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Anti-spike IgG antibody response after second vaccine dose: preliminary analysis on data to 5 July 2021

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Summary

186,957 survey participants received at least one dose of AZ/Pfizer/Moderna vaccine and had at least one antibody measurement from 90 days before the first vaccination through to 5th July 2021.

- 88,601 participants and 47,675 participants who did not have evidence of prior infection (positive swab or antibody as defined in https://www.medrxiv.org/content/10.1101/2021.04.22.21255911v1) received two doses of the AZ and Pfizer vaccine, respectively.
- 9,311 and 4,060 participants who had evidence of prior infection received two doses of the AZ and Pfizer vaccine, respectively.
- These four cohorts entered our main analysis of changes in antibody levels post-second vaccination. The characteristics of the four cohorts and other cohorts are summarised in the table on **p12-14**.

Summary of anti-trimeric spike IgG response following first and second vaccination [p3-4]

We used linear generalized additive models (GAMs) to model anti-trimeric spike IgG antibody response after first and second vaccination by vaccine type and prior infection status, adjusting for age and dosing interval using a tensor product of B-splines to allow for non-linearity and interaction, setting the date of the second vaccination as t=0.

- We excluded those with a dosing interval <49 or >91 days for AZ, and >28 and <49 or >91 days for Pfizer due to small numbers.
- For Pfizer, those whose dosing interval between 17 and 28 days were categorised as 'having a 3-week dosing interval' and modelled separately.

These models confirmed that a linear decline on the log scale was appropriate to assess changes in antibody levels post second vaccine dose, and that all groups could be modelled together, given the estimated uncertainty.

- We excluded non-responders to first and second dose from these models (~5%, details p15)
- We modelled antibody decline **starting from 21 days (peak level) after the second dose for both AZ and Pfizer**.
- 44,584 participants who received AZ and 36,520 participants who received Pfizer had at least one antibody measurement from 21 days after their 2nd dose.
- Due to long running time, a randomly selected 20,000 participants were included in separate multivariable Bayesian linear mixed models for each vaccine, including age, sex, ethnicity, reported long-term health condition, whether working in patient-facing healthcare, deprivation, dosing interval, and prior infection status as covariates. Population-level fixed effects, individual-level random effects for intercept and slope, and covariance between random effects were included in the model. The outcome was right-censored at 800 reflecting truncation of IgG values at 800 ng/ml.

Findings: AZ post second dose [p5-7]

- At the reference category (see p5), the mean peak level was 305 ng/ml, and the half-life (time for levels to drop by half, constant for log-linear decline) was 82 days.
- More factors were associated with peak (7 factors) than half-life (one factor), and most effects were relatively small (the exception being prior infection).
- The peak after second dose was lower in males, those reporting white ethnicity or long-term health conditions, and those not working in healthcare. There were very small effects of deprivation (lower peak in less deprived areas) and dosing interval (the time between second and first dose) (lower peak with shorter dosing interval).
- **The largest effects were from prior infection, which was associated with a substantially higher peak level and a longer half-life than in participants without prior infection.**
- **There was no evidence of an effect of age on peak or half-life.**

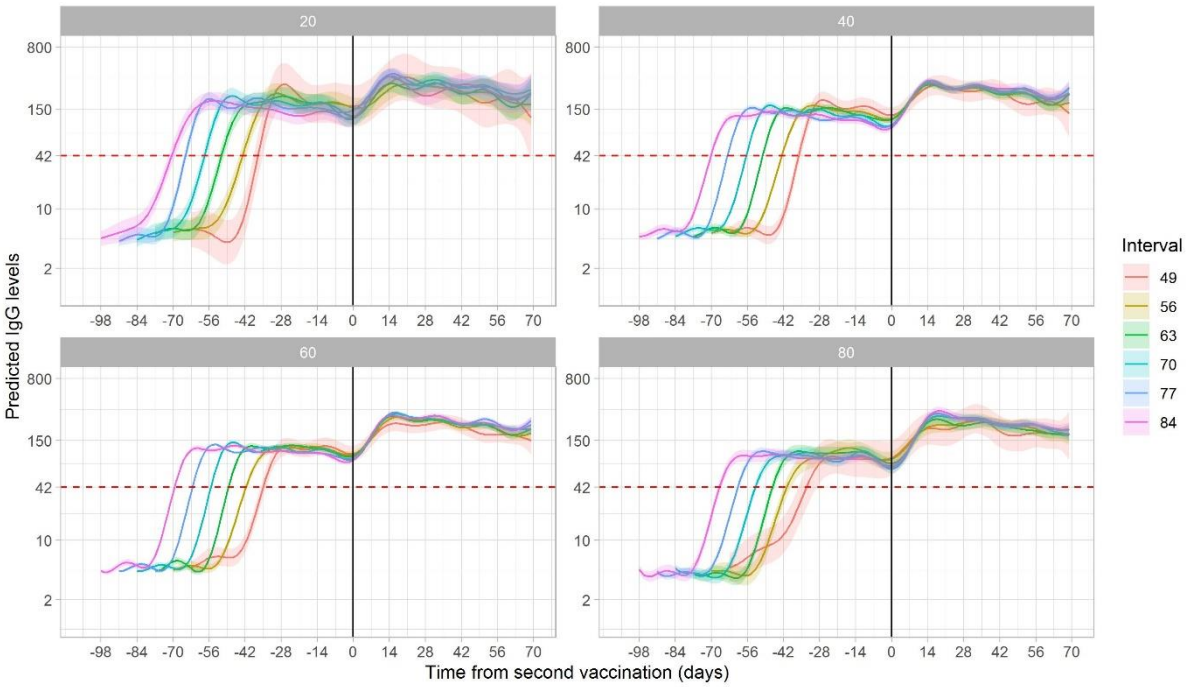
Findings: Pfizer post second dose [p8-11]

- At the reference category (see p8, identical to reference category for AZ), the mean peak level was 766 ng/ml, and the half-life was 130 days.
- Many factors were associated with peak (6 factors) and half-life (6 factors): generally where associated with both peak and half-life, those levels associated with a lower peak also had a shorter half-life (excepting 3 week dosing interval).
- The peak after second dose was lower in males, older individuals and those reporting long-term health conditions or not working in healthcare. It was also lower in those with a longer dosing interval >49 days.
- The half-life was shorter in males, older individuals and those reporting white ethnicity or long-term health conditions.
- Participants with prior infection had a longer half-life than participants without prior infection, but there was no difference in peak. The lack of evidence of difference in peak may be a consequence of saturation of the assay at 800 ng/ml, as other studies have suggested substantially higher peak levels associated with prior infection for Pfizer.
- This initial preliminary analysis suggests that participants with a 3-week dosing interval had a lower peak and a longer half-life. However, this may be a consequence of modelling time from 21 days after the second dose; whilst this corresponds to the peak for the vast majority of participants, those with a 3 week dosing interval may still be responding to the first dose as well (p3, bottom panel). Future analysis will exclude measurements for longer after the second dose in these participants so findings may change.
- **The largest effects were from age, prior infection and 3-week dosing interval.**

