An observational cohort study on the incidence of SARS-CoV-2 infection and B.1.1.7 variant infection in healthcare workers by antibody and vaccination status: Supplementary material

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Supplementary methods

PCR assays

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 (Thermo Fisher TaqPath assay).

Vaccinations

Staff vaccinations provided by the hospital were recorded on an electronic database linked to testing data; staff were also able to supply details of vaccinations from other providers when requesting a symptomatic or asymptomatic PCR test.

Whole genome sequencing

Sequencing was attempted in all PCR positive samples that had been stored, regardless of cycle threshold (Ct) value. Samples were sequenced using a multiplex PCR based approach with the ARTIC LoCost protocol and v3 primers[1] using R9.4.1 flow cells (Oxford Nanopore Technologies, Oxford, UK). Consensus sequences were generated using ARTIC fieldbioinformatics v1.2.1.[2] All sequences underwent quality control, requiring >50% consensus genome coverage at ≥20 depth, and agreement between Pangolin[3] and Nextclade v2.3.2[4] assignments of lineage B.1.1.7. Duplicate samples from the same individual were excluded from analysis.

Statistical analysis

We used Poisson regression to model incidence of SARS-CoV-2 infection per day-at-risk by study group.

We adjusted for calendar month, self-reported age, sex, ethnicity and staff occupational role and patient contact. We grouped self-reported staff ethnicity into 4 categories, white, Asian, Black, other. Similarly, we grouped occupational roles to ensure groups previously noted to be at higher risk of infection were represented separately, including nurses and healthcare assistants, therapists, porters and domestic staff[5]. To address possible bias introduced by prioritisation of vaccines for those staff most at risk of infection initially, we also adjusted for working on a non-ICU ward caring for Covid patients (previously shown to increase risk[5]), which included those working in acute medical, respiratory and infectious disease specialties. Complete covariate data were available for all HCWs analysed. We fitted separate models for PCR-confirmed symptomatic SARS-CoV-2 infection and any PCR-positive result.

We tested for non-linear effects of age using natural cubic splines with up to 5 knots, choosing the best fitting model (a linear model) based on the Bayesian information criterion. All analyses were performed in R version 4.03, using the splines library for non-linear effects, and the car and multicomp libraries to compare IRRs between follow-up groups.

To investigate differences in protection by vaccine type (i.e. Pfizer-BioNTech, Oxford AstraZeneca), we divided the vaccinated follow-up groups by type and formally tested for heterogeneity by vaccine

received. To estimate the onset of protection conferred by vaccination we classified days-at-risk in vaccinated individuals from day 1 post vaccination.

We used stacked Poisson regression[6] to test for variation in the incidence of PCR-positive results with and without SGTF considering only events from 01 December 2020 where S gene PCR results were available. Similarly, for cases with available sequencing data, we identified all B.1.1.7 cases (considering all cases without SGTF to be non-B.1.1.7 cases) and compared incidence of B.1.1.7 vs. non-B.1.1.7 infection by follow-up group using stacked regression. For all stacked models we adjusted for non-SGTF/SGTF and B.1.1.7/non-B.1.1.7 calendar month separately.

For positive samples analysed using the Thermo Fisher TaqPath assay (i.e. the most commonly used assay), we compared cycle threshold (Ct) values between symptomatic and asymptomatic infections and by study follow-up group. We used the mean Ct value per sample across all detected targets. We used multivariable quantile regression (R package quantreg) to analyse the joint impact on Ct value of symptom status, and seropositivity/vaccination.

