Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Incidence and outcomes of healthcare-associated COVID-19 infections: significance of delayed diagnosis and correlation with staff absence

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SUMMARY

Background: The sudden increase in COVID-19 admissions in hospitals during the SARS-CoV-2 pandemic of 2020 led to onward transmissions among vulnerable inpatients.
Aims: This study was performed to evaluate the prevalence and clinical outcomes of healthcare-associated COVID-19 infections (HA-COVID-19) during the 2020 epidemic and study factors which may promote or correlate with its incidence and transmission in a Teaching Hospital NHS Trust in London, UK.
Methods: Electronic laboratory, patient and staff self-reported sickness records were interrogated from 1st March to 18th April 2020. HA-COVID-19 was defined as COVID-19 with symptom onset within >14 days of admission. Test performance of a single combined throat and nose swab (CTNS) for patient placement was calculated. The effect of delayed RNA positivity (DRP, defined as >48 h delay), staff self-reported COVID-19 sickness absence, hospital bed occupancy, and community incidence of COVID-19 was compared for HA-COVID-19. The incidence of other significant hospital-acquired bacterial infections (HAB) was compared with previous years.
Results: Fifty-eight HA-COVID-19 (7.1%) cases were identified. When compared with community-acquired admitted cases (CA-COVID-19), significant differences were observed in age (P=0.018), ethnicity (P<0.001) and comorbidity burden (P<0.001) but not in 30-day mortality. CTNS-negative predictive value was 60.3%. DRP was associated with greater mortality (P=0.034) and incidence of HA-COVID-19 correlated positively with DRP (R = 0.7108) and staff sickness absence (R = 0.7815). For the study period HAB rates were similar to the previous 2 years.
Conclusions: Early diagnosis and isolation of COVID-19 patients would help to reduce transmission. A single CTNS has limited value in segregating patients into positive and negative pathways.

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Introduction

The COVID-19 (SARS-CoV-2) outbreak started in China in late December 2019 and was declared a Public Health Emergency of International Concern on 30th January 2020. The first cases identified in the UK were in international travellers, but local transmission was soon observed. London experienced the largest number of COVID-19 cases in any UK region [1] while a large part of the total burden of disease was in south-east London.

To increase capacity for intensive care of severely ill COVID-19 patients in our hospital, elective work was minimized. Subsequently, specific wards and intensive care units (ICUs) became cohort areas for affected patients and only non-COVID-19 emergency work continued. Due to the high prevalence of infection during the peak of the outbreak, one of the suggested strategies to prevent healthcare transmission was to screen all patients on admission with a single combined nose and throat swab. This was assessed for SARS-CoV-2 RNA to enable segregation into COVID-19 positive and non-COVID-19 cohort wards.

Recent publications have identified advanced age, comorbidities and male gender as major risk factors for severity and mortality in COVID-19 [2,3] and the impact of ethnicity is being explored [4]. Healthcare-associated COVID-19 infections (HA-COVID-19) have been reported in other studies [5] but the literature on epidemiology, risk factors and outcomes of acquisition is lacking.

This study was performed to determine the burden, risk factors and clinical outcomes of adult HA-COVID-19 infections and evaluate factors which may correlate with the incidence and transmission of HA-COVID-19. Factors studied included the utility of a single combined throat and nose swab (CTNS) for patient placement, delayed RNA positivity (DRP), self-reported COVID-19 sickness absence among hospital staff, total hospital bed occupancy, community incidence of COVID-19 (CIC19) and the change in incidence of other significant hospital-acquired bacterial infections (HAB).

Methods

Setting

This study was conducted at the main site of a tertiary care teaching hospital in south-east London from 1st March to 18th April 2020. Before the COVID-19 outbreak, the capacity was 960 beds including 73 adult intensive care beds. The hospital caters to a wide mix of specialities including haemato-oncology, liver transplantation, neurosciences, women's health, paediatrics, renal, respiratory and endocrinology and serves a socio-economically deprived region of London.

All patients who were SARS-CoV-2 RNA positive from a respiratory sample and who were admitted to hospital for at least an overnight stay were included in the study.

Case definitions

COVID-19 infection: either clinical or radiological evidence of pneumonia or acute respiratory distress syndrome, or influenza-like illness with fever $\geq$37.8°C and acute onset of at least one of the following: persistent cough (with or without sputum), hoarseness, nasal discharge or congestion, shortness of breath, sore throat, wheezing, sneezing within the Public Health England (PHE) estimated incubation period (range 1–14 days, median 5 days) [6,7].

Community-associated COVID-19 infection (CA-COVID-19): (1) all symptoms on admission in keeping with above symptoms of COVID-19; and (2) respiratory sample positive for SARS-CoV-2 RNA at some point in their admission corresponding with the above symptoms.

Hospital-associated COVID-19 infection (HA-COVID-19): (1) an alternative proven aetiology for all presenting symptoms on admission (non-COVID-19); and (2) symptoms of COVID-19 developed >14 days after admission; and (3) respiratory sample positive for SARS-CoV-2 RNA within >14 days of admission.

