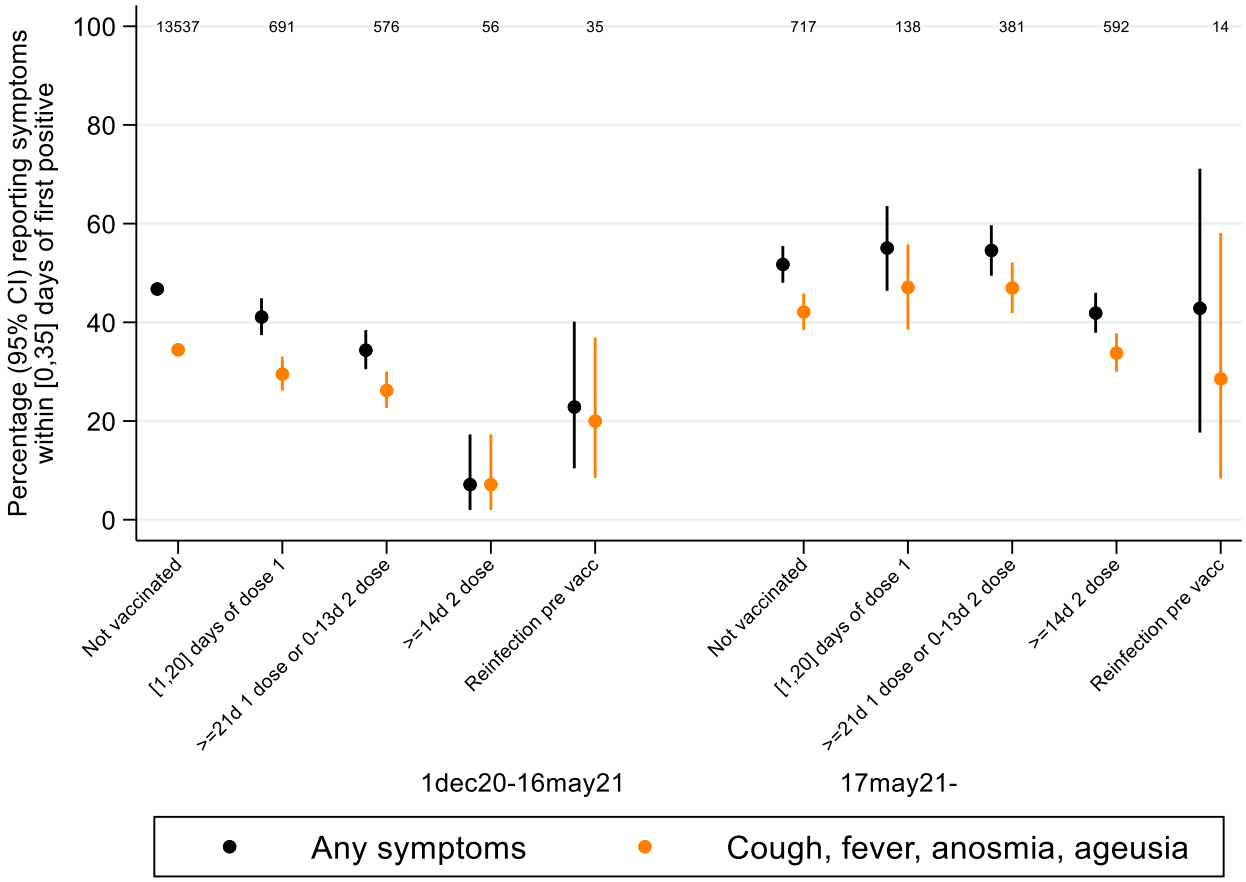
	Median (IQR) in AZ [N]	Median (IQR) in Pf [N]	p (ranksum)	Change in median Ct (95% CI)
14jun21-	24.0 (18.7-31.9) [N=352]	26.9 (20.0-33.3) [N=133]	0.02	+2.9 (+0.1,+5.7)

Note: 5 vaccine types respectively unknown or mixed.