Supplementary tables

Test reason	Follow-up group	Tests performed	Days at risk	Rate per 10,000 days at risk	Incidence rate ratio vs. unvaccinated seronegative HCWs (95% CI)
Asymptomatic	Unvaccinated seronegative	42,080	2,274,675	185	1 (reference)
Asymptomatic	Unvaccinated seropositive	2,521	198,520	127	0.69 (0.66-0.71)
Asymptomatic	Vaccinated once, previously seronegative	4,892	289,134	169	0.91 (0.89-0.94)
Asymptomatic	Vaccinated twice, previously seronegative	638	39,222	163	0.88 (0.81-0.95)
Asymptomatic	Vaccinated, previously seropositive	563	33,709	167	0.90 (0.83-0.98)
Symptomatic	Unvaccinated seronegative	2,470	2,274,675	10.9	1 (reference)
Symptomatic	Unvaccinated seropositive	192	198,520	9.7	0.89 (0.77-1.03)
Symptomatic	Vaccinated, previously seronegative	242	289,134	8.4	0.77 (0.68-0.88)
Symptomatic	Vaccinated twice, previously seronegative	40	39,222	10.2	0.94 (0.69-1.28)
Symptomatic	Vaccinated, previously seropositive	30	33,709	8.9	0.82 (0.57-1.17)

Table S1. Testing rates by follow-up group.

Variable		Person-days of follow-up	Total HCWs in this follow group	Symptomatic PCR-confirmed infection					Any PCR-positive result				
				Events	Rate per 10,000 person-days	Unadjusted IRR	95% CI	p value	Events	Rate per 10,000 person-days	Unadjusted IRR	95% CI	p value
Age	Age, per 10 year increase					0.85	0.78 - 0.93	<0.001			0.89	0.83 - 0.94	<0.001
Sex	Female (Reference)	2,131,174	9,765	246	1.15	1.00			544	2.55	1.00		
	Male	699,684	3,321	80	1.14	0.99	0.77 - 1.27	0.94	169	2.42	0.95	0.80 - 1.12	0.53
	Other	4,402	23	1	2.27	1.97	0.28 – 14.0	0.50	1	2.27	0.89	0.13 - 6.30	0.91
Patient facing role	No (Reference)	626,307	2,888	61	0.97	1.00			134	2.14	1.00		
	Yes	2,208,953	10,221	266	1.20	1.24	0.94 - 1.63	0.14	580	2.63	1.23	1.02 - 1.48	0.03
Covid ward	Not working in Covid ward	2,603,522	12,019	634	2.44	1.00			290	1.11	1.00		
	Working in non-ICU Covid ward	231,738	1,090	80	3.45	1.43	1.02 - 2.02	0.04	37	1.60	1.42	1.12 - 1.79	0.003
Month	April - July 2020 (Reference)	686,122	9,691	24	0.35	1.00			86	1.25	1.00		
	August 2020	302,581	9,892	5	0.17	0.47	0.18 - 1.24	0.13	7	0.23	0.18	0.09 - 0.40	<0.001
	September 2020	301,711	10,250	5	0.17	0.47	0.18 - 1.24	0.13	11	0.36	0.29	0.16 - 0.54	<0.001
	October 2020	323,494	10,647	21	0.65	1.86	1.03 - 3.33	0.04	38	1.17	0.94	0.64 - 1.37	0.74
	November 2020	322,268	11,028	55	1.71	4.88	3.02 - 7.88	<0.001	109	3.38	2.70	2.03 - 3.58	<0.001
	December 2020	319,105	11,308	94	2.95	8.42	5.38 - 13.2	<0.001	217	6.80	5.43	4.22 - 6.97	<0.001
	January 2021	261,497	12,111	92	3.52	10.10	6.42 - 15.8	<0.001	184	7.04	5.61	4.34 - 7.26	<0.001
	February 2021	318,482	12,695	31	0.97	2.78	1.63 - 4.74	<0.001	62	1.95	1.55	1.12 - 2.15	0.008
Follow up group	Unvaccinated seronegative (Reference)	2,274,675	10,513	294	1.29	1.00			635	2.79	1.00		
	Unvaccinated seropositive	198,520	1,273	1	0.05	0.04	0.01 - 0.28	0.001	12	0.60	0.22	0.12 - 0.38	<0.001
	Vaccinated once, previously seronegative	289,134	9,711	31	1.07	0.83	0.57 - 1.2	0.32	64	2.21	0.79	0.61 - 1.03	0.08
	Vaccinated twice, previously seronegative	39,222	940	0	0.00	0.00	No events		2	0.51	0.18	0.05 - 0.73	0.02
	Vaccinated, previously seropositive	33,709	974	1	0.30	0.23	0.03 - 1.64	0.14	1	0.30	0.11	0.01 - 0.76	0.03
Ethnic group	White (Reference)	2,062,810	9,411	197	0.96	1.00			455	2.21	1.00		
	Asian	466,176	2,157	91	1.95	2.04	1.59 - 2.62	<0.001	170	3.65	1.65	1.39 - 1.97	<0.001
	Black	106,027	532	13	1.23	1.28	0.73 - 2.25	0.38	34	3.21	1.45	1.03 - 2.06	0.04
	Other	200,247	1,009	26	1.30	1.36	0.90 - 2.05	0.14	55	2.75	1.25	0.94 - 1.65	0.13
Role	Other (Reference)	839,609	4,046	86	1.02	1.00			179	2.13	1.00		
	Junior doctor	165,087	942	25	1.51	1.00	0.95 - 2.31	0.09	42	2.54	1.19	0.85 - 1.67	0.30
	Senior doctor (Consultant)	197,533	834	8	0.40	0.4	0.19 - 0.82	0.01	21	1.06	0.5	0.32 - 0.78	0.003
	Healthcare assistant	266,636	1,263	45	1.69	1.65	1.15 - 2.36	0.01	103	3.86	1.81	1.42 - 2.31	<0.001
	Nurse	832,203	3,579	118	1.42	1.38	1.05 - 1.83	0.02	248	2.98	1.4	1.15 - 1.69	<0.001