Indeterminate acquisition: (1) proven alternate aetiology for all presenting symptoms on admission; and (2) COVID-19 symptom developed within 48 h but $\leq$14 days after admission; and (3) respiratory sample positive for SARS-CoV-2 RNA.

Among the indeterminate cases those presenting from 8 to 14 days after admission were designated late indeterminate.

Asymptomatic COVID-19: patients who did not have any symptoms of COVID-19 14 days after SARS-CoV-2 RNA positive result or up to the time of discharge.

Community incidence (CIC19) of COVID-19 was defined as the Department of Health (UK) published incidence of COVID-19 in the community (different from community presentations to hospital, i.e. CA-COVID-19).

Testing strategy

Patients presenting to the hospital with any symptoms compatible with COVID-19 were tested for SARS-CoV-2 by CTNS. All patients admitted to the hospital were reviewed daily and any who developed symptoms listed above were tested for COVID-19 and other common causes (including viruses and bacteria as per presentation). Repeat testing for COVID-19 was performed on a case by case basis, e.g., if there was a continued suspicion of infection in spite of a negative test. Clinicians were encouraged to send a deep sample, e.g., bronchoalveolar lavage not a CTNS in such cases.

Infection prevention and control (IPC) measures

All patients suspected of having a respiratory illness compatible with COVID-19 were triaged at the emergency department. If inpatient care was required, they were admitted to a ward designated as a holding area (18 *en suite* single rooms) while awaiting results of investigations. If a swab was SARS-CoV-2 RNA positive, then they were kept in a side room with IPC precautions or in a designated COVID-19 cohort ward/ICU. If the swab was SARS-CoV-2 RNA negative, they were placed with other non-COVID-19 patients.

Local SARS-CoV-2 RNA testing by real-time polymerase chain reaction (PCR) with mean turn-around time of 6 h was introduced on 29th February 2020. This enabled rapid movement of patients from the holding area. When the requirement for beds with ventilator support increased, other areas of the hospital were repurposed to accommodate 102 ICU beds.

Negative pressure rooms were limited in the hospital and a risk assessment was carried out to reduce the impact of aerosols. A separate area for donning and doffing personal protective equipment (PPE) was established for each ward. When side room availability reached capacity, parts of the ward were

created as cohort areas with bed spaces segregated from the other, curtains always to be closed, and where possible, allotted a separate toilet and dedicated nurse. There is a large variation in the design of each ward in the hospital. Cohort areas were segregated by at least a passageway and the beds allocated to COVID-19 patients clearly signposted as the cohort area. For the majority of the duration of the study, whole wards were either COVID-19 cohort wards or non-COVID-19 wards. Staff members were advised to wear PPE and FFP3 masks as appropriate. Training and mask fit testing sessions were organized continuously from February 2020. PHE guidance and updates were followed for all other aspects of infection prevention and control.

Cleaning of environmental surfaces and clinical equipment was implemented as per PHE recommendations. Curtains were changed if a non-COVID-19 patient was to be admitted to the bed space vacated by a COVID-19 patient.

When an HA-COVID-19 case was identified, actions included staff refresher training for correct PPE usage, rapid transfer of patients to a COVID-19-positive cohort ward, deep cleaning (washing walls and carpets) followed by increasing the cleaning frequency until no further transmission was seen (defined as no new symptom onset within two weeks of last known case and in haematology and geriatrics a CNTS was tested for SARS-CoV-2 RNA twice weekly for all contacts up to two weeks from last positive case regardless of symptoms).

Virological methods

A combined throat and nose swab (CTNS) in VTM, or respiratory fluid such as bronchoalveolar lavage (BAL), were assessed using RdRp gene for SARS-CoV-2 RNA. Local interpretation of PCR curves was performed using PCR: AI machine-learning software [8].

Clinical, laboratory and outcome data

SARS-CoV-2 RNA results data was extracted from the laboratory information management system (WinPath) and clinical and demographic details from electronic patient records (EPR). Age, gender and ethnicity (as Black Asian and Minority Ethnicities (BAME) or non-BAME), chronic kidney disease (CKD), hypertension, malignancy, dementia, chronic obstructive pulmonary disease (COPD), diabetes and the Charlson Comorbidity Index (CCI-age adjusted) were noted. Patients without electronic clinical records were excluded. Patients were followed up for 30 days. Duration of hospital stay, readmission after discharge and 7-, 14- and 30-day mortality were recorded. ICU admission within 7 days of COVID-19 diagnosis was used as a marker for severe disease and a subset analysis was performed.

Test performance of single CNTS

This was calculated to evaluate the efficiency of a single CTNS on admission to segregate patients into positive and negative pathways. True positives were all cases fitting the definition of CA-COVID-19 and positive on the first CTNS (taken within 48 h of admission), true negatives were patients with a negative CTNS swab within 48 h of admission and had a minimum follow up stay of 14 days wherein they remained SARS-CoV-2 RNA negative and/or did not develop symptoms of COVID-19. All positive PCR reactivity was reviewed by virologists before releasing the results to rule out contamination. If contamination was suspected samples were retested on a new PCR run and a repeat sample was requested. Hence false positives were ruled out prior to result authorization. False negatives were all cases fitting the definition of CA-COVID-19 (and RNA positive after 48 h) but were negative on the first CTNS (within 48 h).