Best fitting mixture model (based on BIC) for new positives >=14 days after second vaccine dose had two distributions, as above, with similar means and similar percentages in the low Ct/higher viral burden subpopulation:

>=14days after second dose	14jun21- [N=485]	
	% in class	Mean Ct
Higher viral burden	68%	21.3 (20.6-22.1)
Lower viral burden	32%	33.2 (32.9-33.5)

Symptoms reported in new positive cases by vaccination/reinfection status 1dec20-16may21 (Alpha-dominant) and 17may21- (Delta-dominant)

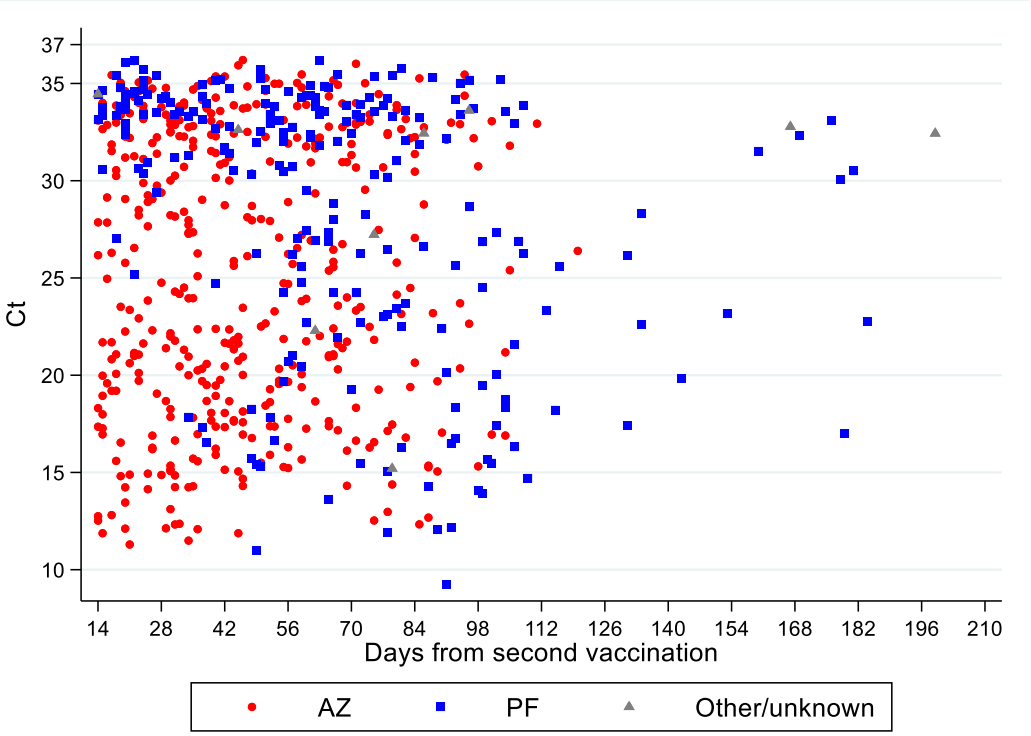


	Any symptoms		Cough, fever, anosmia, ageusia	
	p (trend)*	p unvaccinated vs in >=14d post second dose (exact)	p (trend)*	p unvaccinated vs in >=14d post second dose (exact)
1dec20-16may21 (Alpha-dominant)	<0.0001	<0.0001	<0.0001	<0.0001
17may21- (Delta-dominant)	0.02	<0.0001	0.01	<0.0001

