Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Incidence of SARS-CoV-2 infection in healthcare workers by antibody status: Supplementary Appendix

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Supplementary Methods

Sample labelling and tracking

All samples were labelled with electronic barcoded labels generated from the hospital's electronic healthcare record system. Prior to attaching labels to sample collection tubes each participant was asked to confirm their name and date of birth as detailed on the label, additionally the participant's hospital record number on the label was confirmed against the testing database. The label barcodes were used for sample receipt and tracking in the hospital's microbiology laboratory to minimise the chance of sample labelling and handling errors.

Serological assays

Serological investigations were performed using an enzyme-linked immunosorbent assay platform developed by the University of Oxford detecting IgG to SARS-CoV-2 trimeric spike antigen, using net-normalised signal cut-off of ≥8 million to determine antibody presence.[1,2] Additional serology for IgG to nucleocapsid protein was performed using the Abbott Architect i2000 chemiluminescent microparticle immunoassay (Abbott, Maidenhead, UK). Antibody levels ≥1.40 arbitrary units were considered positive. In a previous head-to-head evaluation of five immunoassays using 976 pre-pandemic blood samples and 536 samples from PCR-confirmed SARS-CoV-2 infected patients at least 20 days post symptom onset the reported sensitivity and specificity of the anti-spike assay was 99.1% (95%CI 97.8-99.7) and 99.0% (98.1-99.5) and for the anti-nucleocapsid assay 92.7% (90.20-94.8) and 99.9% (99.4-100) respectively.[1]

PCR platforms

RT-PCR was performed using the Public Health England SARS-CoV-2 assay (targeting the RdRp gene), one of five commercial assays: Abbott RealTime (targeting RdRp and N genes; Abbott, Maidenhead, UK), Altona RealStar (targeting E and S genes; Altona Diagnostics, Liverpool, UK), Cepheid Xpert® Xpress SARS-CoV-2 (targeting N2 and E; Cepheid, California, USA), BioFire® Respiratory 2.1 (RP2.1) panel with SARS-CoV-2 (targeting ORF1ab and ORF8; Biofire diagnostics, Utah, USA), Thermo Fisher TaqPath assay (targeting S and N genes, and ORF1ab; Thermo Fisher, Abingdon, UK) or using the ABI 7500 platform (Thermo Fisher, Abingdon, UK) with the US Centers for Disease Control and Prevention Diagnostic Panel of two probes targeting the N gene.

PCR-positive results from community-based symptomatic testing of Oxford University Hospitals (OUH) healthcare workers (HCWs) forwarded by public health agencies were also included (n=37, Thermo Fisher TaqPath assay).

Statistical analysis

We used Poisson regression to model incidence of PCR-positive infection per day at risk by baseline antibody status. Models adjusted for changes in overall incidence by including calendar month at risk as a categorical or calendar time as continuous variable (allowing for non-linear effects using natural cubic splines with up to 5 knots, at default positions, and choosing the final number of knots based on the best model fit using the Akaike information criterion). Additionally, we adjusted for age (allowing for non-linear effects similarly) and self-reported gender. We also fitted models considering baseline antibody titre instead of binary antibody status, using allowing for non-linear effects as above.

Those who were initially antibody-negative and then seroconverted were allowed to contribute to the analysis twice; once while at risk of infection and antibody-negative and then subsequently while antibody-positive. Robust standard errors were used to account for this.

Software

All analyses were performed using R, version 3.6.3. Natural cubic splines were fitted with the splines library, using the default spline locations.