Delayed SARS-CoV-2 RNA positivity (DRP) was defined as: (1) no RNA positive results within 48 h of presentation (for CA-COVID-19); or (2) no RNA positive results within 48 h of symptom onset (for indeterminate and HA-COVID-19).

The outcomes of patients with DRP were compared with those without a delay.

Source and incubation period of HA-COVID-19 and late indeterminate cases

If an index case patient was found in the same ward as a HA-COVID-19 case (within 14 days prior) they were recorded as a potential source. Duration of exposure of each HA-COVID-19 case to a known positive patient was calculated and the incubation period was determined using the midpoint of the exposure period up to the development of symptoms and expressed as a range from the earliest and latest contact with the known positive. Asymptomatic cases were excluded from this analysis.

Staff self-reported absence

The Workforce Development database (Health-Roster) was interrogated for staff absences due to: (1) COVID-19, (2) cold, cough and flu-like illness, (3) chest and respiratory problems. This did not include those self-isolating or shielding as per UK government advice [9]. Absences due to (2) and (3) above from 2019 were evaluated for comparison. Staff were grouped as per patient facing roles (G1: nurses, doctors, additional clinical services and allied health professionals), non-patient facing, high nosocomial exposure risk (G2: estates and ancillary, Scientific and Technical and Healthcare Scientists) and non-clinical (G3: Administrative and Clerical) to compare association with healthcare contact. Only one episode of sickness was recorded per 14-day period for each staff member. Staff members deployed to other roles were excluded. Records for staff not directly employed by the hospital Trust (e.g., porters and catering staff) were not available.

Hospital bed occupancy data, CIC19 and HAB

Bed occupancy was derived from the Business Intelligence Unit of the Hospital and community incidence of COVID-19 (CIC19) was derived from national population data [10] and Department of Health reports of COVID-19 cases [1]. HAB included bloodstream infections due to *Staphylococcus aureus* (meticillin-resistant *Staphylococcus aureus* (MRSA) and meticillin-sensitive *Staphylococcus aureus* (MSSA)), *Escherichia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*, and vancomycin-resistant enterococci and toxigenic *Clostridioides difficile* infections detected within 48 h of admission. The incidence for the duration of this study was compared with the average incidence from 2018 and 2019 during March, April and May.

Statistical methods

Categorical variables were compared using chi-squared or Fisher's exact test. Continuous variables not normally distributed were presented as median with interquartile range and Mann–Whitney *U*-test used for significance testing. Logistic regression was applied to explore risk factors associated with the outcomes and route of acquisition. To build the logistic regression model, forward selection was used and variables with $P<0.10$ were entered in the model. Results were not adjusted for BAME, because of unevenly distributed missing data. Likelihood ratio test was used to determine significant effect on the outcome after adjusting for the other variables in the model. Kaplan–Meier plots were utilized to assess mortality.

Pearson test was used for correlations between HA-COVID-19 and hospital bed occupancy, DRP, CIC19 and staff self-reported COVID-19 sickness.

All data was collated in Excel and analysed in STATA (version 16).

Results

On 25th Feb 2020 the first case of COVID-19 was recorded in the hospital. Subsequently, until 18th April 2020, approximately 5000 people were tested, of which 1729 tested positive (Figure 1). Of these, 865 (50%) were admitted to hospital within 14 days of testing for at least an overnight stay or already admitted to hospital at the time of testing. Due to the possibility of multiple acquisition sites, patients who had a second hospital admission within 14 days prior to testing ($N = 32$) were excluded. Patients <18 years of age ($N = 9$) and those where no clinical data was available ($N = 3$) were also excluded. Full classification of COVID-19 cases based on acquisition are described in Figure 1.

A total of 775 (82.8%) admitted COVID-19 cases were classified as CA-COVID-19, 58 (7.1%) as HA-COVID-19 and 32(3.7%) as indeterminate. Fifteen (1.7%) patients were classed as asymptomatic (two SARS-CoV-2 RNA positive within 48 h to seven days of admission, two cases eight to 14 days post-admission and 11 cases within >14 days of admission). For HA-COVID-19, time from admission to symptom onset ranged from 15 to 250 days (median 32.5 and interquartile range (IQR) 21–65 days). Figure 2 illustrates the primary reason for admission of HA-COVID-19 and indeterminate cases. Incidence of HA-COVID-19 during this period was 133 per 100,000 bed-days. During the study period 551 patients who stayed as inpatients >14 days were classed as not having acquired COVID-19 (tested on an average 1.5 times, range: 0–8).

Tables I and II summarize the clinical features and outcomes of CA- and HA-COVID-19. Overall, the HA-COVID-19 population was more likely to be >65 years of age and have a CCI ≥5, but less likely to be BAME. Diabetes, CKD, malignancy and a longer post-COVID-19 length of stay (median 28 days, $P<0.001$) were common with HA-COVID-19 but no overall difference in mortality was observed (Table I and Supplementary Figure S1).