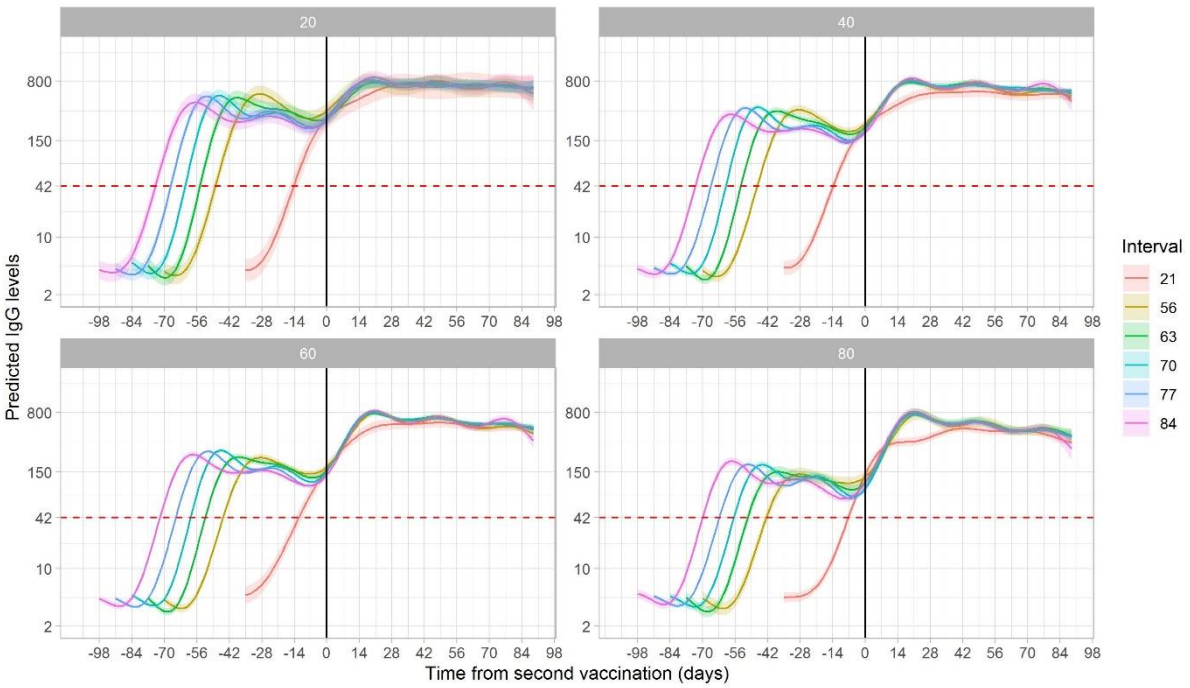
In comparison, following seroconversion post natural infection
(https://www.medrxiv.org/content/10.1101/2021.07.02.21259897v1)

- At the same reference category, the peak was 185 ng/ml, and the half-life 233 days
- The peak after natural infection was higher only in older individuals (conditional on seroconversion)
    - There was no evidence of an effect on the peak of sex, long-term health conditions (if anything a trend towards higher in those reporting long-term health conditions, again conditional on seroconversion)
- The half-life was shorter in males, and those reporting non-white ethnicity.

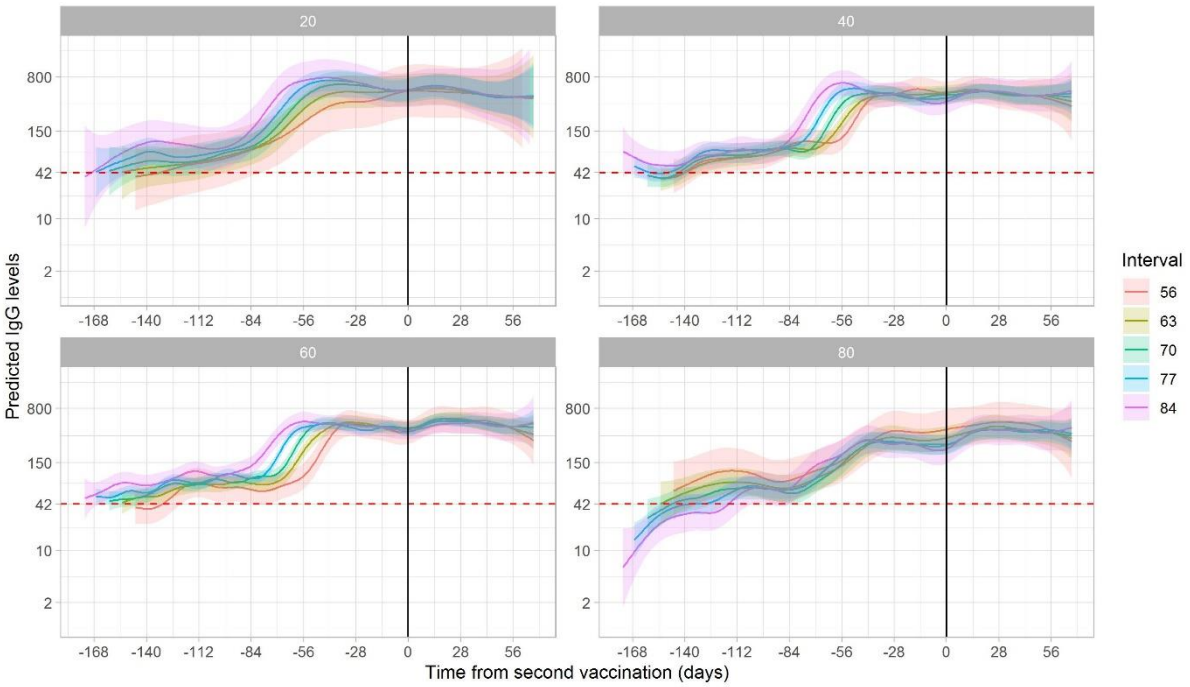
AZ no prior infection: each panel is a different age (20y, 40y, 60y, 80y; lines represent different dosing intervals (time between second and first vaccine)



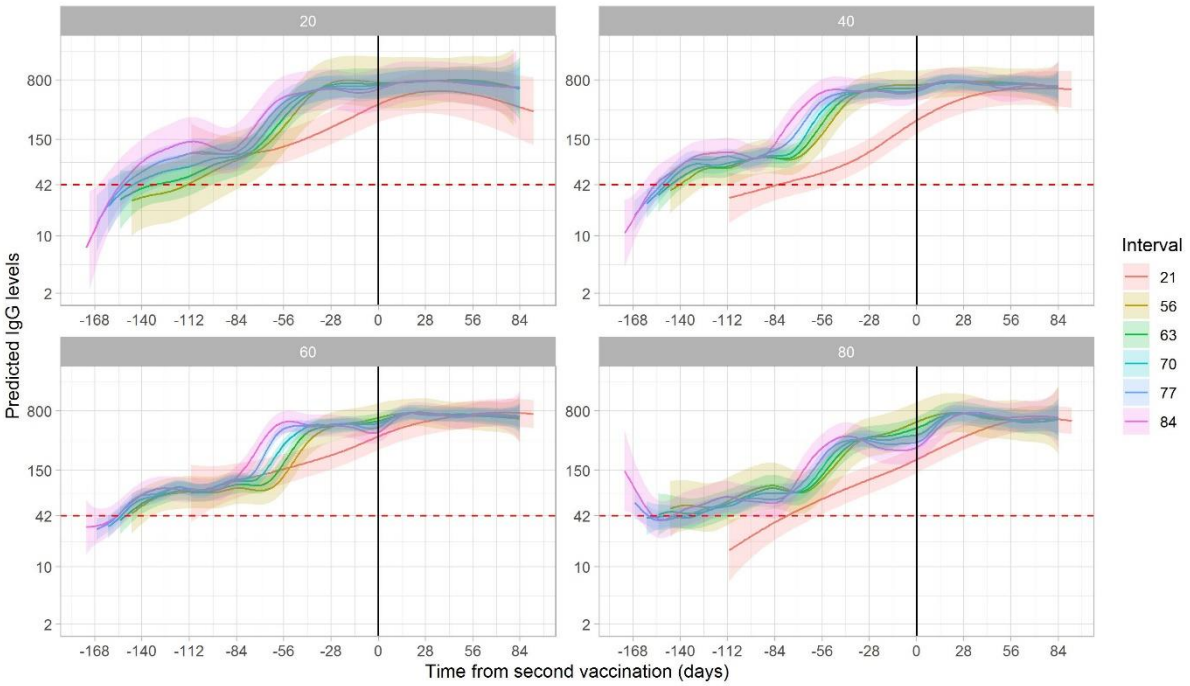
Pfizer no prior infection: each panel is a different age (20y, 40y, 60y, 80y; lines represent different dosing intervals (time between second and first vaccine)



AZ with prior infection: each panel is a different age (20y, 40y, 60y, 80y; lines represent different dosing intervals (time between second and first vaccine)