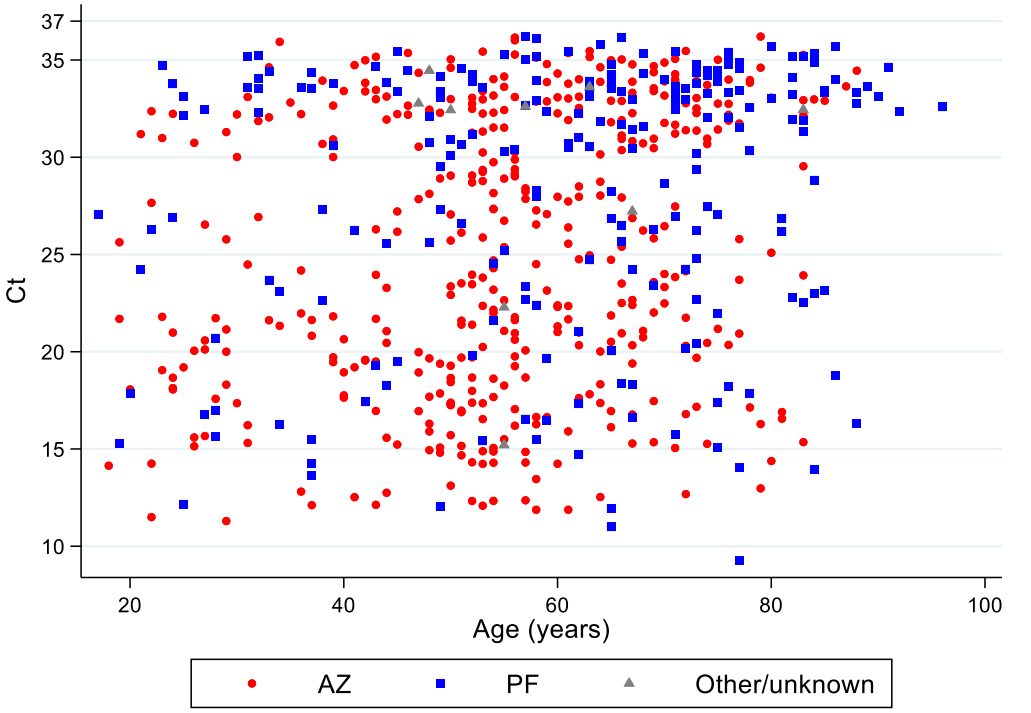
* estimating average change in odds of symptoms comparing [1,20] days after 1st dose vs unvaccinated, >=21 days after first dose through to 13 days post second dose vs [1,20] days after 1st dose, >=14 days post second dose vs >=21 days after first dose through to 13 days post second dose – ie trend in ymptoms across the first 4 categories above (excluding re-infection).

Characteristics of new positive cases >=14d post second vaccine dose

No overall evidence of association with time from second vaccination (Spearman rho=-0.06, p=0.10), although stronger for Pf (Spearman rho=-0.41, p<0.0001) than AZ (Spearman rho=0.04, p=0.45), potentially consistent with waning antibody.