Risk factors were similar for the 245 patients admitted to ICU (Supplementary Tables S1A and S1B) and there were no statistically significant differences in any outcome measures.

Supplementary Table S2 summarizes the performance a single CTNS taken within 48 h to detect CA-COVID-19 for use in patient placement on admission in symptomatic patients. Overall, sensitivity was 92.2% (95% confidence interval (CI) 92.9–93.6) and specificity 100% and negative predictive value 60.3% (57.3–63.3%).

A DRP was seen in 53 patients (Table III). In 14 cases the cause was delay in sampling and in 39 cases samples was taken within 48 h, but SARS-CoV-2 RNA was negative. For DRP patients, age >65 years, non-BAME ethnicity, diabetes and malignancy, CCI>5 were more common as was 30-day mortality ($P=0.01$). This association remained significant in the multivariate model (Table IV). Forty-five cases (85%) were not isolated appropriately as a result of the negative RNA test.

For the 58 HA-COVID-19 patients, a potential source patient was found for 44 cases and 14 late indeterminate and 11 asymptomatic late indeterminate (Table V). CA-COVID-19 with DRP was the largest single contributing group of HA-COVID-19 and late indeterminate cases (34.5 %).

Supplementary Figure S2A shows the incidence of self-reported staff sickness from 2019 and 2020 and Supplementary Figure S2B shows the self-reported COVID-19

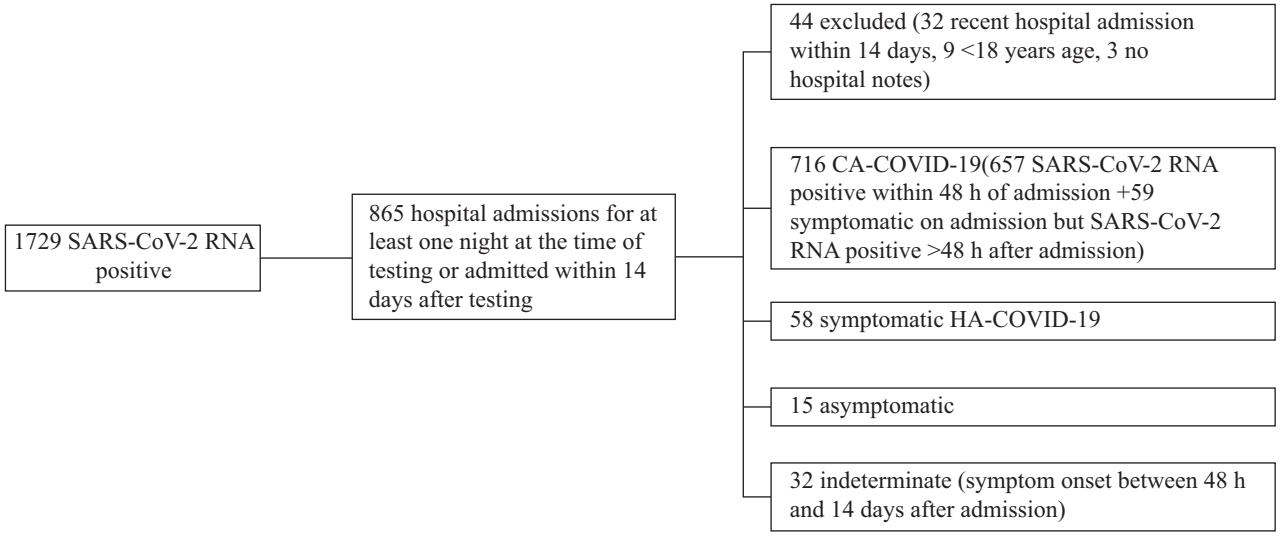

Figure 1. Classification of COVID-19 cases based on acquisition.