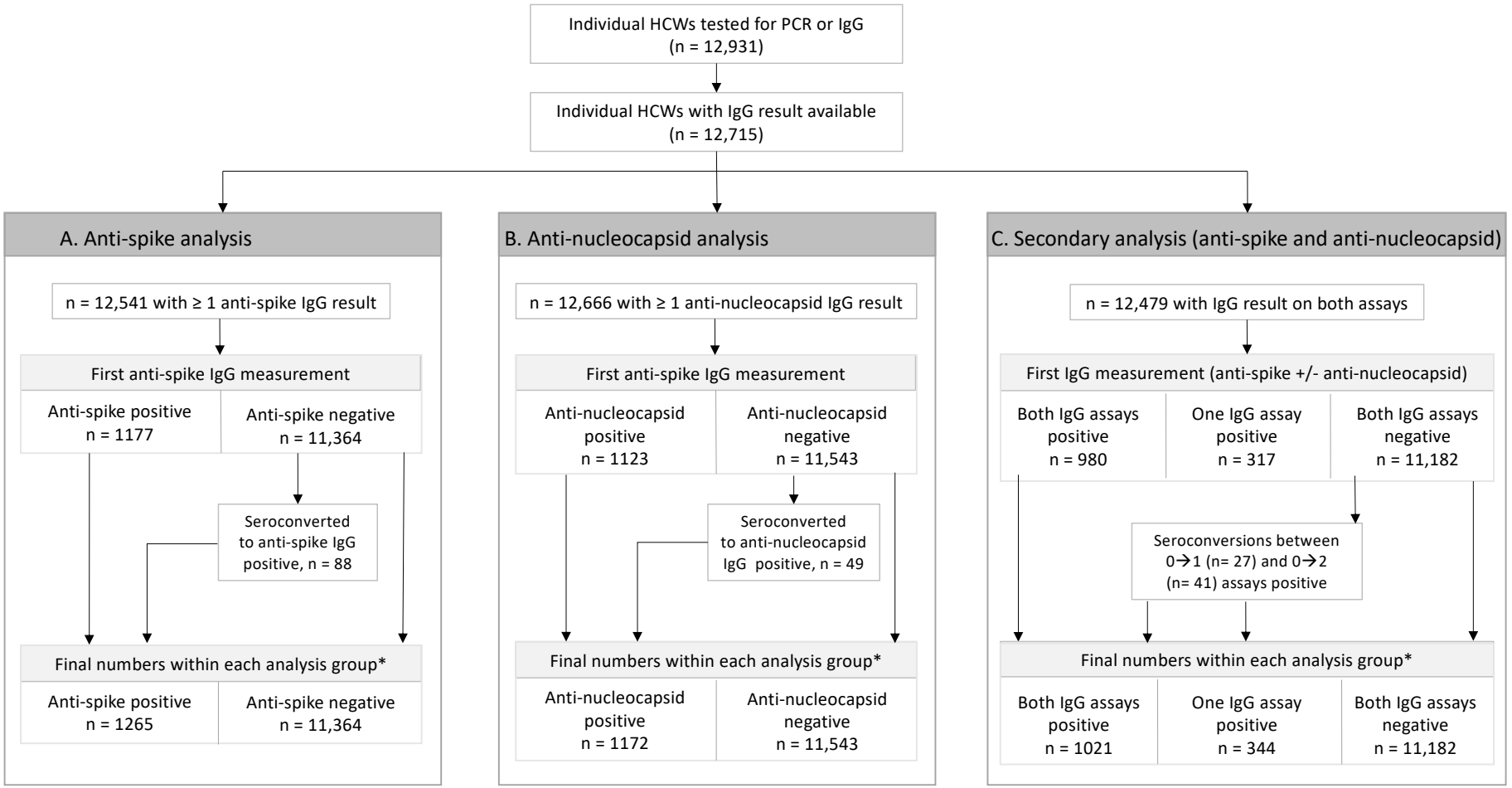
Sensitivity analysis

Rates of asymptomatic testing varied by antibody status, with seronegative healthcare workers (HCWs) attending more frequently than seropositive HCWs. To assess the impact on our results we performed a sensitivity analysis where we randomly removed PCR tests from the dataset. PCR tests were removed at random, irrespective of the result, from individuals with negative baseline serology until the overall rate of testing per 10,000 days at risk was equivalent in the seropositive and seronegative HCW groups. We used the resulting dataset to repeat our analysis.

We also conducted additional analysis where we extended the window period following a positive PCR test such that those with a positive antibody test were considered at risk of (re)infection from 90 days after their first positive antibody result. In this analysis we also only considered PCR-positive tests occurring ≥90 days after the previous PCR-positive test.

In a final sensitivity analysis, we considered both seronegative and seropositive HCWs at risk of infection from 60 days after the baseline antibody result, i.e. applying the same 60 day window period to seronegative HCWs as used for seropositive HCWs in the main analysis.

Supplementary Figures



* NB HCWs who seroconvert during follow up were allowed to contribute to the analysis twice, once while at risk of infection and IgG negative and then subsequently while IgG positive.

Figure S1. Flow diagram demonstrating cohort numbers from enrollment to final categorization into seropositive and seronegative groups. Panel A shows the cohort used in the anti-spike IgG analysis. Panel B shows the cohort used in the anti-nucleocapsid IgG analysis. Panel C shows the cohort used in the secondary analysis, using both anti-spike and anti-nucleocapsid IgG results.