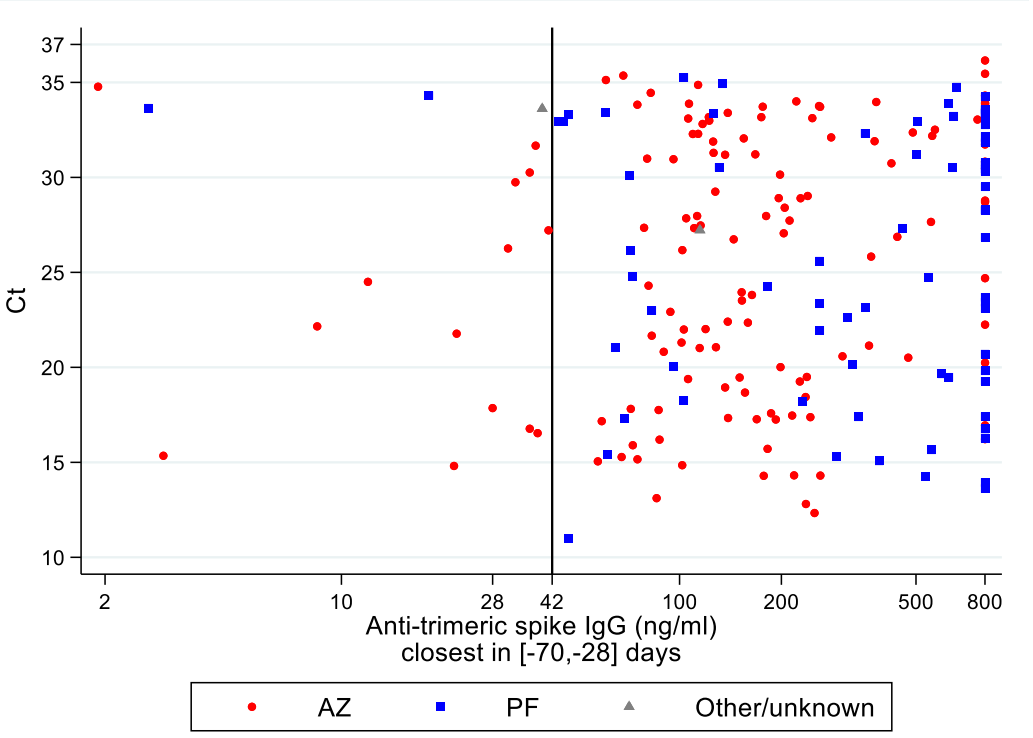


At most, modest association with age (Spearman rho=0.23, p<0.0001), although slightly stronger for AZ (Spearman rho=0.23, p<0.0001) than Pfizer (Spearman rho=0.15, p=0.03).



Most recent prior antibody 28-70 days prior to new positive cases

204/648 (31%) of positive cases who were >=14 days post vaccination at their positive swab had an S-antibody measurement 28-70 days previously (window to allow for late detection causing immediately preceding antibody measurements to be due to the current infection). Overall association between Ct values and S-antibody was low (Spearman rho=0.10, p=0.17); although it was slightly higher for AZ (Spearman rho=0.19, p=0.03) than Pfizer (Spearman rho=-0.01, p=0.94), there was no formal evidence of heterogeneity (p=0.25).