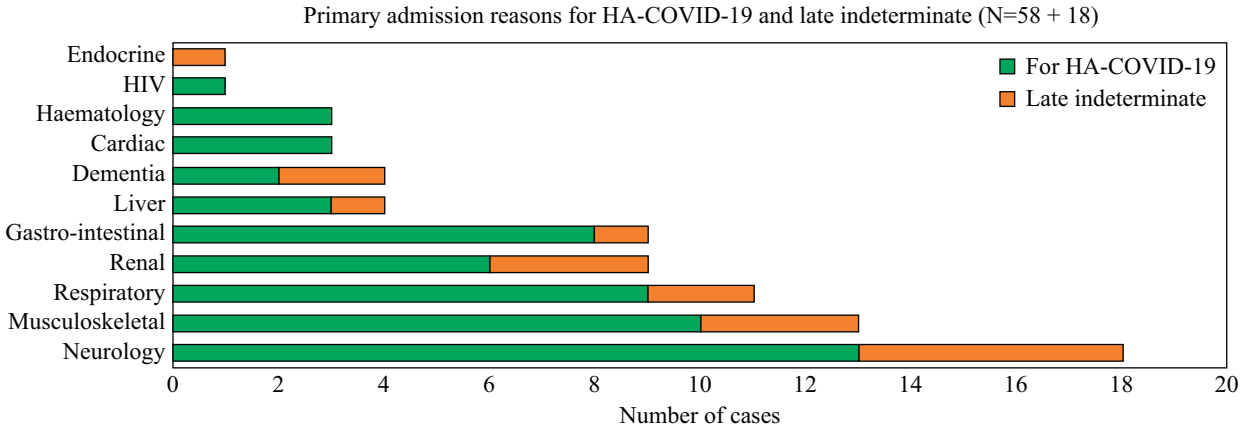

Figure 2. Primary admission diagnosis of healthcare-associated (HA)-COVID-19 and late indeterminate cases.

sickness absence for groups with high (G1 and G2 combined) and low (G3) risk of nosocomial exposure.

Bed occupancy varied during the study period as seen in Supplementary Figure S3, with an early fall in bed occupancy reflecting the reduction of elective activity and expedited discharge of non-COVID-19 patients in anticipation of increasing COVID-19 admissions.

Correlation between weekly incidence of HA-COVID-19 (including late indeterminate cases) and staff self-reported sickness absence, DRP cases, CIC19 and Trust COVID-19 bed occupancy is displayed in Figure 3. Significant correlation was observed with the former two but neither with COVID-19 bed occupancy nor the incidence in the community.

The incidence of HAB during the study period was not significant when compared with the average of the previous two years (Supplementary Figure S4).

Supplementary Tables S3 and S4 provide risk factors and outcome analysis including for the indeterminate cases. Supplementary Table S5 provides additional outcome measures for DRP associated cases. Supplementary Table S6 and Figure S5 provide the estimated incubation period for 44 HA-COVID-19 patients.

Table I
Risk factors and outcomes of patients with healthcare-associated (HA)-COVID-19 vs community-acquired (CA)-COVID-19

	CA-COVID-19 $N = 716$	%	HA-COVID-19 $N = 58$	%	Total $N = 774$	*P*
Overall risk factors						
Male	422	58.9	29	50	451 (58.3%)	0.184
>65 years old	353	49.3	38	65.5	391 (50.2%)	0.018
BAME	434	67.2	19	33.9	453 (64.5%)	<0.001
Not BAME	212	32.8	37	66.1	249 (35.5%)	
Dementia	83	11.6	10	17.2	93 (12.2%)	0.203
Hypertension	407	56.8	32	55.2	439 (56.3%)	0.805
COPD/Asthma	229	32.0	19	32.8	248 (32.0%)	0.903
Malignancy	61	8.5	19	32.8	80 (10.3%)	<0.001
CKD	142	19.8	19	32.8	161 (20.8%)	0.02
Diabetes	159	22.2	20	34.5	179 (23.1%)	0.033
CCI ≥5	292	40.8	37	63.8	329 (42.5%)	<0.001
Overall outcomes						
7-day mortality	104	14.5	4	6.9	108 (14.0%)	0.107
14-day mortality	156	21.8	12	20.7	168 (21.6%)	0.845
30-day mortality	187	26.1	15	25.9	202 (26.1%)	0.966
Discharged within 30 days	440	61.5	23	39.7	463 (59.8%)	0.001
Median LOS survivors after COVID-19 diagnosis	9 (IQR: 5–20)		28 (IQR: 14–30)			<0.001
ICU admission within 30 days of diagnosis	232	32.4	13	20.41	245(31.7%)	0.116
ICU admission: first 7 days of detection/symptoms onset	221	30.9	12	20.7	233 (30.1%)	0.104
How many of the discharged patients have been readmitted within 30 days $N = 464$	42	9.6	2	8.7	44 (9.5%)	0.892

CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; LOS, length of stay.
*BAME (Black Asian and Minority Ethnicities): not recorded for 72 patients.

Table II
Univariate and multivariate analysis for outcomes

Variables	Univariate			Model 1			Model 2		
				Multivariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Outcome: mortality									
HA-COVID-19	0.99	0.53–1.81	0.966	0.78	0.41–1.47	0.438	0.80	0.42–1.52	0.498
CCI ≥5	3.59	2.56–5.0	<0.001	3.69	2.62–5.2	<0.001			
Male	1.84	1.31–2.59	<0.001	1.87	1.31–2.67	<0.001	2.03	1.42–2.91	<0.001
>65 years	3.48	2.45–4.9	<0.001				3.29	2.28–4.73	<0.001
CKD	2.35	1.63–3.40	<0.001				1.80	1.22–2.67	0.003
Outcome: discharged within 30 days									
HA-COVID-19	0.41	0.24–0.72	0.011	0.44	0.25–0.78	0.005	0.44	0.25–0.78	0.005
CCI≥5	0.47	0.35–0.63	<0.001	0.50	0.37–0.67	<0.001			
Male	0.59	0.43–0.79	<0.001	0.57	0.41–0.77	<0.001	0.56	0.41–0.76	<0.001
>65 years	0.53	0.40–0.71	<0.001				0.60	0.43–0.81	<0.001
CKD	0.54	0.38–0.77	<0.001				0.68	0.47–1.00	0.048
Diabetes	0.55	0.39–0.78	<0.001				0.68	0.48–0.98	0.036
Outcome: ICU admission									
HA-COVID-19	0.6	0.32–1.14	0.116	0.76	0.39–1.46	0.409	0.78	0.40–1.51	0.461
CCI ≥5	0.4	0.31–0.61	<0.001	0.43	0.31–0.60	<0.001			
Male	2.1	1.48–2.84	<0.001	2.13	1.53–3.00	<0.001	2.05	1.47–2.85	<0.001
>65 years	0.4	0.26–0.50	<0.001				0.40	0.28–0.55	<0.001
CKD	0.4	0.29–0.68	<0.001				0.59	0.38–0.92	0.021