	Physio-, occupational or speech/language therapist	91,033	419	5	0.55	0.54	0.22 - 1.32	0.18	20	2.20	1.03	0.65 - 1.64	0.90
	Porter, domestic staff	72,794	338	7	0.96	0.94	0.43 - 2.03	0.87	19	2.61	1.22	0.76 - 1.97	0.40
	Administrator	370,365	1,688	33	0.89	0.87	0.58 - 1.3	0.50	82	2.21	1.04	0.8 - 1.35	0.78

Table S2. Follow-up, events and unadjusted incidence rate ratios (IRRs) by age, sex, month and follow-up group. The 33 HCWs with undisclosed, trans or other gender are omitted from multivariable regression models as this group as a whole had only 1 PCR-positive result. Note that as follow-up after vaccination occurred during a period of higher incidence overall, univariable IRRs shown are confounded and do not reflect vaccine effectiveness, see Table 1 for adjusted results.

Variable		Symptomatic PCR-confirmed infection			Any PCR-positive result		
		Adjusted IRR	95% CI	p value	Adjusted IRR	95% CI	p value
Age	Age, per 10 year increase	0.92	0.84 - 1.02	0.11	0.99	0.99 - 1	0.08
Sex	Female (reference)	1.00			1.00		
	Male	1.14	0.87 - 1.49	0.33	1.12	0.93 - 1.35	0.23
Patient facing role	No (reference)	1.00			1.00		
	Yes	1.04	0.75 - 1.46	0.80	1.10	0.88 - 1.39	0.40
Covid ward	Not working in Covid ward	1.00			1.00		
	Working in non-ICU Covid ward	1.47	1.04 - 2.07	0.03	1.43	1.13 - 1.81	0.003
Month	April - July 2020 (Reference)	1.00			1.00		
	August 2020	0.53	0.2 - 1.4	0.20	0.21	0.1 - 0.46	<0.001
	September 2020	0.54	0.2 - 1.42	0.21	0.34	0.18 - 0.63	<0.001
	October 2020	2.11	1.17 - 3.8	0.01	1.08	0.74 - 1.59	0.69
	November 2020	5.54	3.4 - 9.01	<0.001	3.12	2.33 - 4.17	<0.001
	December 2020	9.57	6.06 - 15.1	<0.001	6.31	4.88 - 8.16	<0.001
	January 2021	15.00	9.4 - 23.8	<0.001	8.39	6.41 - 11	<0.001
	February 2021	7.05	3.87 - 12.9	<0.001	3.81	2.6 - 5.59	<0.001
Follow up group	Unvaccinated seronegative (Reference)	1.00			1.00		
	Unvaccinated seropositive	0.02	0 - 0.17	<0.001	0.14	0.08 - 0.26	<0.001
	Vaccinated once, previously seronegative	0.35	0.22 - 0.55	<0.001	0.38	0.28 - 0.53	<0.001
	Vaccinated twice, previously seronegative	No events			0.10	0.02 - 0.39	0.001
	Vaccinated, previously seropositive	0.07	0.01 - 0.51	0.009	0.04	0.01 - 0.28	0.001
Ethnic group	White (Reference)	1.00			1.00		
	Asian	1.99	1.54 - 2.56	<0.001	1.65	1.37 - 1.98	<0.001
	Black	1.15	0.65 - 2.02	0.64	1.33	0.94 - 1.88	0.11
	Other	1.34	0.89 - 2.02	0.16	1.27	0.95 - 1.68	0.10
Role	Other (Reference)	1.00			1.00		
	Junior doctor	1.44	0.92 - 2.26	0.11	1.18	0.84 - 1.66	0.34
	Senior doctor (Consultant)	0.54	0.26 - 1.14	0.11	0.63	0.39 - 1	0.05
	Healthcare assistant	1.73	1.19 - 2.5	0.004	1.85	1.44 - 2.37	<0.001
	Nurse	1.49	1.1 - 2.02	0.01	1.48	1.2 - 1.82	<0.001
	Physio-, occupational or speech/language therapist	0.63	0.25 - 1.57	0.32	1.15	0.72 - 1.83	0.57
	Porter, domestic staff	1.22	0.55 - 2.68	0.62	1.60	0.98 - 2.6	0.06
	Administrator	0.99	0.65 - 1.53	0.98	1.19	0.9 - 1.58	0.23