Additional information on Methods

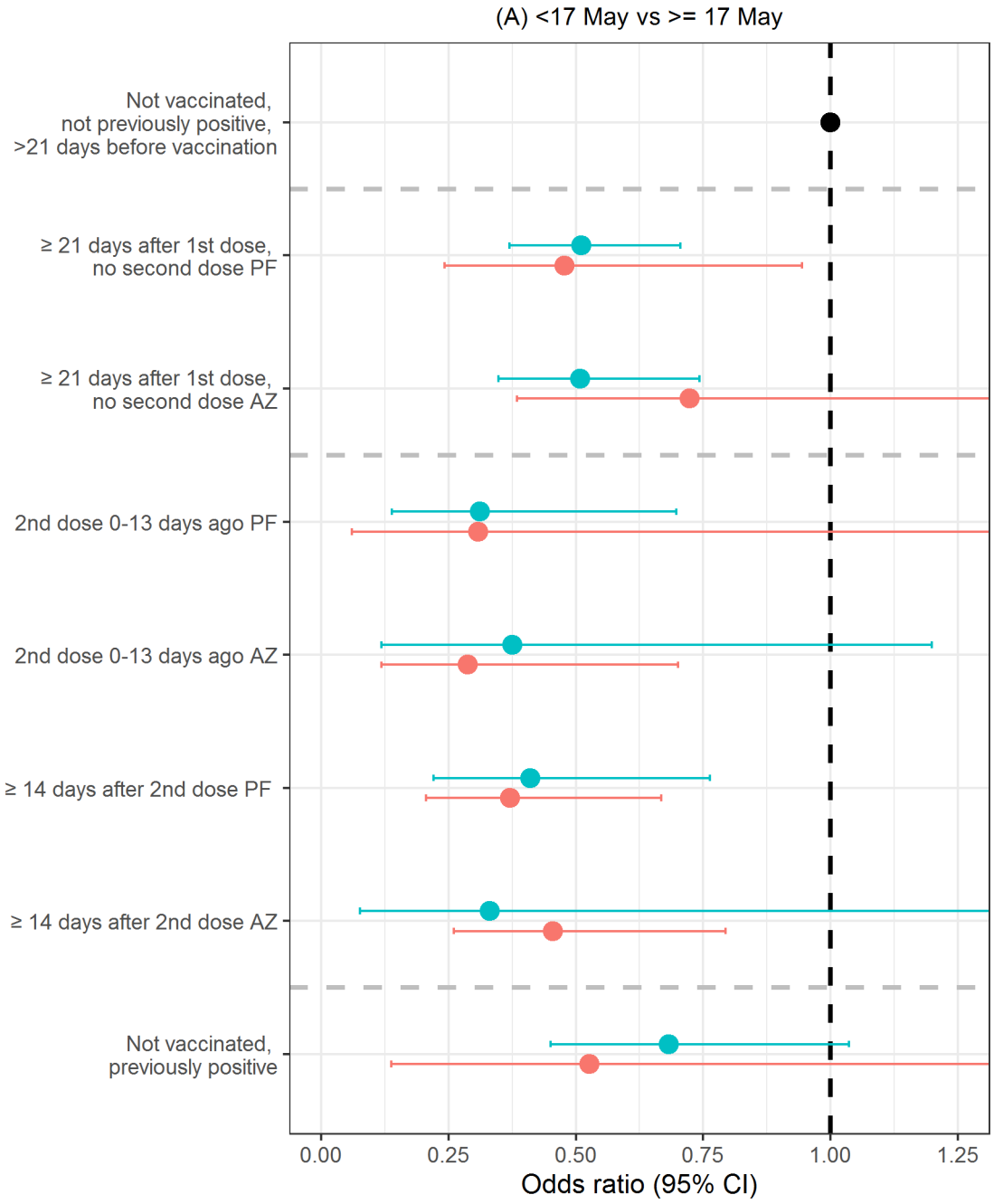
Associations between the different vaccination/reinfection exposure groups and outcome (first positive test in an infection episode vs test-negative) were evaluated with generalised linear models with a logit link. Robust standard errors were used to account for multiple visits per-participant. To adjust for substantial confounding by calendar time and age, with non-linear effects of age which are also different by region, we included both as restricted cubic splines with knots at the 20%, 40%, 60%, and 80% percentiles of unique values and interactions between these splines and region/country (regions for England and country for Northern Ireland, Scotland and Wales). Furthermore, given previous observations of different positivity rates by age over time, we added a tensor spline to model the interaction between age and calendar time with the restriction that the interaction is not doubly non-linear. The following potential confounders were adjusted for in all models as potential risk factors for acquiring SARS-CoV-2 infection: geographic area and age in years (see above), sex, ethnicity (white vs non-white as small numbers), index of multiple deprivation (percentile, calculated separately for each country in the UK), working in a care-home, having a patient-facing role in health or social care, presence of long-term health conditions, household size, multigenerational household, rural-urban classification, direct or indirect contact with a hospital or care-home, smoking status, and visit frequency.

Positive episode

We included in analyses the first positive test in each 'positive episode', (arbitrarily) defined as a new positive >120 days after an index positive with the preceding test being negative, or a new positive after 4 consecutive negative tests. Each positive episode was classified as triple positive if the S-gene was ever detected within it (by definition, in combination with either N or ORF1ab or both N+ORF1ab), otherwise Alpha-compatible if positive at least once for ORF1ab+N, and otherwise "other" (all positives N-only or ORF1ab-only), and by the minimum Ct value across positive tests in the episode. Presence or absence of specific symptoms and any self-reported symptoms overall (i.e. including the generic symptoms question) included reports at any (test positive or negative or failed) visit within [0,+35] days of the first positive per episode (i.e. spanning [-7,+35] days given the question timeframe (over the last 7 days)). We excluded all negative tests following an infection episode until the first visit where the participant could have been classified as a new infection episode, were the test to have been positive. All other negative visits formed the comparator group.