CCI, Charlson Comorbidity Index; CI, confidence interval; CKD, chronic kidney disease; HA-COVID-19, healthcare-associated COVID-19; ICU, intensive care unit; OR, odds ratio.

Discussion

A recent survey from 46 acute hospitals in the UK reported an average of approximately 8–9% of patients with a positive COVID-19 whose diagnosis was identified 14 days after admission (interquartile range 3.8–12%) (Written communication). In our study 7.1% were symptomatic HA-COVID-19 and an additional 2.2% were symptomatic late indeterminate cases. In addition, 11 asymptomatic cases were identified after 14 days and two were identified eight to 14 days from admission. We identified asymptomatic cases as part of contact screening in high-transmission-risk situations, but if outbreak management programmes included consistent testing of all asymptomatic contacts, potentially more cases would be identified.

Both in the overall analysis and in those admitted to ICU, distinct differences in the risk factors between CA-COVID-19 and HA-COVID-19 were observed. The HA-COVID-19 group was older with more comorbidities and may represent the population hospitalized at that time. However, the lower seven-day mortality (14.5% vs 6.9%) and lower proportion admitted to ICU (32.4 vs 20.4%) may be because CA-COVID-19 cases were only admitted to hospital if they were severe. Overall, 30-day mortality appears similar between CA-COVID-19 and HA-COVID-19. We also observed a trend in CA-COVID-19 for more cases of BAME origin (67.2% vs 33.9%, $P<0.001$) but as data were missing for 72 patients, results are not conclusive.

In our setting, the sensitivity of a single CTNS taken within 48 h to predict the potential to transmit SARS-CoV-2 was 92.2% and the negative predictive value was 60.3%. Wang et al. [11] highlighted the variability in detection of the viral RNA by PCR in different sample types with maximum positivity rate in bronchoalveolar lavage (93%), followed by sputum (72%) and nasal swabs (63%).

Table III
Risk factors and outcomes of patients who had delayed SARS-CoV-2 RNA positivity

	Delayed RNA detection ($N = 53$)	%	No delay in RNA detection ($N = 753$)	%	Total ($N = 806$)	P
Risk factors						
Age >65 years	36	67.9	381	50.60	417 (52.7 %)	0.015
Male	30	56.6	433	57.50	463 (57.4%)	0.898
BAME[a]	16	33.33	450	65.98	466 (63.8%)	0.001
Dementia	9	16.98	89	11.82	98 (12.2%)	0.266
Hypertension	35	66.00	427	56.71	462 (57.3%)	0.184
Diabetes	26	49.06	169	22.40	195 (24.2%)	<0.001
Asthma/COPD	18	33.96	241	32.01	259 (32.1%)	0.768
Malignancy	12	22.64	76	10.09	88 (10.9%)	0.005
CKD	16	30.20	156	20.70	172 (21.3%)	0.104
CCI≥5	30	56.60	326	43.29	356 (44.1%)	0.059
Outcome						
7-day mortality	1	1.89	108	14.34	109 (13.5 %)	0.01
14-day mortality	8	15.09	166	22.05	174 (21.6%)	0.235
30-day mortality	22	41.51	191	25.37	213 (26.4%)	0.01
Discharged	20	37.74	459	60.96	479 (59.4%)	0.001
How many of the discharged patients have been readmitted within 30 days $N = 479$	2	10.00	44	9.59	46 (9.6%)	0.951
ICU admission	18	33.96	236	31.34	254 (32.5%)	0.691
ICU admission <7 days	16	30.20	224	29.60	240 (29.8%)	0.946
Median length of stay	24 (IQR: 15–30)		10 (IQR: 5–22)		11 (IQR: 5–23)	<0.001

CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay.
[a] BAME (Black Asian and Minority Ethnicities) not recorded for 76 patients.