Pfizer with prior infection: each panel is a different age (20y, 40y, 60y, 80y; lines represent different dosing intervals (time between second and first vaccine)

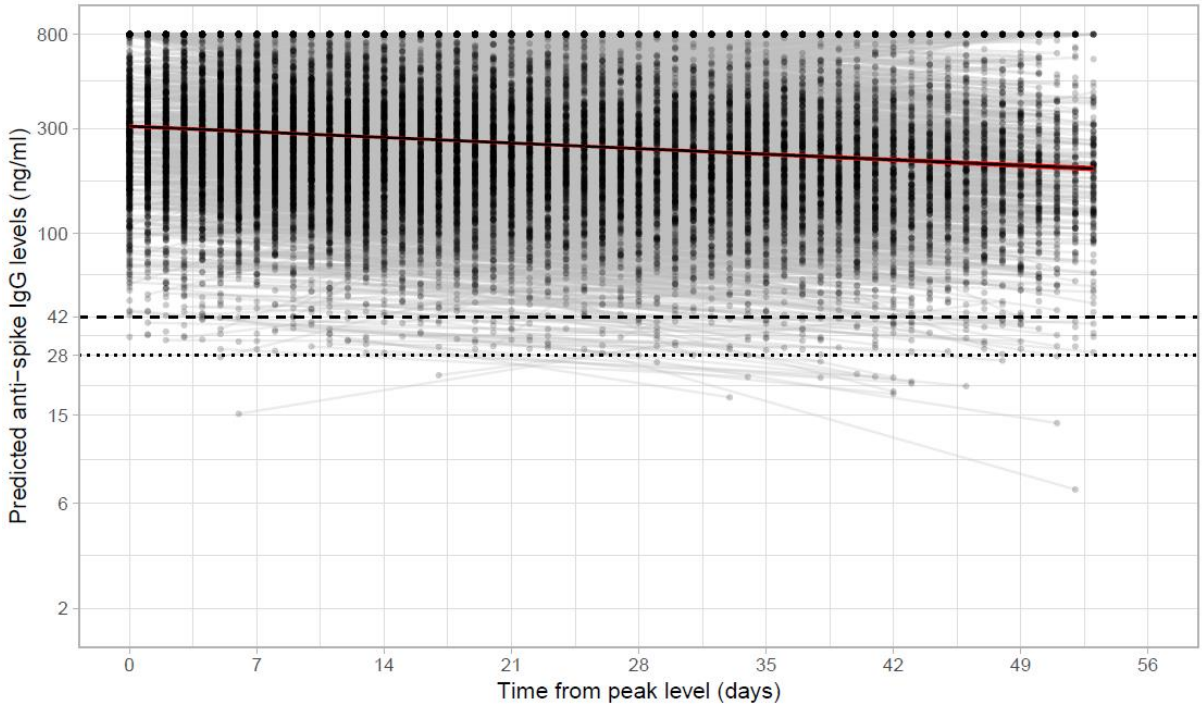


Results for changes in antibody after second AZ dose:

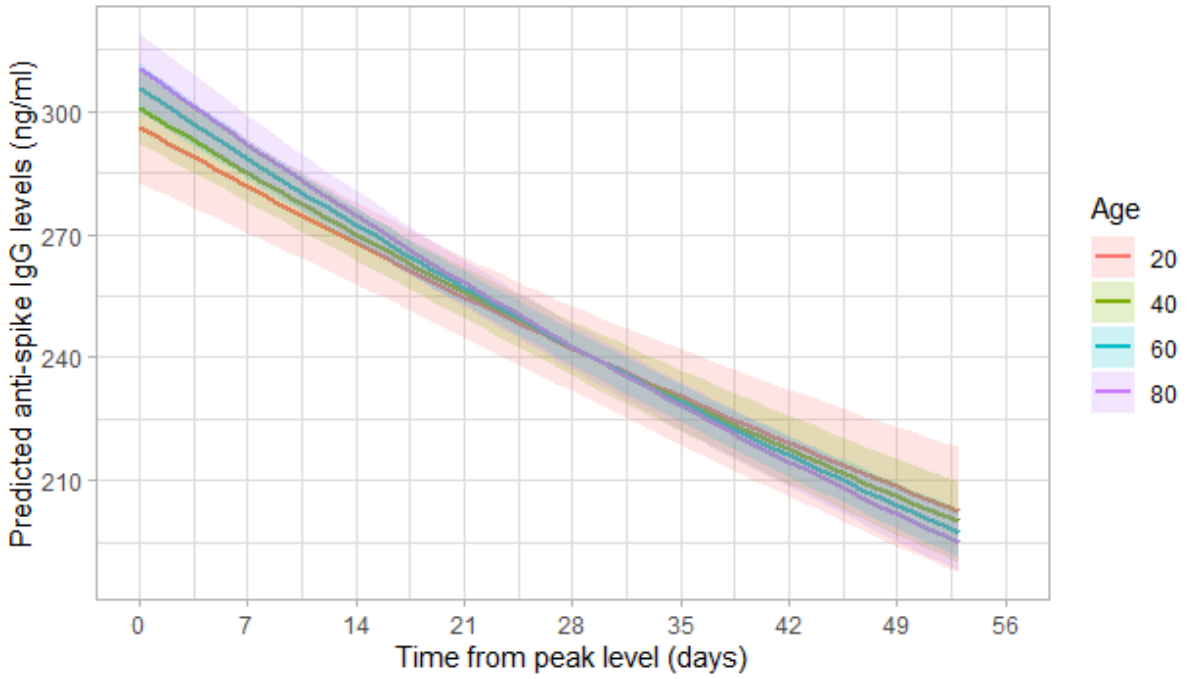
At the reference category, the mean peak level was 305 ng/ml, and the half-life was 82 days. Males had a lower peak level than females. Non-whites had a higher peak level than whites. Participants with long-term health conditions had a lower peak level than those without. Healthcare workers had a higher peak level than non-healthcare workers. Participants in less deprived area had a lower peak level but the difference was small. Participants with a longer dosing interval had a higher peak level. Lastly, participants with prior infection had a higher peak level and a longer half-life than participants without prior infection.

		MULTIVARIABLE MODEL		
		Posterior mean	95% CrI	
BASELINE	Peak level (Intercept)	305	292	311
	IgG half-life (slope)	82	76	88
AGE	Peak level: 65 years (median)			
	IgG half-life: 65 years (median)			
	Change in peak level: per 10-year older	2	-1	6
	Change in half-life: per 10-year older	-3	-6	1
SEX	Peak level: Female			
	IgG half-life: Female			
	Change in peak level: Male	**-11**	**-19**	**-4**
	Change in half-life: Male	-2	-10	6
ETHNICITY	Peak level: White			
	IgG half-life: White			
	Change in peak level: Non-white	**59**	**38**	**81**
	Change in half-life: Non-white	-5	-20	15
LTHC	Peak level: No			
	IgG half-life: No			
	Change in peak level: Yes	**-11**	**-19**	**-4**
	Change in half-life: Yes	-4	-11	4
HCW	Peak level: No			
	IgG half-life: No			
	Change in peak level: Yes	**38**	**6**	**72**
	Change in half-life: Yes	-6	-25	23
DEPRIVATION	Peak level: 60 (median)			
	IgG half-life: 60 (median)			
	Change in peak level: per 10 percentile higher	**-2**	**-4**	**-1**
	Change in half-life: per 10 percentile higher	1	0	3
DOSING INTERVAL	Peak level: 70 (median)			
	IgG half-life: 70 (median)			
	Change in peak level: per 7 day longer	**5**	**2**	**9**
	Change in half-life: per 7 day longer	3	-1	7
PRIOR INFECTION	Peak level: No			
	IgG half-life: No			
	Change in peak level: Yes	**274**	**249**	**300**
	Change in half-life: Yes	**47**	**15**	**97**