Additional results

Infections with Ct≥30: <17 May (cyan) vs >=17 May (coral)



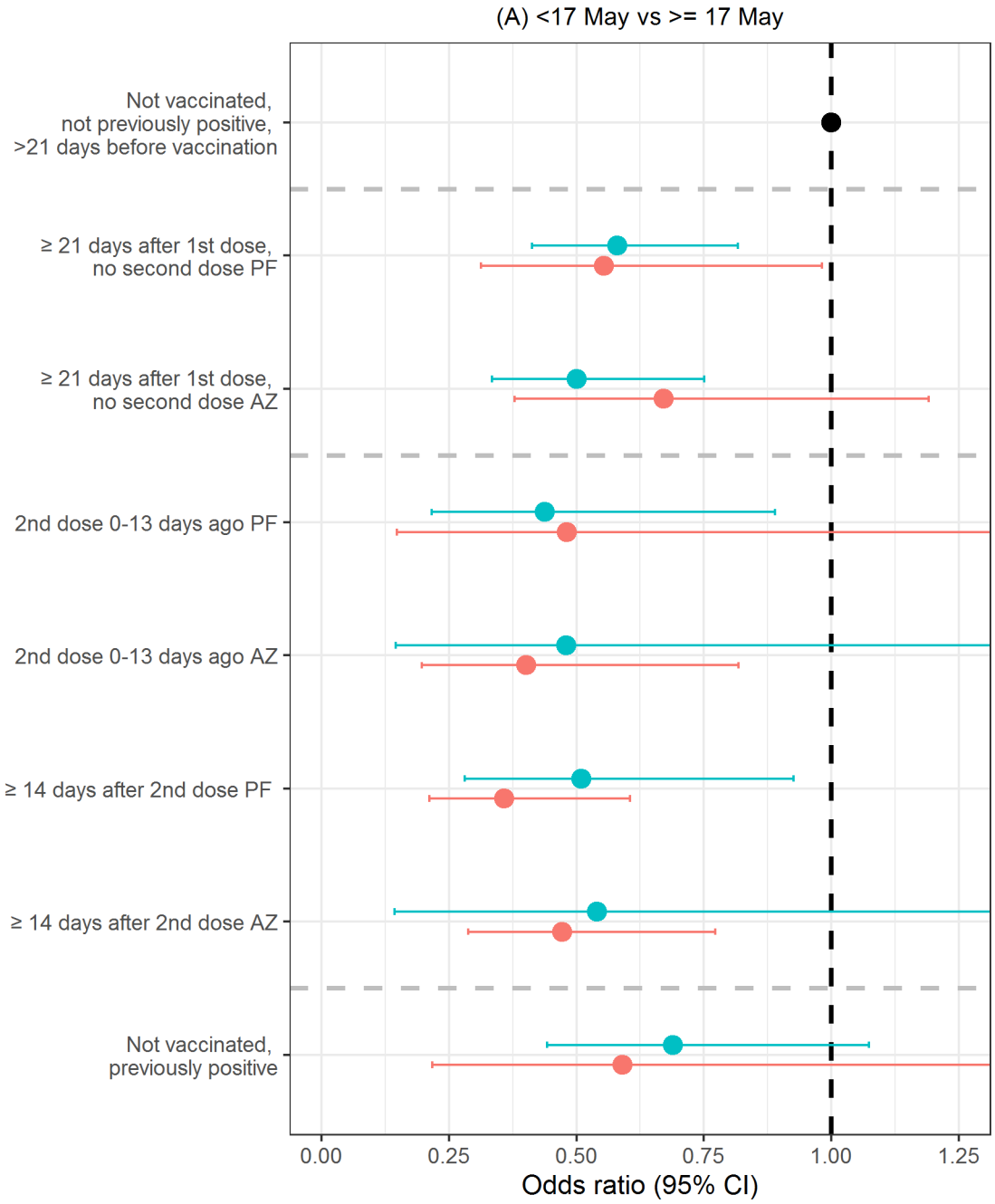
Note: see table on last page for VE estimates (=100%*(1-OR)). Unadjusted heterogeneity p-values:

	One dose ≥21 days	Second dose 0-13 days ago	Second dose ≥14 days
Pf: pre vs post 17may21	0.62	0.98	0.58
AZ: pre vs post 17may21	0.02	0.99	0.34
Pre 17may21: Pf vs AZ	1.00	1.00	1.00
Post 17may21: Pf vs AZ	0.80	1.00	0.95