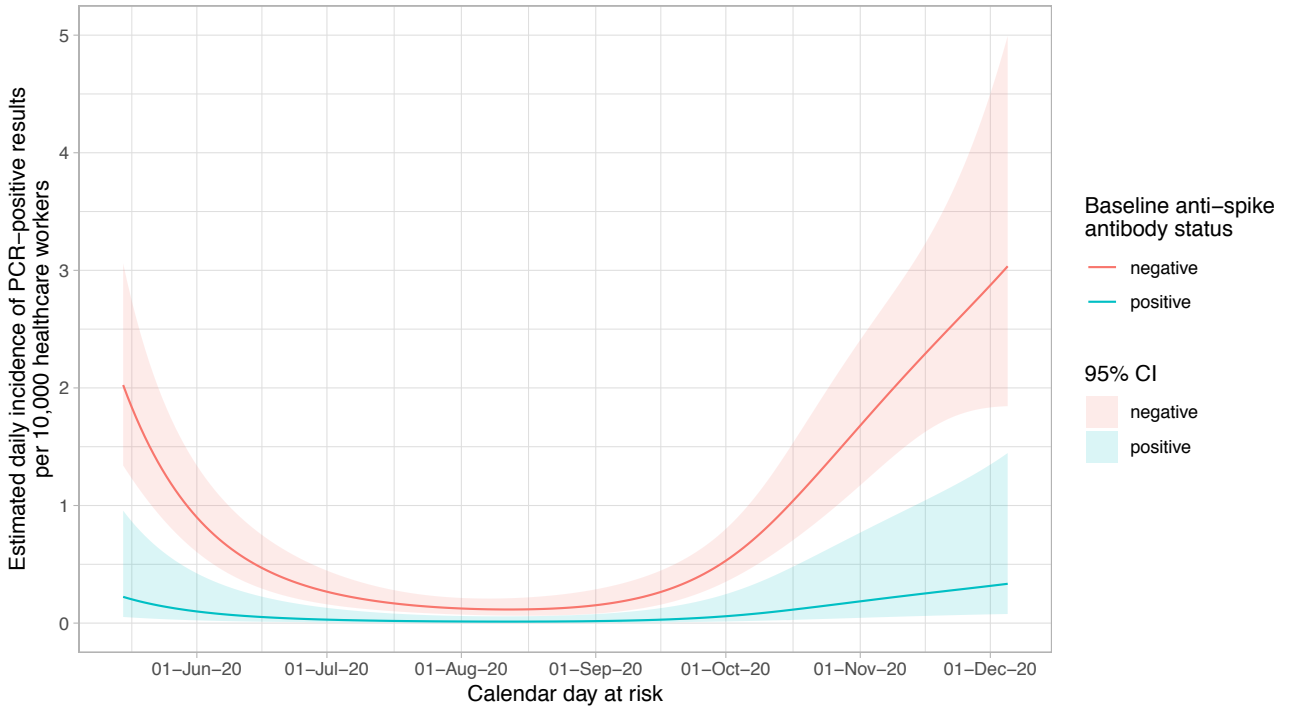


Figure S2. Estimated incidence of SARS-CoV-2 positive PCR results by baseline anti-spike IgG antibody status. The figure shows the estimated daily incidence of SARS-CoV-2 positive PCR results per 10,000 HCW days at risk, by baseline antibody status (95% confidence intervals are indicated by the coloured ribbons). The Poisson regression model is adjusted for age (using a 5 knot spline, similar to Supplementary Figure S5, set to median, 38 years for plotting), gender (set to female) and calendar time (fitted as a continuous variable, using a 5 knot natural cubic spline with default knot positions).

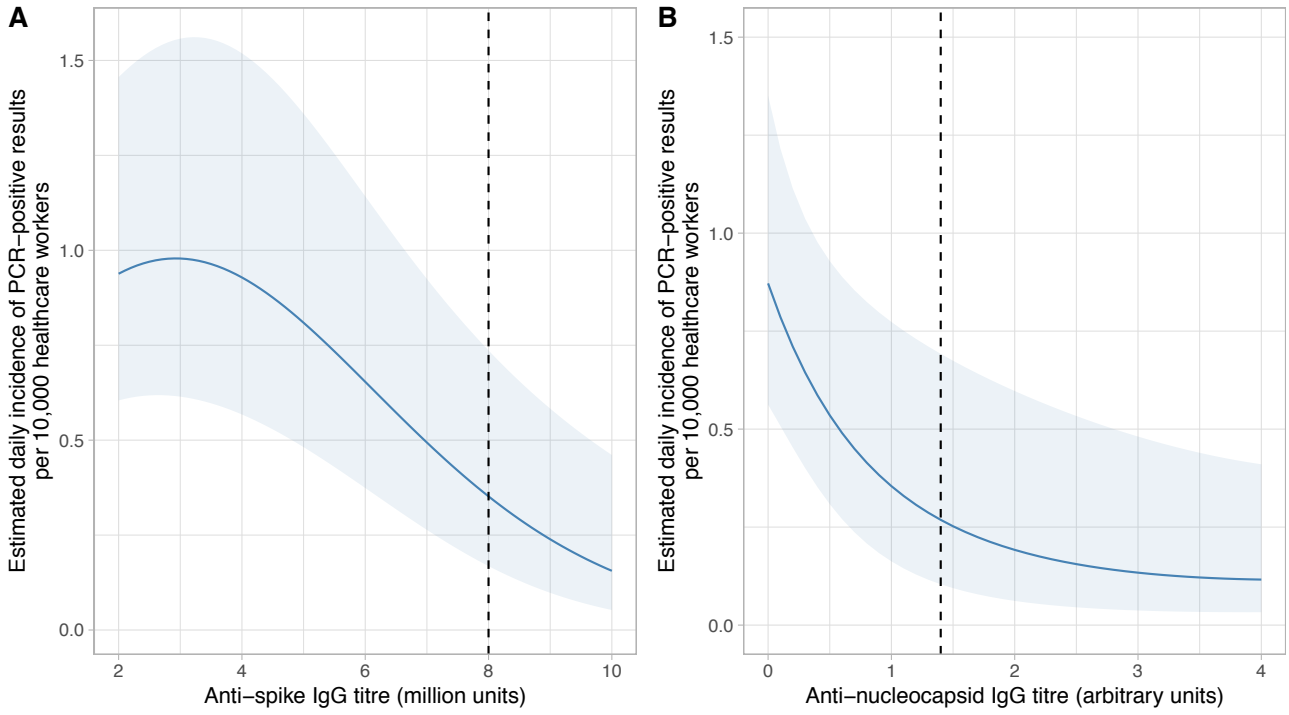


Figure S3. Estimated incidence of SARS-CoV-2 positive PCR results by quantitative baseline antibody status. Panel A and B show the estimated incidence of positive PCR results by baseline anti-spike (panel A, using a 3 knot spline, p-value vs. no trend <0.001) and anti-nucleocapsid (panel B, using a 3 knot spline, p-value vs. no trend <0.001) titre. Both analyses adjust for age (set at the median, 38 years), gender (set as female) and calendar month (set as October 2020). The ribbons show the 95% confidence intervals, and the vertical dotted lines the assay positive cut-offs.