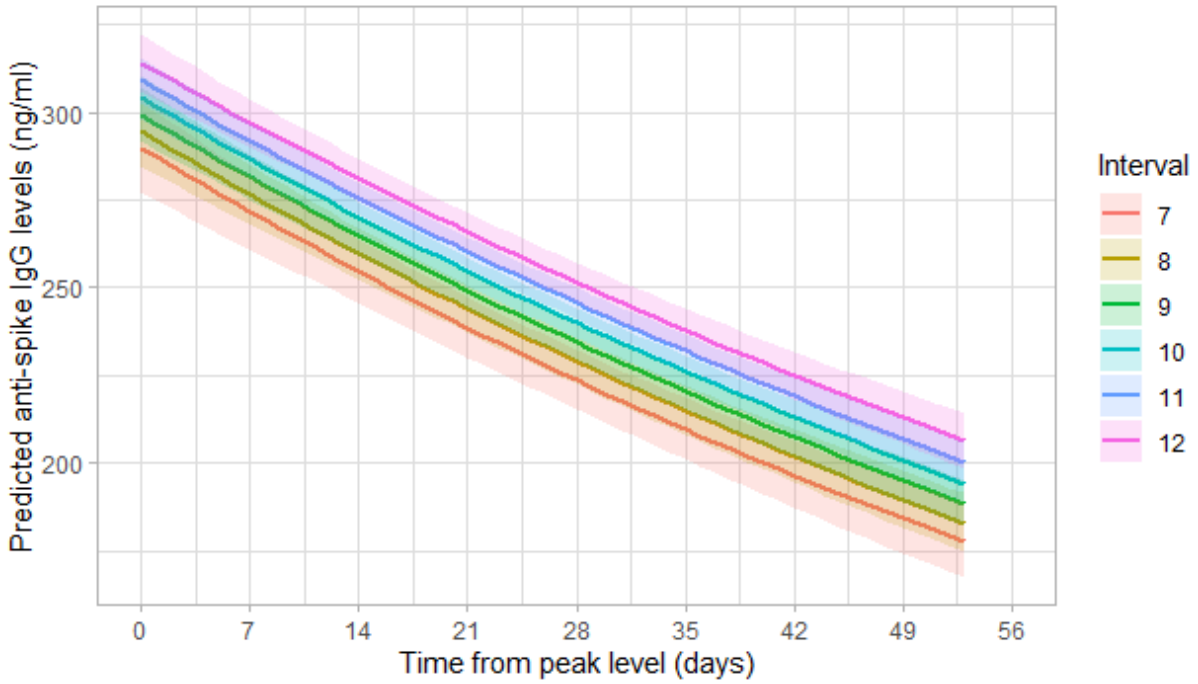
AZ Individual trajectories and population-level estimate of antibody waning.



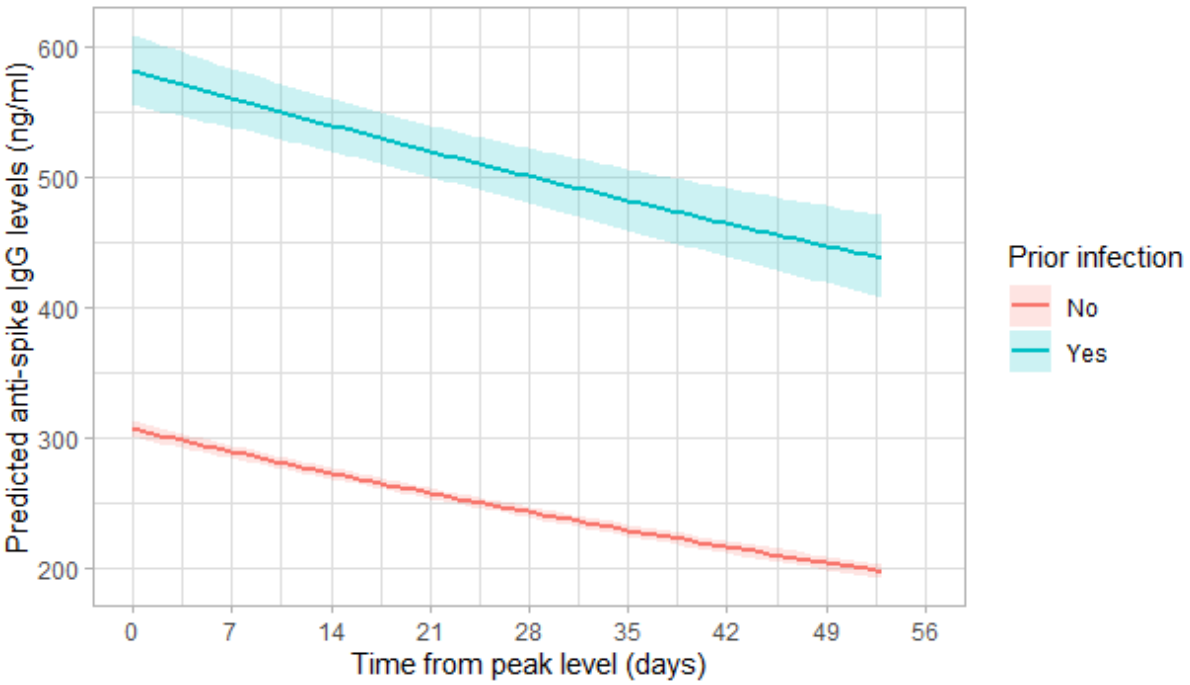
AZ - Age: no evidence of effect on peak or half-life



AZ – Dosing interval: small effect on peak, no evidence of effect on half-life



AZ – Prior infection: strong evidence of effect on peak and half-life (on log-scale)

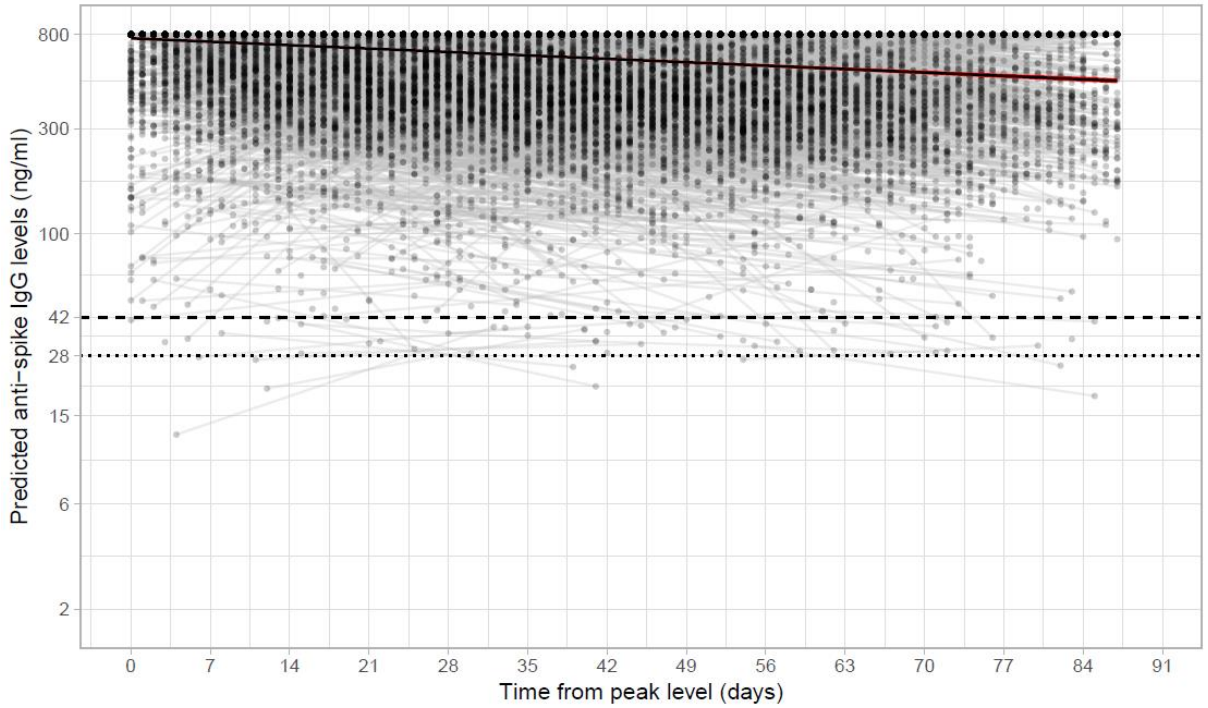


Results for change in antibody after second Pfizer dose:

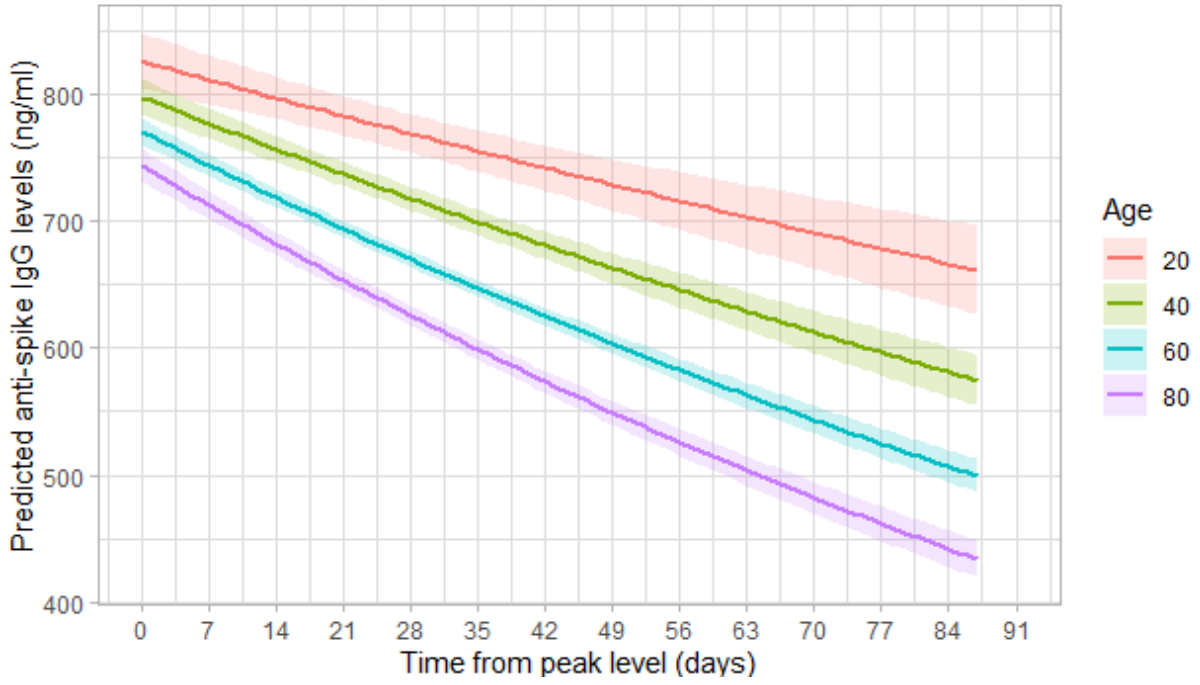
At the reference category, the mean peak level was 766 ng/ml, and the half-life was 130 days. Males had a lower peak level and a shorter half-life than females, as did older participants. Non-whites had a longer half-life than whites. Participants with long-term health conditions had a lower peak level and a shorter half-life than those without. Healthcare workers had a higher peak level than non-healthcare workers. Participants with a 3-week dosing interval had a lower peak level but waned more slowly. Among those with 49-91 day's dosing interval, participants with a longer dosing interval had a lower peak level. Lastly, participants with prior infection had a longer half-life than participants without prior infection.

		MULTIVARIABLE MODEL		
		Posterior mean	95% CrI	
BASELINE	Peak level (Intercept)	766	744	777
	IgG half-life (slope)	130	121	140
AGE	Peak level: 65 years (median)			
	IgG half-life: 65 years (median)			
	Change in peak level: per 10-year older	**-13**	**-18**	**-9**
	Change in half-life: per 10-year older	**-13**	**-17**	**-10**
SEX	Peak level: Female			
	IgG half-life: Female			
	Change in peak level: Male	**-18**	**-31**	**-5**
	Change in half-life: Male	**-23**	**-34**	**-13**
ETHNICITY	Peak level: White			
	IgG half-life: White			
	Change in peak level: Non-white	16	-11	42
	Change in half-life: Non-white	**33**	**1**	**80**
LTHC	Peak level: No			
	IgG half-life: No			
	Change in peak level: Yes	**-20**	**-34**	**-7**
	Change in half-life: Yes	**-13**	**-25**	**-2**
HCW	Peak level: No			
	IgG half-life: No			
	Change in peak level: Yes	**46**	**22**	**71**
	Change in half-life: Yes	-13	-28	3
DEPRIVATION	Peak level: 60 (median)			
	IgG half-life: 60 (median)			
	Change in peak level: per 10 percentile higher	0	-2	2
	Change in half-life: per 10 percentile higher	1	-1	4
3 WEEK	Peak level: No			
	IgG half-life: No			
	Change in peak level: Yes	**-188**	**-217**	**-158**
	Change in half-life: Yes	**233**	**82**	**574**
DOSING INTERVAL	Peak level: 70 (median)			
	IgG half-life: 70 (median)			
	Change in peak level: per 7 day longer	**-10**	**-16**	**-4**
	Change in half-life: per 7 day longer	6	0	13
PRIOR INFECTION	Peak level: No			
	IgG half-life: No			
	Change in peak level: Yes	6	-17	30
	Change in half-life: Yes	**207**	**90**	**445**

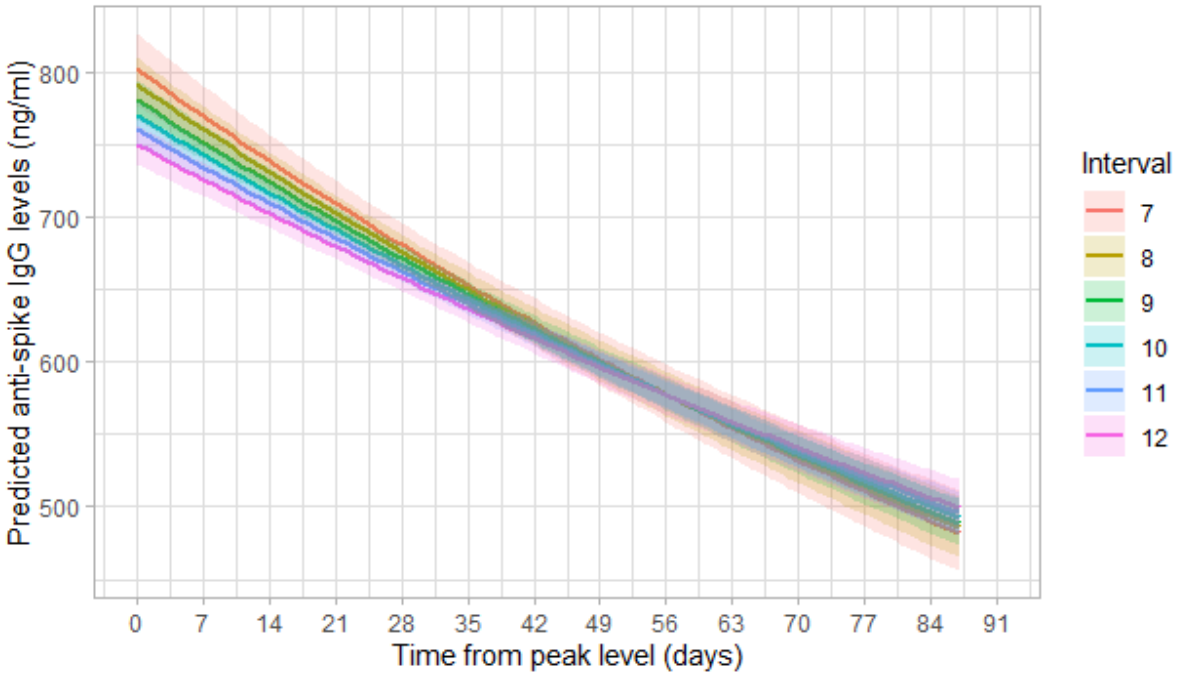
Pfizer Individual trajectories and population-level estimate of antibody waning.