Note: re-infection pre vs post 17may21 p=1.00

	Second dose ≥14 days vs one dose ≥21 days pre may 2021	Second dose ≥14 days vs one dose ≥21 days post may 2021	Second dose ≥14 days vs reinfection post may 2021
Pf	1.00	0.99	1.00
AZ	1.00	0.17	1.00

Infections with no symptoms reported within [0,35] days of first positive test: <17 May (cyan) vs >=17 May (coral)



Note: see table on last page for VE estimates (=100%*(1-OR)). Unadjusted heterogeneity p-values:

	One dose ≥21 days	Second dose 0-13 days ago	Second dose ≥14 days
Pf: pre vs post 17may21	0.96	0.98	1.00
AZ: pre vs post 17may21	0.26	1.00	1.00
Pre 17may21: Pf vs AZ	0.99	1.00	1.00
Post 17may21: Pf vs AZ	1.00	1.00	0.42

Note: re-infection pre vs post 17may21 p=1.00

	Second dose ≥14 days vs one dose ≥21 days pre may 2021	Second dose ≥14 days vs one dose ≥21 days post may 2021	Second dose ≥14 days vs reinfection post may 2021
Pf	1.00	0.37	0.95
AZ	1.00	0.49	1.00

Summary of vaccine effectiveness (VE) estimates (95% CI): VE=100%*(1- odds ratio (OR) from figures on p3-5, 11-12) – that is these, estimates reproduce the figures exactly.

	Pf: one dose ≥21 days		AZ: one dose ≥21 days		Pf: second dose 0-13 days ago		AZ: second dose 0-13 days ago		Pf: second dose ≥21 days		AZ: second dose ≥21 days		Not vaccinated, previously positive*	
VE: All infections, unbiased ascertainment at scheduled visits														
1Dec20-16May21 (Alpha)	60%	49-69%	63%	50-72%	77%	58-88%	72%	32-89%	78%	62-87%	79%	32-94%	63%	47-74%
17May21- (Delta)	58%	38-71%	34%	5-54%	75%	36-90%	63%	41-77%	77%	67-84%	62%	47-72%	61%	17-82%
VE: Ct<30														
1Dec20-16May21 (Alpha)	70%	56-80%	74%	59-83%	84%	57-94%	79%	14-95%	94%	78-98%	87%	5-98%	86%	69-93%
17May21- (Delta)	59%	36-74%	34%	-3-58%	77%	27-93%	59%	27-76%	83%	73-89%	65%	48-77%	66%	15-86%
VE: Self-reported symptoms														
1Dec20-16May21 (Alpha)	75%	64-83%	73%	59-82%	93%	73-98%	85%	42-96%	98%	86-100%	97%	24-100%	82%	66-91%
17May21- (Delta)	64%	41-78%	33%	-8-58%	90%	39-98%	64%	33-81%	87%	78-92%	67%	50-78%	74%	19-92%
VE: Ct>=30														
1Dec20-16May21 (Alpha)	49%	29-63%	49%	26-65%	69%	30-86%	62%	-20-88%	59%	24-78%	67%	-43-92%	32%	-4-55%
17May21- (Delta)	52%	6-76%	28%	-36-62%	69%	-60-94%	71%	30-88%	63%	33-79%	55%	21-74%	47%	-101-86%
VE: No self-reported symptoms														
1Dec20-16May21 (Alpha)	42%	18-59%	50%	25-67%	56%	11-78%	52%	-58-85%	49%	7-72%	46%	-103-86%	31%	-7-56%
17May21- (Delta)	45%	2-69%	33%	-19-62%	52%	-57-85%	60%	18-80%	64%	39-79%	53%	23-71%	41%	-61-78%

* re-infection will be a variable amount of time previously but no power to split this.

Note: calendar time split into two epochs when the majority of cases detected in the survey were ORF1ab+N positive (Alpha-compatible) and then when triple positives became more dominant (Delta-compatible). Estimates from the former are similar to those previously published in Nature Medicine on data to 8 May 2021 (https://www.nature.com/articles/s41591-021-01410-w), but with slightly wider 95% confidence intervals due to splitting time after second dose at 14 days and splitting calendar time at 17 May 2021