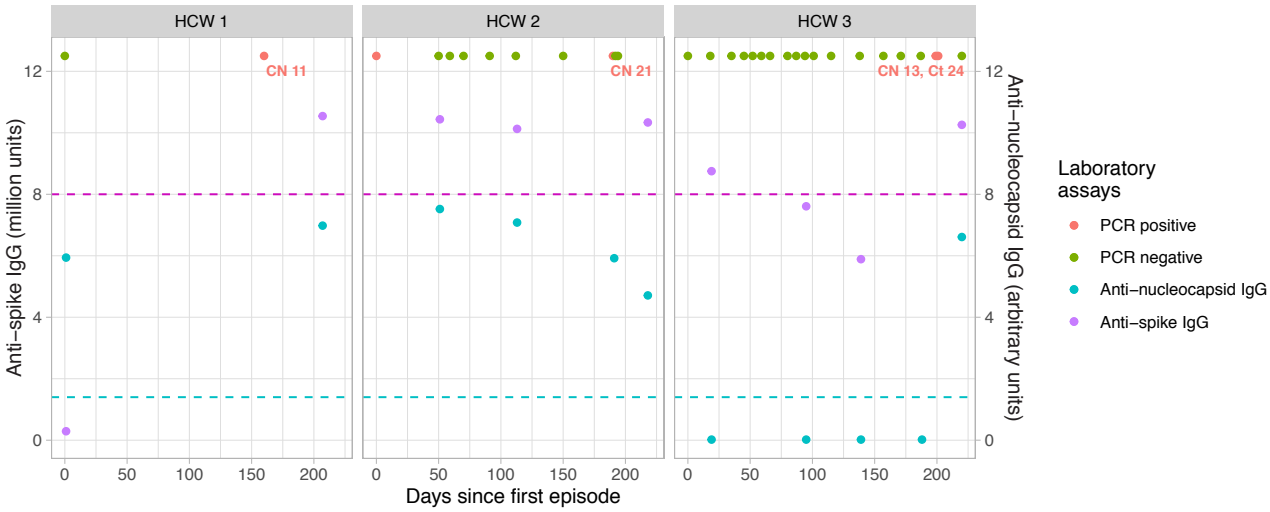


Figure S4. Antibody trajectories and PCR results for three seropositive individuals with subsequent positive PCR results. The x axis shows time since the first episode, defined as date of symptom onset if symptomatic, or first attendance at clinic if asymptomatic and no PCR performed during presumed index infection. Anti-spike and anti-nucleocapsid assay thresholds are shown by lilac and blue dotted lines. CN (for the Abbott PCR assay) and Ct values (for all other PCR assays) are given for positive PCR results. Further details in Table 2.

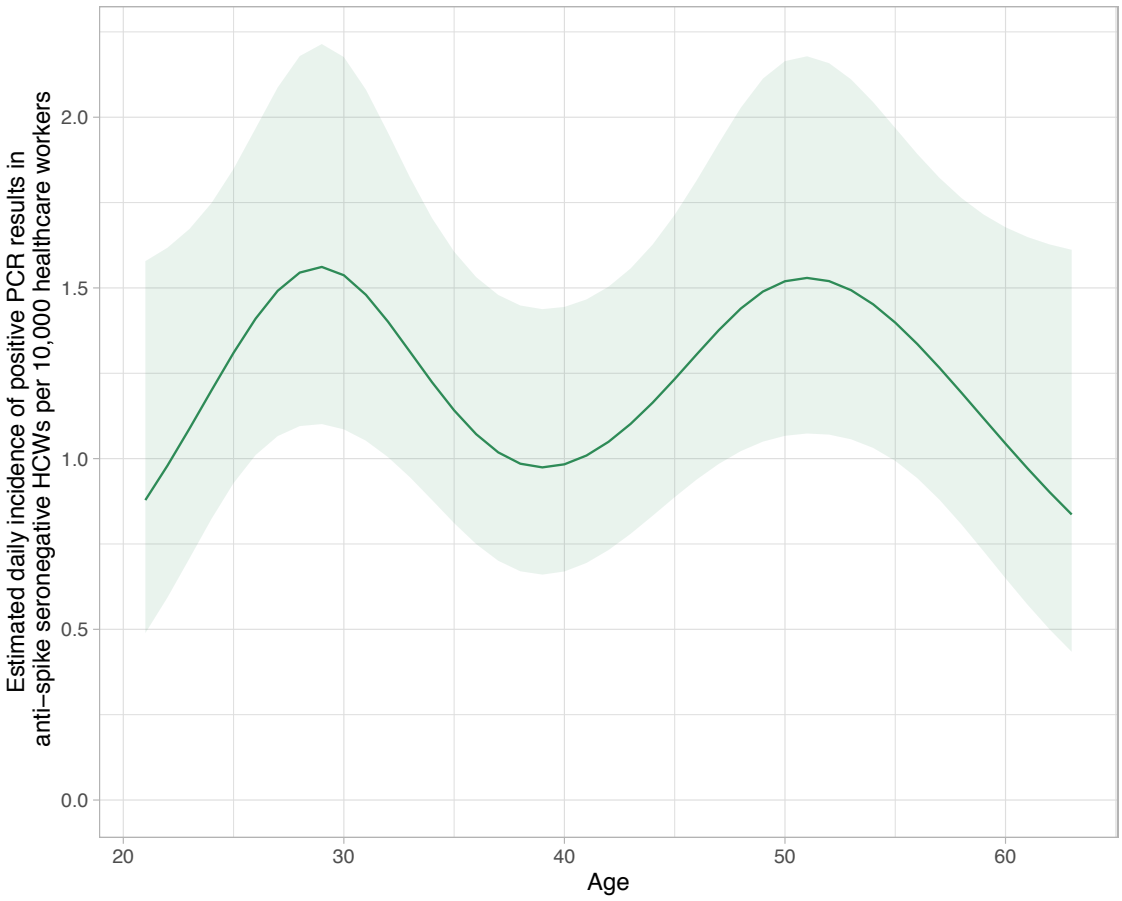


Figure S5. Non-linear relationship between age and incidence of PCR-positive results in HCWs with anti-spike antibody measurements. Estimates shown are adjusted for gender (set to female for plotting), month (set to October 2020), and baseline antibody status (set to negative).