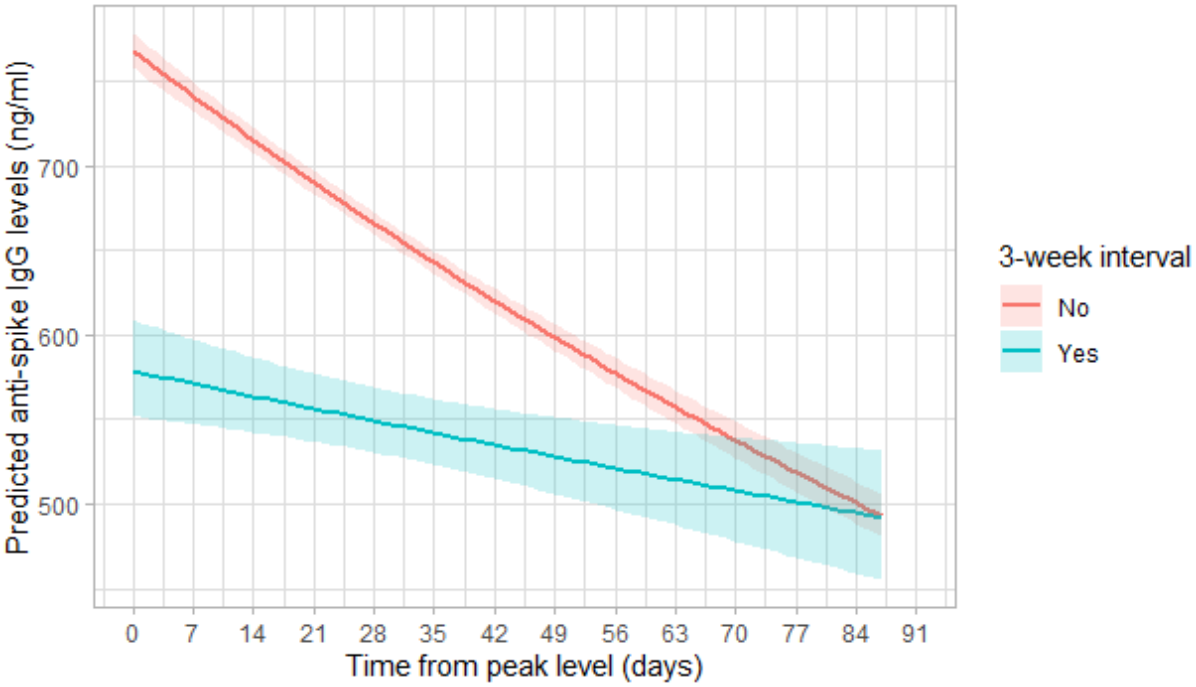


Pfizer - Age: strong evidence of effect on peak and half-life

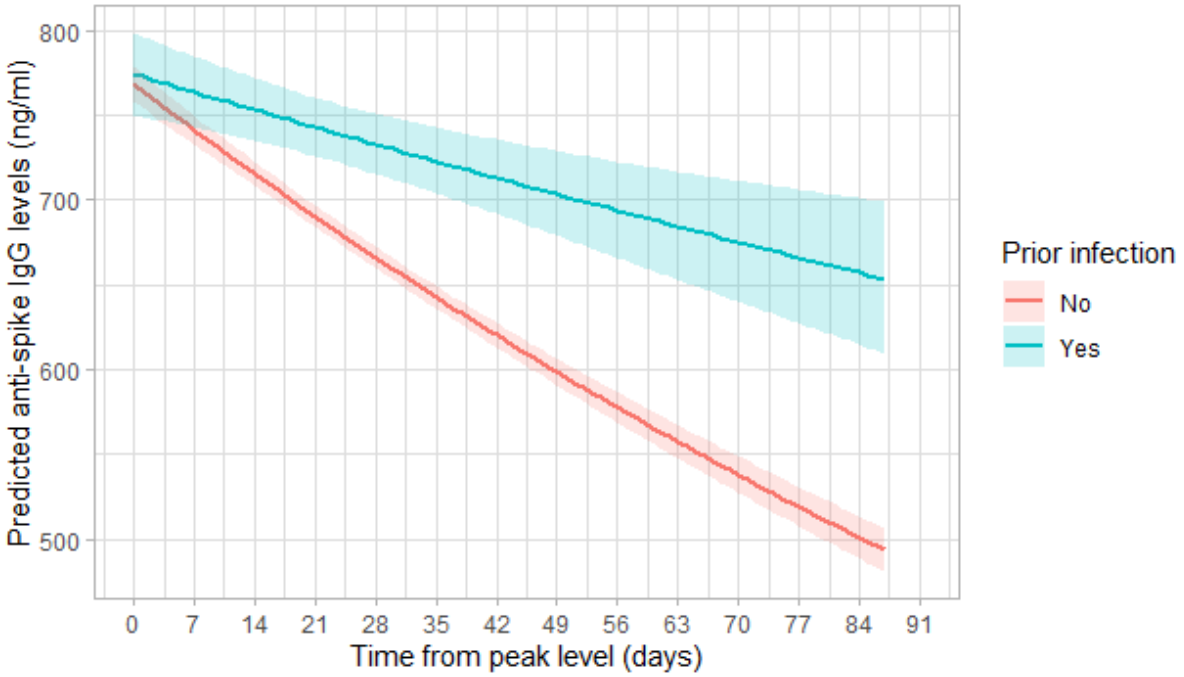


Pfizer – Dosing interval: strong evidence of lower peak and longer half-life with 3 weeks, small effect of longer dosing interval >49d on peak





Pfizer – Prior infection: strong evidence of effect on half-life but not peak

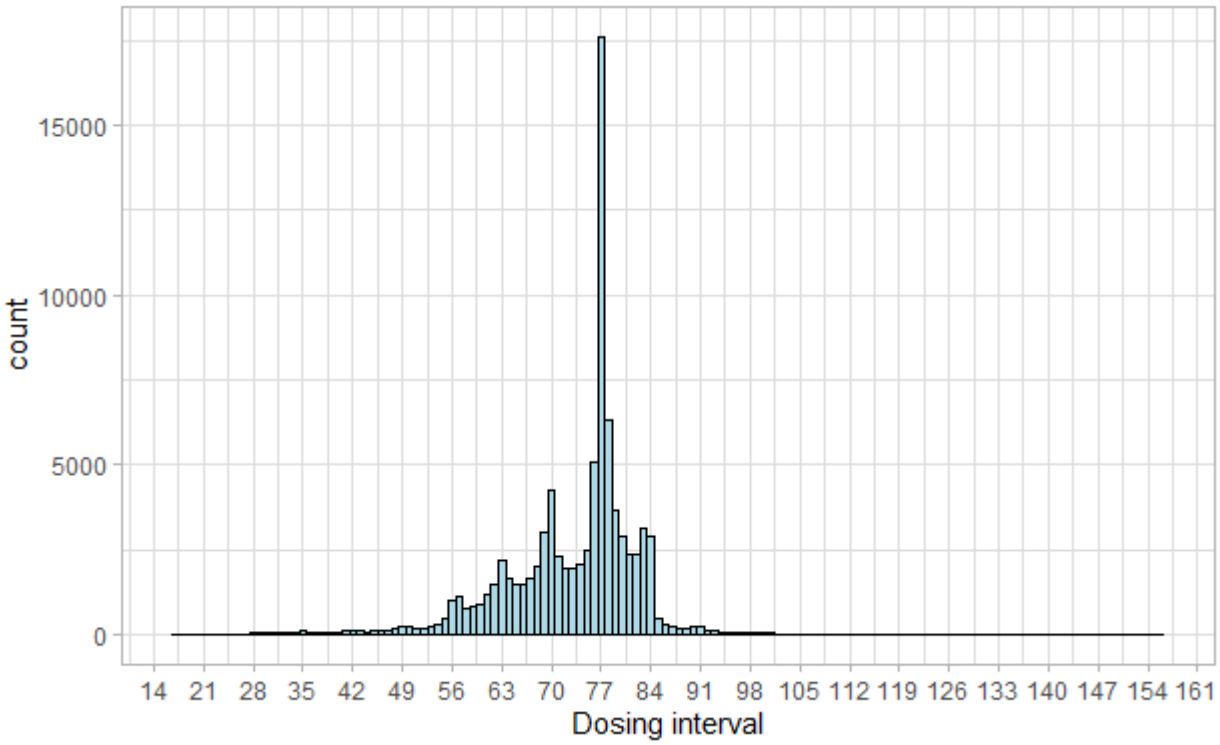


Characteristics of participants with at least one antibody measurement from 90 days before the first vaccination through to 5th July (including in both one and two dose groups if received 2 doses)