In the present study, 53 patients had a DRP result in keeping with the recent report of Kucirka et al. [12] who reviewed the variation in false-negative SARS-CoV-2 RT PCR results from upper respiratory tract samples. They concluded that the probability of a false-negative result in an infected person varied with days from symptom onset; the median false-negative rate varying from 38% (CI, 18–65%) on day of symptom onset to 20% (CI, 12–30%) three days after symptom onset. Because patients can present at any stage of the illness, we conclude one CTNS is insufficient to prevent onward transmission, if the decision to segregate patients is based on this result alone. Gao et al. [5] have described two nosocomial outbreaks in Wuhan where the index was a misdiagnosed case of CA-COVID-19. Our results also suggest that 34.5% of all HA-COVID-19 and late indeterminate infections could be traced back to cases where the acquisition was from a community case but an RNA-based diagnosis could not be made within 48 h of admission (Table V). The weekly incidence of DRP also correlated with the incidence of HA-COVID-19.

Among DRP cases, co-morbidities (CCI>5) were higher than in those without a delay (56.6% vs 43.3%, P=0.058) and may explain the difficulty in making a clear diagnosis in the presence of multiple clinical features. However, the higher 30-day mortality (P=0.01) (Tables III and IV) in this patient group emphasizes the need to identify a more accurate method of ruling out COVID-19 in the initial stages of presentation. A combination of detailed history taking, successive swabs, deeper respiratory sample and radiology and biochemical

Table IV
Univariate and multivariate analysis for factors associated with delayed SARS-CoV-2 RNA positivity and mortality

Variables	Univariate			Model 1			Model 2		
				Multivariate			Multivariate		
Outcome: mortality	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Delayed SARS-CoV-2 RNA positivity	2.088	1.18–3.70	0.01	1.91	1.05–3.50	0.034	1.78	0.99–3.25	0.056
CCI ≥5	3.542	2.54–4.93	<0.001	3.58	2.55–5.0	<0.001			
Male	1.897	1.36–2.64	<0.001	2.01	1.42–2.83	<0.001	2.17	1.53–3.07	<0.001
Age >65 years	3.178	1.26–2.46	<0.001				2.64	1.83–3.81	<0.001
CKD	2.28	1.59–3.26	<0.001				1.6	1.09–2.36	0.017
Hypertension	1.619	1.13–2.29	0.007				1.56	1.08–2.26	0.019

CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; CI, confidence interval; OR, odds ratio.

Table V
Potential patient source for HA-COVID-19 and late indeterminate cases

Source patient	No. of HA-COVID-19 $N = 44$[a]	No. of late indeterminate cases $N = 14$[b]	% (HA-COVID-19 + late indeterminate) $N = 58$
CA-COVID-19	4	3	12.07
CA-COVID-19 delayed diagnosis	14	6	34.48
HA-COVID-19	15	3	31.03
Indeterminate (total)	11	2	
Late indeterminate	8	2	17.24
Early indeterminate	3	0	5.17

A potential source was also found for 11 asymptomatic late indeterminate (one community-acquired (CA)-COVID-19, seven healthcare-associated (HA)-COVID-19 and three indeterminate).
[a] Potential patient source not established for 14 patients.
[b] Potential patient source not established for four patients.

markers should be evaluated in the future to help determine the best strategy to reduce onward transmission in hospital settings.

During Feb–April 2020, reported staff sickness due to cold, cough, flu and chest and respiratory problems decreased from the second week of the study probably due to the similarity of symptoms with COVID-19 and the introduction of a new staff sickness code (S13 COVID-19, Supplementary Figure S2A). COVID-19 sickness, on the other hand, increased in the first three weeks of the study and then started decreasing from week 4 which coincides with the Government introduction of community-wide restriction on movement and closure of non-essential businesses. This finding is similar to the recent report by Hunter et al. [13] which found an increase in staff positivity from 5 to 20% from 10th to 31st March 2020. They compared positivity rates amongst staff in patient-facing, non-