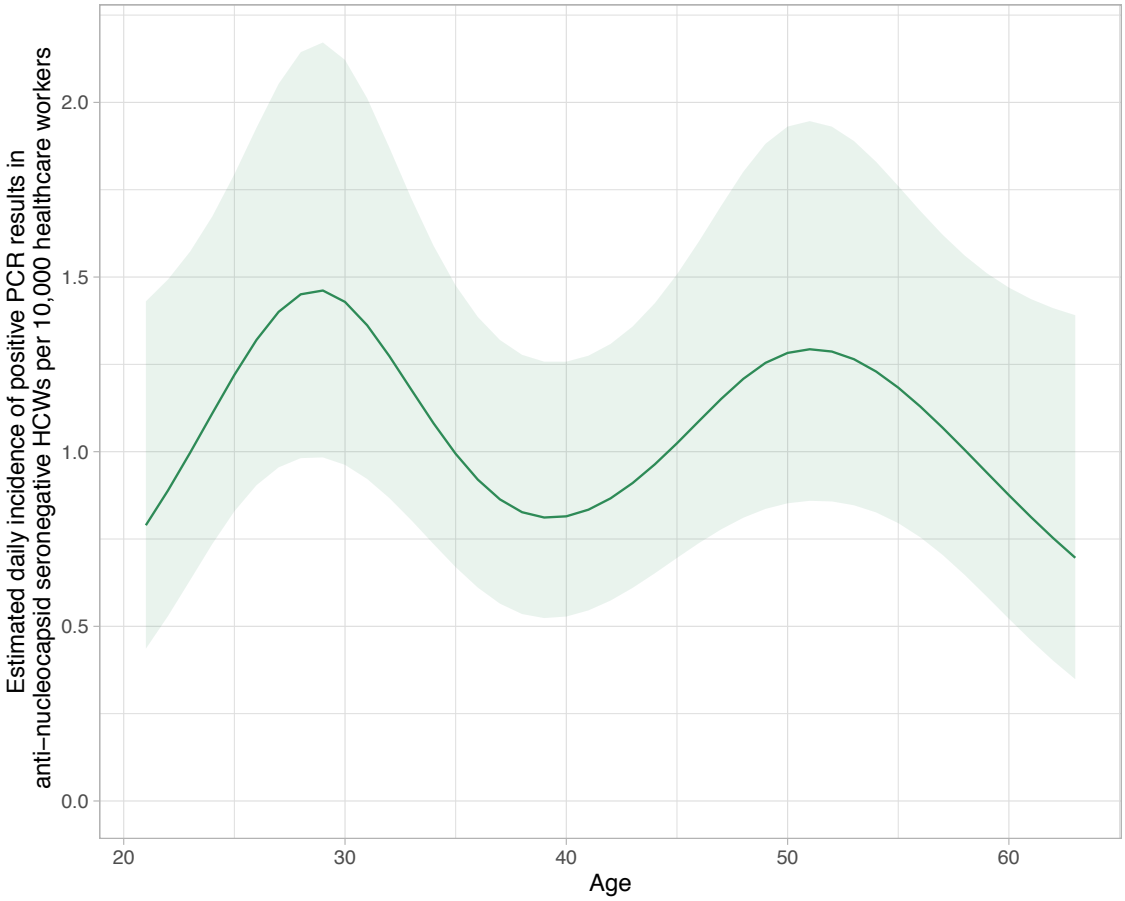


Figure S6. Non-linear relationship between age and incidence of PCR-positive results in HCWs with anti-nucleocapsid antibody measurements. Estimates shown are adjusted for gender (set to female for plotting), month (set to October 2020), and baseline antibody status (set to negative).