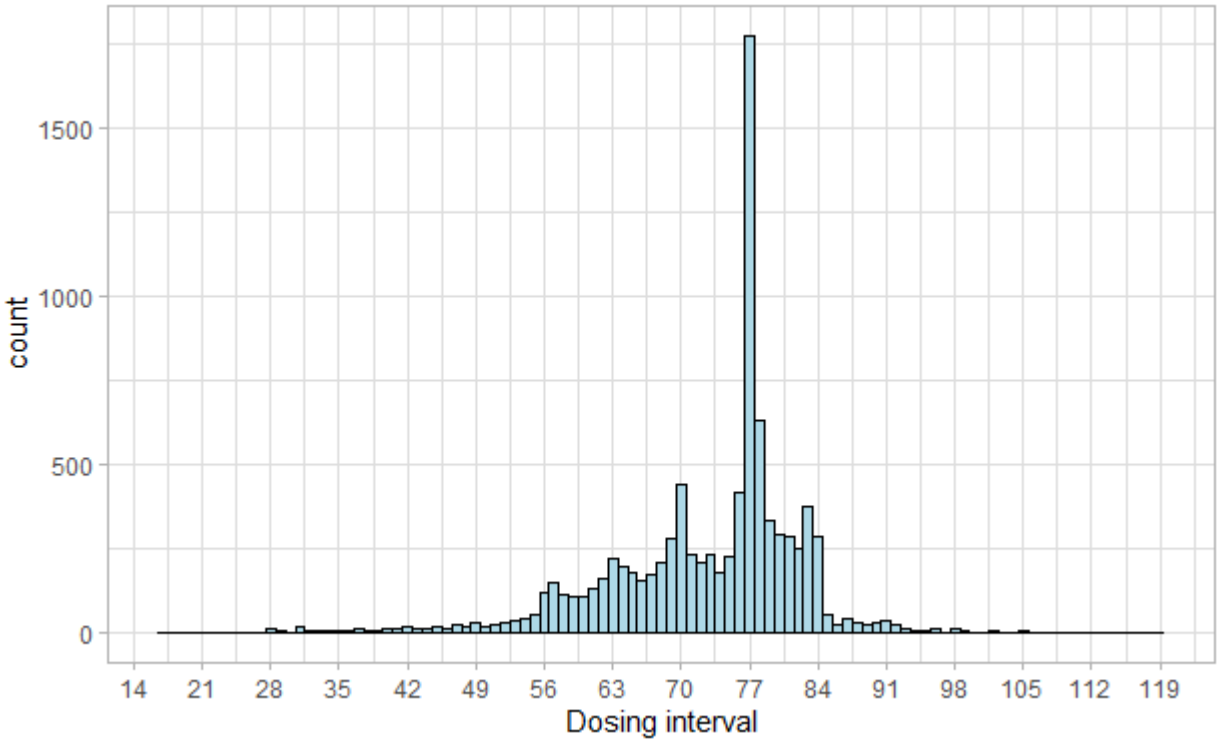
	No prior infection					With prior infection						
	AZ one dose (N=12207)	AZ two dose (N=88601)	Pfizer one dose (N=16901)	Pfizer two dose (N=47675)	Moderna one dose (N=2455)	AZ one dose (N=1782)	AZ two dose (N=9311)	Pfizer one dose (N=3488)	Pfizer two dose (N=4060)	Moderna one dose (N=477)	Total (N=186957)	p value
Age												< 0.001
Median	45	59	33	65	37	44	55	32	58	35	56	
Q1, Q3	41, 49	51, 68	28, 38	52, 73	31, 43	41, 48	47, 64	26, 37	44, 68	30, 41	43, 67	
Sex												< 0.001
Female	6206 (50.8%)	47408 (53.5%)	8777 (51.9%)	27625 (57.9%)	1200 (48.9%)	935 (52.5%)	5016 (53.9%)	1842 (52.8%)	2359 (58.1%)	211 (44.2%)	101579 (54.3%)	
Male	6001 (49.2%)	41193 (46.5%)	8124 (48.1%)	20050 (42.1%)	1255 (51.1%)	847 (47.5%)	4295 (46.1%)	1646 (47.2%)	1701 (41.9%)	266 (55.8%)	85378 (45.7%)	
Ethnicity												< 0.001
Non-white	878 (7.2%)	4559 (5.1%)	1719 (10.2%)	2704 (5.7%)	201 (8.2%)	198 (11.1%)	699 (7.5%)	500 (14.3%)	390 (9.6%)	78 (16.4%)	11926 (6.4%)	
White	11329 (92.8%)	84042 (94.9%)	15182 (89.8%)	44971 (94.3%)	2254 (91.8%)	1584 (88.9%)	8612 (92.5%)	2988 (85.7%)	3670 (90.4%)	399 (83.6%)	175031 (93.6%)	
Household size												< 0.001
1	1957 (16.0%)	17224 (19.4%)	2039 (12.1%)	10406 (21.8%)	335 (13.6%)	264 (14.8%)	1520 (16.3%)	346 (9.9%)	736 (18.1%)	55 (11.5%)	34882 (18.7%)	
2	4143 (33.9%)	45126 (50.9%)	6862 (40.6%)	25768 (54.0%)	984 (40.1%)	535 (30.0%)	4151 (44.6%)	1312 (37.6%)	1931 (47.6%)	188 (39.4%)	91000 (48.7%)	
3	2314 (19.0%)	12903 (14.6%)	3618 (21.4%)	5649 (11.8%)	510 (20.8%)	333 (18.7%)	1640 (17.6%)	795 (22.8%)	659 (16.2%)	87 (18.2%)	28508 (15.2%)	
4	2792 (22.9%)	9853 (11.1%)	3103 (18.4%)	4108 (8.6%)	475 (19.3%)	469 (26.3%)	1413 (15.2%)	700 (20.1%)	510 (12.6%)	106 (22.2%)	23529 (12.6%)	
5+	1001 (8.2%)	3495 (3.9%)	1279 (7.6%)	1744 (3.7%)	151 (6.2%)	181 (10.2%)	587 (6.3%)	335 (9.6%)	224 (5.5%)	41 (8.6%)	9038 (4.8%)	
deprivation												< 0.001
Median	62	63	57	62	57	58	60	54	56	53	61	
Q1, Q3	37, 82	39, 82	34, 79	39, 82	34, 80	34, 79	35, 81	30, 76	31, 78	29, 77	38, 82	
Report working in patient facing healthcare												
No	12119 (99.3%)	87503 (98.8%)	16749 (99.1%)	43767 (91.8%)	2440 (99.4%)	1759 (98.7%)	9105 (97.8%)	3456 (99.1%)	3622 (89.2%)	476 (99.8%)	180996 (96.8%)	
Yes	88 (0.7%)	1098 (1.2%)	152 (0.9%)	3908 (8.2%)	15 (0.6%)	23 (1.3%)	206 (2.2%)	32 (0.9%)	438 (10.8%)	1 (0.2%)	5961 (3.2%)	
Report having long-term health condition												
No	9964 (81.6%)	62277 (70.3%)	14603 (86.4%)	30886 (64.8%)	2154 (87.7%)	1503 (84.3%)	6875 (73.8%)	3104 (89.0%)	2740 (67.5%)	427 (89.5%)	134533 (72.0%)	
Yes	2243 (18.4%)	26324 (29.7%)	2298 (13.6%)	16789 (35.2%)	301 (12.3%)	279 (15.7%)	2436 (26.2%)	384 (11.0%)	1320 (32.5%)	50 (10.5%)	52424 (28.0%)	