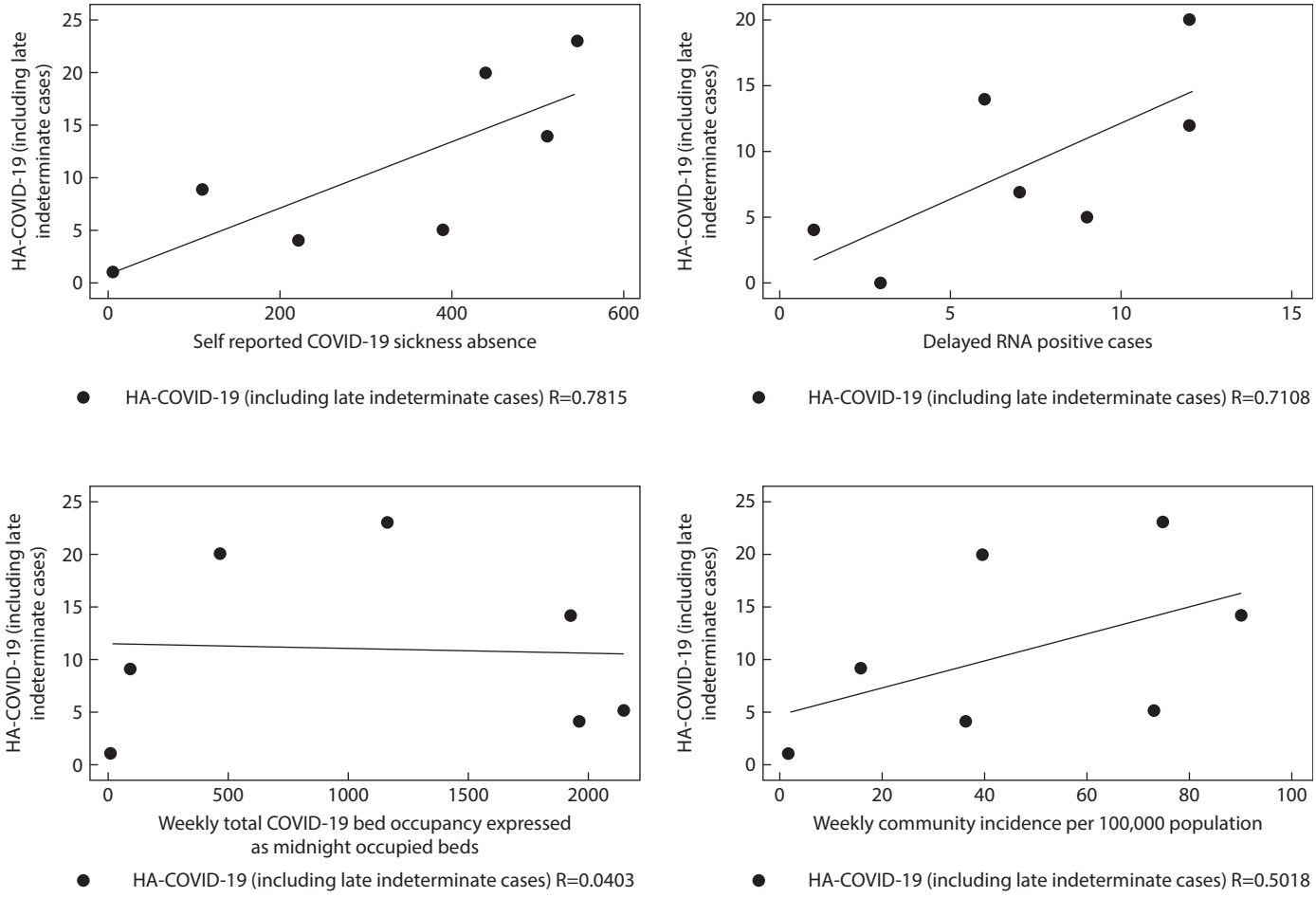

Figure 3. Correlation between weekly incidence of healthcare-associated (HA)-COVID-19 (including late indeterminate cases) and staff self-reported sickness absence, delayed RNA positive cases, community incidence of COVID-19 and COVID-19 bed occupancy.

patient-facing and non-clinical roles and found no significant difference between these groups suggesting nosocomial transmission from patients to staff was not an important factor during the study period. However, in their study, data on clinical roles were only available for one-third of included staff. Our study compared staff self-reported COVID-19 sickness rates between patient-facing high nosocomial risk and non-clinical staff and found the difference increased after social distancing was implemented. We hypothesize that working for home may be an easier option for non-patient-facing staff that may not need to take sickness leave even if mild symptoms are present.

Previous work has shown that healthcare staffing potentially influences the incidence of HAIs [14]. In the present study, the incidence of HA-COVID-19 correlated positively with healthcare staff absence due to COVID-19. The reasons for this correlation are likely to be multifactorial since the reduction in healthcare staff to patient ratios may have a negative influence on appropriate IPC measures, but may independently be a reason for SARS-CoV-2 transmission from infected healthcare staff to patients.

Dona et al. [15] recently discussed the potential impact of COVID-19 on hospital transmission of multi-drug-resistant organisms, based on how risk factors such a healthcare absence, hospital overcrowding, PPE usage and patient demographics are distributed in a healthcare setting. In our study, the effect of the measures taken and the demographics did not have a significant impact on the rate of multi-drug-resistant healthcare-associated infections when compared with the average of the previous two years.

Our study does have some limitations. Staff members were tested for SARS-CoV-2 via a regulated pathway from 27th March 2020. Prior to this, testing was on special request only and has not been included in this report. Due to the high community prevalence at the time it was not possible to determine the source of the infection linked to staff members. Recent reports suggest SARS-CoV-2 can be transmitted by asymptomatic carriers [16,17]. We have observed this in HA-COVID-19 clusters, but this study did not extend to include detection of asymptomatic infections. It is possible our HA-COVID-19 rates are lower during this period because a large proportion of elective work had stopped which limited the number of susceptible patients in the hospital. Cases with suspicion of COVID-19 but with multiple RNA negative samples were out of the scope of this analysis.

This study shows that hospital transmission of COVID-19 can be initiated by carriers who may not show symptoms and could be admitted for other reasons. Screening for asymptomatic or early infection on admission is one approach recently advocated to segregate COVID-19 and non-COVID-19 patients. However, the use of a single CTNS for this purpose is limited. Further work on appropriate use of resources in patient pathways to limit transmission is recommended.

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Conflict of interest statement
The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2020.10.006.

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