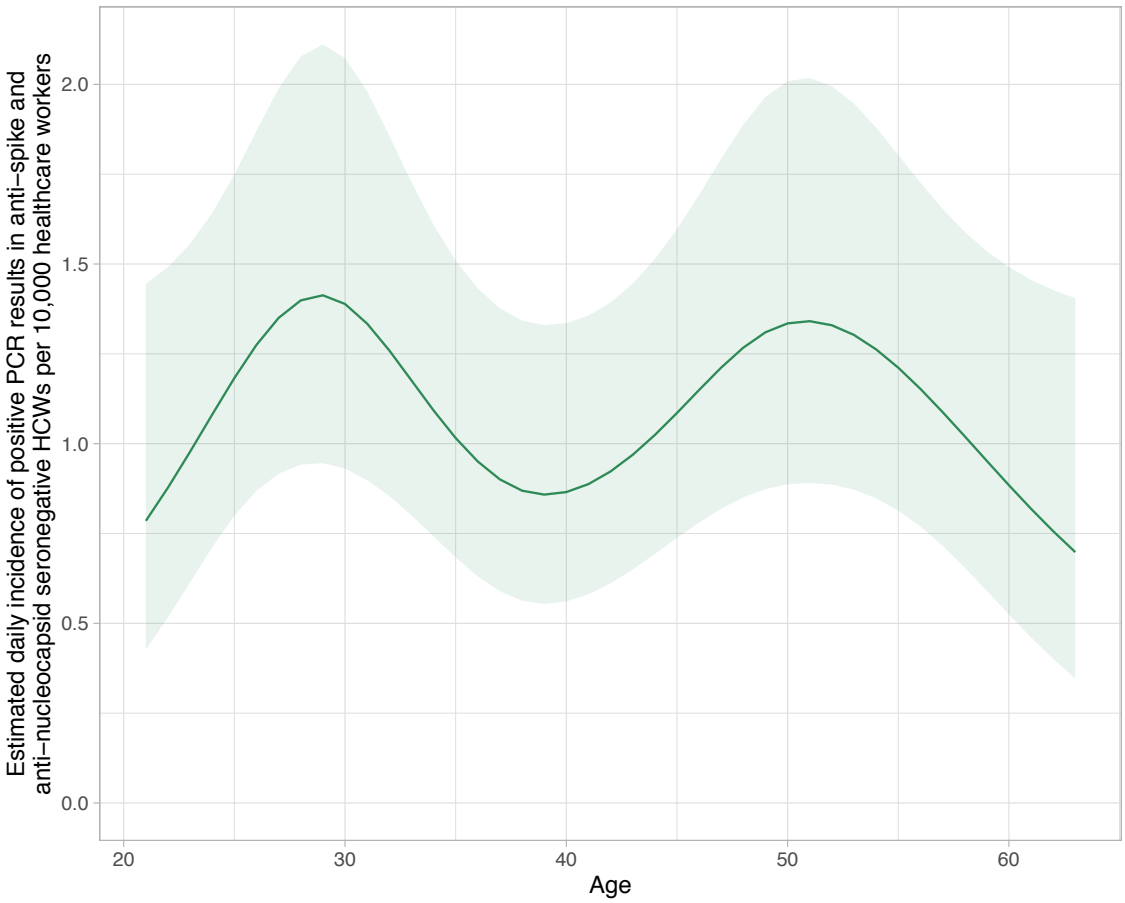


Figure S7. Non-linear relationship between age and incidence of PCR-positive results in HCWs with both anti-spike and anti-nucleocapsid antibodies. Estimates shown are adjusted for gender (set to female for plotting), month (set to October 2020), and baseline antibody status (set to negative).

Supplementary Tables

		Unadjusted IRR	Unadjusted 95% CI	Adjusted IRR	Adjusted 95% CI
Antibody status	**Anti-spike IgG negative**	1.00 (referent)		1.00 (referent)	
	Anti-spike IgG positive	0.12	0.03, 0.47	0.11	0.03, 0.44
Calendar month	**April-June**	1.00 (referent)		1.00 (referent)	
	July	0.17	0.08, 0.37	0.18	0.08, 0.39
	August	0.18	0.09, 0.38	0.20	0.09, 0.42
	September	0.25	0.13, 0.48	0.28	0.14, 0.53
	October	0.79	0.52, 1.19	0.87	0.58, 1.31
	November	2.24	1.62, 3.08	2.48	1.80, 3.42
Gender	**Female**	1.00 (referent)		1.00 (referent)	
	Male	1.02	0.75, 1.37	1.03	0.77, 1.39
Age	**Age***				

Table S1. Estimated incidence rate ratios (IRRs) by anti-spike IgG antibody status as a binary variable adjusting for age, gender and incidence by calendar month. 19 HCWs identifying as trans or with a non-disclosed gender are not shown, as there were zero PCR-positive results in these individuals, 16 of whom were seronegative and 3 of whom were seropositive. *Age was fitted as a continuous variable with a 5 knot spline (Supplementary Figure S5). The IRRs for each month are shown unadjusted and adjusted for all variable listed, i.e. they represent the IRR averaged over the seropositive and seronegative HCWs.

		Adjusted incidence rate ratio	Adjusted 95% CI
Antibody status	**Anti-spike negative**	1.00 (referent)	
	Anti-spike positive	0.11	0.03, 0.45
Calendar month at risk	**April-July**	1.00 (referent)	
	August	0.78	0.26, 2.33
	September	1.07	0.39, 2.95
	October	3.24	1.36, 7.75
	November	10.14	4.45, 23.12
Gender	**Female**	1.00 (referent)	
	Male	0.98	0.68, 1.41
Age	**Age***		

Table S2. Estimated incidence rate ratios by anti-spike IgG antibody status as a binary variable adjusting for age, gender and incidence by calendar month starting follow up of both groups 60 days after their baseline serology. Following adjustment of the period at risk for seronegative HCWs (compared to the main analysis), there were 88 PCR-confirmed symptomatic infections in the seronegative group during 1,389,257 person days at risk (0.63 per 10,000 person days) and 63 asymptomatic PCR-positive tests (0.45 per 10,000 person days). 19 HCWs identifying as trans or with a non-disclosed gender are not shown, as there were zero PCR-positive results in these individuals, 16 of whom were seronegative and 3 of whom were seropositive. *Age was fitted as a continuous variable with a 5 knot spline (similar to Supplementary Figure S5). Confidence intervals have not been adjusted for multiplicity and inferences drawn from the intervals may not be reproducible.