Dosing interval:

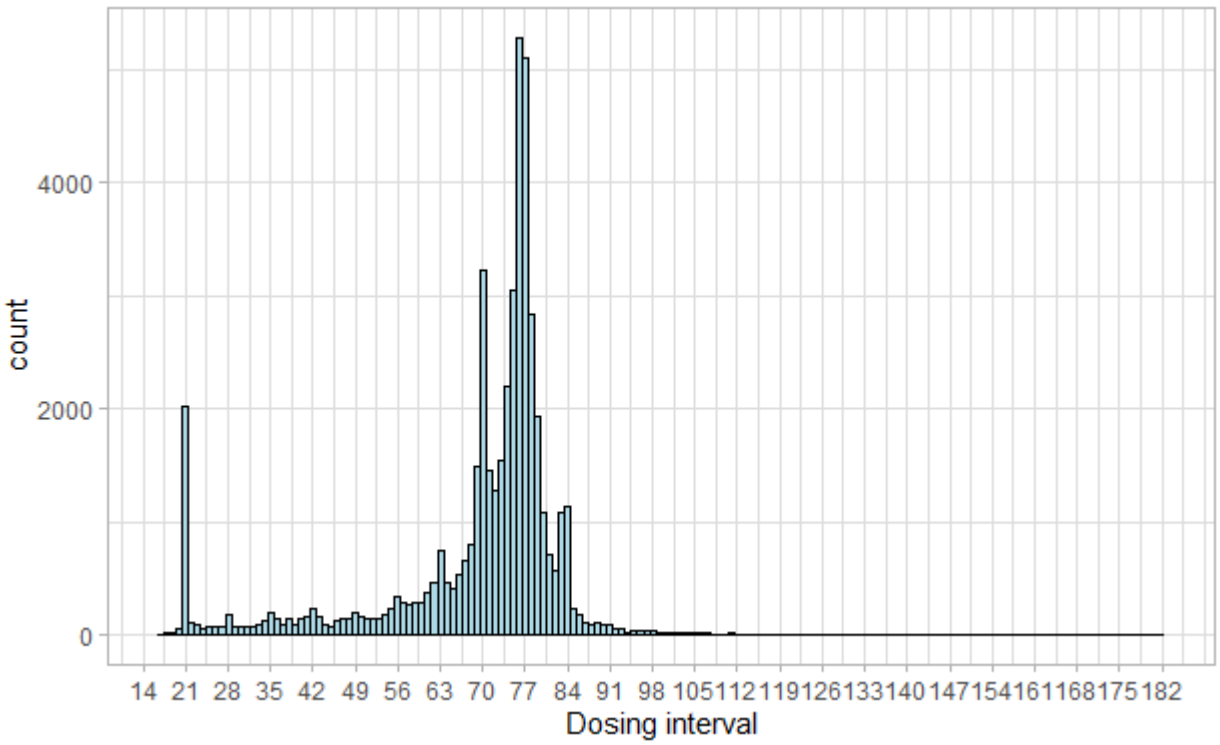
AZ two dose, no prior infection: median(IQR)[range]=76 (69-78) [17-156]



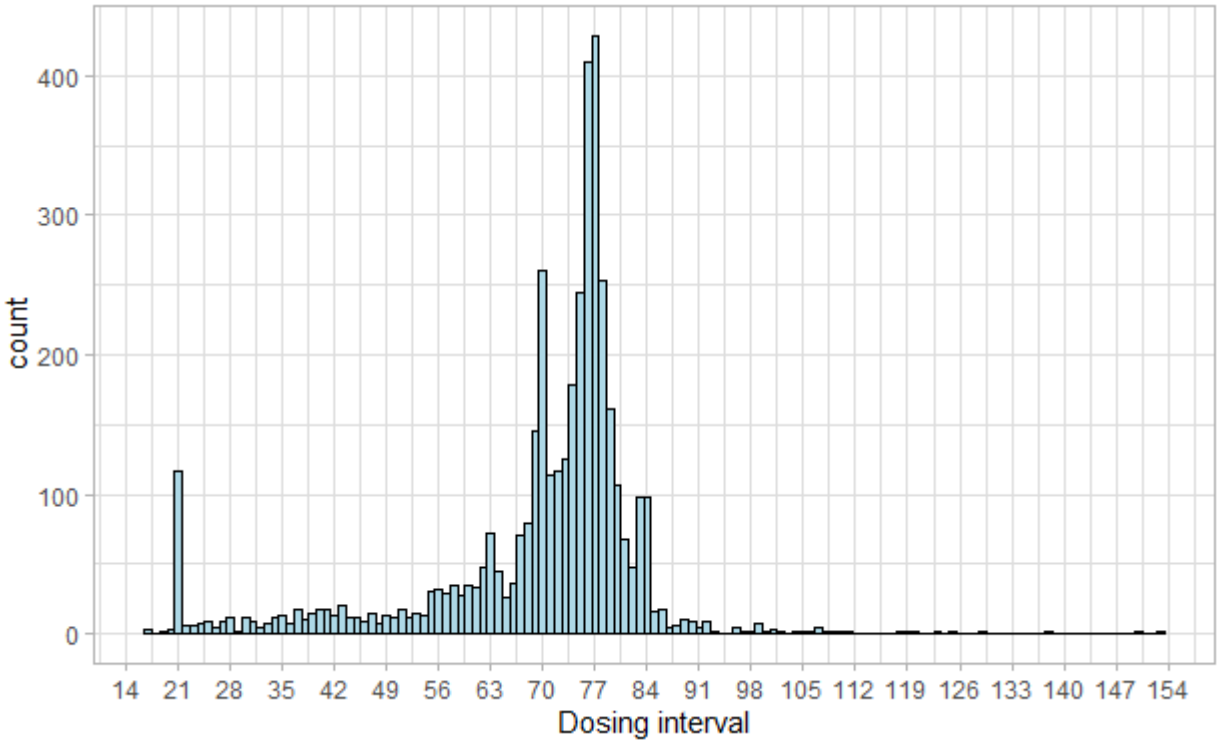
AZ two dose, with prior infection: median(IQR)[range]=76 (68-78) [17-119]



Pfizer two dose, no prior infection: median(IQR)[range]=75 (68-77) [17-182]



Pfizer two dose, with prior infection: median(IQR)[range]=75 (68-77) [17-153]



Excluding non-responders to first and second dose from models for changes after second dose

We used a heuristic rule to exclude non-responders to first or second dose among those who received two doses of vaccine without prior infection, because latent class models would not fit with the large number of observations, defining non-response as all antibody measurements being <28 ng/ml and having at least one antibody measurement 21 days after the first/second dose.

Among 47675 participants who received two doses of Pfizer, 21864 had antibody measurements after first dose, 25811 only had antibody measurements after second dose. Using the above rule, 1273 participants (2.7% in all, 5.8% in those who had antibody measurements after 1st dose) were non-responders to first dose, and 312 (0.7% in all) were non-responders to second dose. Both were excluded.

Among 88601 participants who received two doses of AZ, 56853 had antibody measurements after first dose, 31748 only had antibody measurements after second dose. Using the above rule, 3920 participants (4.4% in all, 6.9% in those who had antibody after 1st dose) were non-responders to first dose, and 626 (0.7% in all) were non-responders to second dose. Both were excluded.

These percentages are similar to those previously found using a latent class mixed model to examine antibody responses after first dose in a smaller population (5.1% in Pfizer and 5.8% in AZ) (in press Nature Microbiology).