Table S3. Adjusted incidence rate ratios (IRRs) for symptomatic PCR-confirmed SARS-CoV-2 infection and any PCR-positive result (symptomatic or asymptomatic) by antibody and vaccine status including only HCWs participating in asymptomatic screening or symptomatic testing from 01 September 2020 onwards.

Variable	Coefficient, i.e. Ct value or change in Ct value	95% CI lower bound	95% CI upper bound
Intercept, i.e., median in unvaccinated seronegative HCWs	19.3	15.8	23.4
Change in median Ct value if symptomatic	-3.0	-6.5	-0.8
Change in median Ct value if unvaccinated and seropositive	+5.7	-0.9	+13.2
Change in median Ct value if vaccinated and previously seronegative	+2.7	-0.5	+6.7

Table S4. Relationship between SARS-CoV-2 PCR cycle threshold (Ct) values and symptoms, antibody and vaccine status. Multivariable results from median regression. All Ct values were obtained using the Thermo Fisher TaqPath assay.

	Seronegative unvaccinated n=387		Seropositive unvaccinated n=10		Vaccinated n=66	
n	Symptomatic 185	Asymptomatic 202	Symptomatic 1	Asymptomatic 9	Symptomatic 31	Asymptomatic 35
Data available	129 (70%)	181 (90%)	1 (100%)	8 (89%)	19 (61%)	24 (68%)
B.1.1.7	65	90	1	2	15	20
Not B.1.1.7*	64	91	0	6	4	4
Failed sequencing**	3 (2%)	20 (10%)	0 (0%)	1 (11%)	0 (0%)	6 (17%)
Sample not available***	53 (29%)	1 (<1%)	0 (0%)	0 (0%)	12 (39%)	5 (14%)

Table S5. Sequencing and SGTF data availability by analysis subgroup for samples from 01 December 2020 onwards. Missing data in the symptomatic group tended to be due to community testing samples not being stored and hence not available for sequencing, missing data in the asymptomatic group was more likely to be due to a failed sequencing attempt (related to higher Ct values in this subgroup).
***Includes those sequenced and identified to be another lineage, and those presumed not to be B.1.1.7 as S gene was detected. In the vaccinated group two B.1.1, one B.1.1.240, one B.1.177 and one B.1.177.16 were identified, in the seropositive group, four B.1.177, one B.1.258 and one B.1.36.17.
**Includes those cases with SGTF whose sample was available, but sequence data was not of high enough quality to confirm lineage.
***Includes all community samples not available for sequencing, and some samples tested at Oxford University Hospitals but not stored.

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