		Adjusted incidence rate ratio	Adjusted 95% CI
Antibody status	**Anti-spike negative**	1.00 (referent)	
	Anti-spike positive	0.12	0.03, 0.48
Calendar month at risk	**April-July**	1.00 (referent)	
	August	0.30	0.14, 0.62
	September	0.41	0.22, 0.78
	October	1.30	0.87, 1.94
	November	3.69	2.71, 5.04
Gender	**Female**	1.00 (referent)	
	Male	1.03	0.76, 1.38
Age	**Age***		

Table S3. Estimated incidence rate ratios by anti-spike IgG antibody status as a binary variable adjusting for age, gender and incidence by calendar month starting follow up of seropositive individuals 90 days after baseline serology or last positive PCR test. Following adjustment of the period at risk for seropositive HCWs (compared to the main analysis), there were zero PCR-confirmed symptomatic infections in the seropositive group during 120,967 person days at risk (0.00 per 10,000 person days) and 2 asymptomatic PCR-positive tests (0.16 per 10,000 person days). 19 HCWs identifying as trans or with a non-disclosed gender are not shown, as there were zero PCR-positive results in these individuals, 16 of whom were seronegative and 3 of whom were seropositive. *Age was fitted as a continuous variable with a 5 knot spline (similar to Supplementary Figure S5). Confidence intervals have not been adjusted for multiplicity and inferences drawn from the intervals may not be reproducible.

		Adjusted incidence rate ratio	Adjusted 95% CI
Antibody status	**Anti-spike negative**	1.00 (referent)	
	Anti-spike positive	0.12	0.03, 0.49
Calendar month at risk	**April-June**	1.00 (referent)	
	July	0.16	0.07, 0.38
	August	0.21	0.10, 0.45
	September	0.30	0.15, 0.57
	October	0.86	0.56, 1.32
	November	2.36	1.68, 3.30
Gender	**Female**	1.00 (referent)	
	Male	1.01	0.74, 1.38
Age	**Age***		

Table S4. Estimated incidence rate ratios by anti-spike IgG antibody status as a binary variable adjusting for age, gender and incidence by calendar month after down-sampling of asymptomatic test results in the seronegative group. 24% of asymptomatic PCR tests undertaken in seronegative HCWs were removed from the dataset at random, such that asymptomatic testing rates in seronegative and seropositive HCWs matched. *Age was fitted as a continuous variable with a 5 knot spline (similar to Supplementary Figure S5). Confidence intervals have not been adjusted for multiplicity and inferences drawn from the intervals may not be reproducible.

		Anti-nucleocapsid seronegative at baseline and throughout follow up (n=11,494)	Initially anti-nucleocapsid seronegative, then converting to seropositive (n=49)	Anti-nucleocapsid seropositive at baseline (n=1123)
Age (years) Median (IQR) [Range]		38 (28-49) [16-86]	35 (28-47) [23-63]	39 (29-49) [17-70]
Gender n (%)	Female	8525 (74.2%)	37 (76%)	795 (70.8%)
	Male	2952 (25.7%)	12 (24%)	326 (29.0%)
	Other**	17 (0.1%)	0 (0%)	2 (0.2%)
Ethnicity n (%)	White	8459 (73.6%)	31 (63%)	661 (58.9%)
	Asian	1755 (15.3%)	9 (18%)	284 (25.3%)
	Black	438 (3.8%)	1 (2%)	78 (6.9%)
	Chinese	125 (1.1%)	0 (0%)	9 (0.8%)
	Other	717 (6.2%)	8 (16%)	91 (8.1%)
Role n (%)	Nurse/HCA	3998 (34.8%)	21 (43%)	547 (48.7%)
	Doctor	1710 (14.9%)	2 (4%)	174 (15.5%)
	Administrative staff	1475 (12.8%)	9 (18%)	82 (7.3%)
	Medical or nursing student	610 (5.3%)	4 (8%)	24 (2.1%)
	Laboratory staff	416 (3.6%)	1 (2%)	34 (3.0%)
	Physio/OT/Speech therapist	353 (3.1%)	2 (4%)	39 (3.5%)
	Porter/Domestic	322 (2.8%)	0 (0%)	60 (5.3%)
	Security/Estates/Catering	242 (2.1%)	4 (8%)	26 (2.3%)
	Other health professionals	2368 (20.6%)	6 (12%)	137 (12.2%)
PCR-positive during follow up (n)	Total	201	25‡	2
	Symptomatic	108	16	1
	Asymptomatic	93	9	1

Table S5. Baseline cohort demographics for 12,666 healthcare workers included in the secondary analysis using anti-nucleocapsid IgG alone. Those who started anti-nucleocapsid antibody negative and then seroconverted were allowed to contribute to the analysis twice, once while at risk of infection and antibody negative and then subsequently while antibody positive and at risk of re-infection. **This category includes trans and non-disclosed gender, amalgamated due to small numbers to prevent inadvertent identification. ‡All PCR positive results in those who seroconverted occurred while in the seronegative group.

		Unadjusted IRR	Unadjusted 95% CI	Adjusted IRR	Adjusted 95% CI
Antibody status	**Anti-nucleocapsid IgG negative**	1.00 (referent)		1.00 (referent)	
	Anti-nucleocapsid IgG positive	0.12	0.03, 0.47	0.11	0.03, 0.45
Calendar month	**April-June**	1.00 (referent)		1.00 (referent)	
	July	0.17	0.08, 0.37	0.18	0.08, 0.40
	August	0.18	0.09, 0.38	0.20	0.10, 0.42
	September	0.28	0.15, 0.51	0.30	0.16, 0.56
	October	0.80	0.53, 1.20	0.87	0.58, 1.32
	November	2.31	1.67, 3.18	2.54	1.84, 3.50
Gender	**Female**	1.00 (referent)		1.00 (referent)	
	Male	0.98	0.72, 1.31	0.99	0.73, 1.33
Age	**Age***				

Table S6. Estimated regression parameters for the Poisson regression with anti-nucleocapsid antibody status as a binary variable adjusting for calendar month. 19 HCWs identifying as trans or with a non-disclosed gender are not shown, as there were zero PCR-positive results in these individuals, 17 of whom were seronegative and 2 of whom were seropositive. *Age was fitted as a continuous variable with a 5 knot spline (Supplementary Figure S6).

		Both assays negative (n=11,182)	Anti-nucleocapsid positive only (n=136)	Anti-spike positive only (n=208)	Both assays positive* (n=1021)
Age Median (IQR), [Range]		38 (29-49) [16-86]	36 (27-47) [20-70]	34 (26-44) [19-67]	40 (30-49) [17-69]
Gender **n (%)**	Female Male Other**	8296 (74.2%) 2870 (25.7%) 16 (0.1%)	102 (75.0%) 34 (25.0%) 0 (0.0%)	156 (75.0%) 51 (24.5%) 1 (0.5%)	719 (70.0%) 300 (29.4%) 2 (0.2%)
Ethnicity **n (%)**	White Asian Black Chinese Other	8244 (73.7%) 1703 (15.2%) 421 (3.8%) 120 (1.1%) 694 (6.2%)	93 (68.4%) 27 (19.9%) 6 (4.4%) 1 (0.7%) 9 (6.6%)	145 (69.7%) 35 (16.8%) 10 (4.8%) 2 (1.0%) 16 (7.7%)	592 (58.0%) 263 (25.8%) 72 (7.1%) 7 (0.7%) 87 (8.5%)
Role **n (%)**	Nurse/HCA Doctor Administrative staff Medical or nursing student Laboratory staff Physio/OT/Speech therapist Porter/Domestic Security/Estates/Catering Other health professionals	3905 (34.9%) 1635 (14.6%) 1446 (12.9%) 581 (5.2%) 406 (3.6%) 340 (3.0%) 312 (2.8%) 241 (2.2%) 2316 (20.7%)	57 (41.9%) 26 (19.1%) 11 (8.1%) 2 (1.5%) 4 (2.9%) 11 (8.1%) 7 (5.1%) 4 (2.9%) 14 (10.3%)	75 (36.1%) 39 (18.8%) 23 (11.1%) 18 (8.7%) 7 (3.4%) 8 (3.8%) 5 (2.4%) 1 (0.5%) 32 (15.4%)	504 (49.4%) 147 (14.4%) 80 (7.8%) 24 (2.4%) 31 (3.0%) 30 (2.9%) 52 (5.1%) 25 (2.4%) 128 (12.5%)
Positive PCR during follow up	Total Symptomatic Asymptomatic	218 121 97	1 1 0	1 0 1	1 0 1

Table S7. Baseline cohort demographics for 12,479 healthcare workers included in the secondary analysis using a combination of anti-nucleocapsid and anti-spike IgG. *Those who started antibody negative and then seroconverted were allowed to contribute to the analysis twice, once while at risk of infection and antibody negative and then subsequently while antibody positive and at risk of re-infection. 27 HCWs seroconverted with a single antibody becoming positive and 41 seroconverted with both antibodies positive (these individuals appear twice in the table, once in each cohort to which they contribute). **This category includes trans and non-disclosed gender, amalgamated due to small numbers to prevent inadvertent identification.

		Unadjusted IRR	Unadjusted 95% CI	Adjusted IRR	Adjusted 95% CI
Antibody status	**Both IgG assays negative**	1.00 (referent)		1.00 (referent)	
	Both IgG assays positive	0.07	0.01, 0.49	0.06	0.01, 0.46
	Only one IgG assay positive	0.46	0.11, 1.84	0.42	0.10, 1.69
Calendar month	**April-June**	1.00 (referent)		1.00 (referent)	
	July	0.18	0.08, 0.39	0.19	0.09, 0.42
	August	0.19	0.09, 0.40	0.21	0.10, 0.44
	September	0.27	0.14, 0.51	0.29	0.15, 0.56
	October	0.84	0.55, 1.27	0.93	0.61, 1.40
	November	2.36	1.70, 3.29	2.63	1.89, 3.66
Gender	**Female**	1.00 (referent)		1.00 (referent)	
	Male	0.99	0.74, 1.34	1.01	0.75, 1.36
Age	**Age***				

Table S8. Estimated regression parameters for the Poisson regression with both anti-spike and anti-nucleocapsid IgG antibody status adjusting for calendar month. 19 HCWs identifying as trans or with a non-disclosed gender are not shown, as there were zero PCR-positive results in these individuals, 16 of whom were seronegative on both tests and 2 of whom were seropositive on both tests and 1 who was seropositive on only one test. *Age was fitted as a continuous variable with a 5 knot spline (Supplementary Figure S7). Of 344 tests where only one assay was positive, 136 were positive for anti-nucleocapsid only and 208 for anti-spike only. Confidence intervals have not been adjusted for multiplicity and inferences drawn from the intervals may not be reproducible.

References

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