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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Real-world SARS CoV-2 testing in Northern England during the first wave of the COVID-19 pandemic

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SUMMARY

Objectives: SARS-CoV-2 emerged in South Asia in 2019 and has resulted in a global pandemic. Public Health England (PHE) Manchester rapidly escalated testing for SARS-CoV-2 in the highest COVID-19 incidence location in England. The results of the PHE Manchester SARS-CoV-2 surveillance during the first wave are presented.

Methods: Retrospective data were collected for patients fitting the PHE SARS-CoV-2 case definition from 11th February to 31st August 2020. Respiratory tract, tissue, faecal, fluid and cerebrospinal (CSF) samples were tested for SARS-CoV-2 by a semi-quantitative real-time reverse-transcription PCR.

Results: Of the 204,083 tests for SARS-CoV-2, 18,011 were positive demonstrating a positivity of 8.90%. Highest positivity was in nasal swabs (20.99%) followed by broncheo-alveolar lavage samples (12.50%). None of the faecal, fluid or CSF samples received were positive for SARS-CoV-2.

Conclusions: There was a high incidence of SARS-CoV-2 patients in the North-West of England during the first UK wave of the Covid-19 pandemic. Highest positivity rate was in nasal specimens suggesting this is the optimum sample type within this dataset for detecting SARS-CoV-2. Further studies are warranted to assess the utility of testing faecal, fluid and CSF samples. Rapid escalation of testing via multiple platforms was required to ensure prompt diagnosis and isolate infected cases to reduce transmission of the virus.

Introduction

On the 30th of December 2019, patients with an unknown aetiology of pneumonia were isolated from multiple hospitals in the city of Wuhan in China.[1] Correspondingly, a novel coronavirus was identified,[2] initially termed 2019-nCoV[3] and subsequently classified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[4] Officially, the clinical disease was termed "COVID-19",[5] with the clinical syndrome ranging from asymptomatic cases to respiratory failure and onto multisystem organ failure with other rare complications such as Guillain-Barre syndrome and meningoencephalitis. The virus spread rapidly, a pandemic was declared by the World Health Organization (WHO) and as of 18th December 2020, 75.1 million people have been infected with 1.67 million deaths globally.[6]

The first case of SARS-CoV-2 diagnosed in the United Kingdom was diagnosed on the 27th of January 2020.[7] As of the 18th of December 2020, 1.94 million cases have been diagnosed, 243,474 patients hospitalized with 76,287 deaths, demonstrating a diagnosed case fatality rate (CFR) of 3.9%.[8]

In the United Kingdom, England is the nation with the highest number of cases (1,664,511; as of 18th December 2020) with the North West of England demonstrating the highest burden with 332,086 cases, a rate of 4523 per 100,000 population.[8] The Public Health England (PHE) Manchester laboratory performs testing for SARS-CoV-2 for hospitalised patients, community outbreaks and asymptomatic staff screening in the North West of England (Pillar 1) whilst the Lighthouse laboratories performs community testing (Pillar 2).[9] We present a detailed analysis of the results of the surveillance and diagnostic testing for SARS-CoV-2 at the PHE Manchester laboratory from the 11th of February to 31st August 2020 during the first wave of the COVID-19 pandemic in England. Consequently, we aim to describe the testing methodology required to rapidly escalate mass-testing and demonstrate the in-

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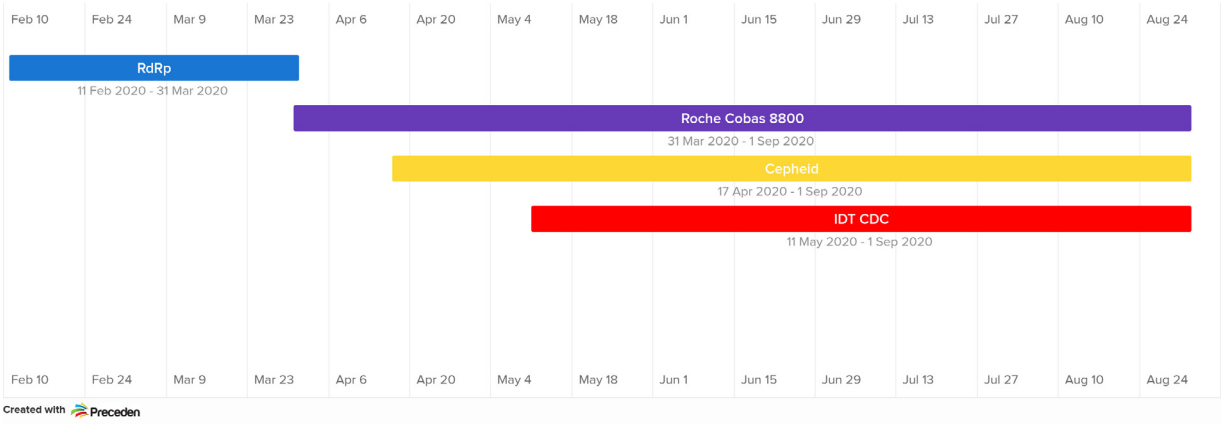

Fig. 1. Timeline of assay rollout.

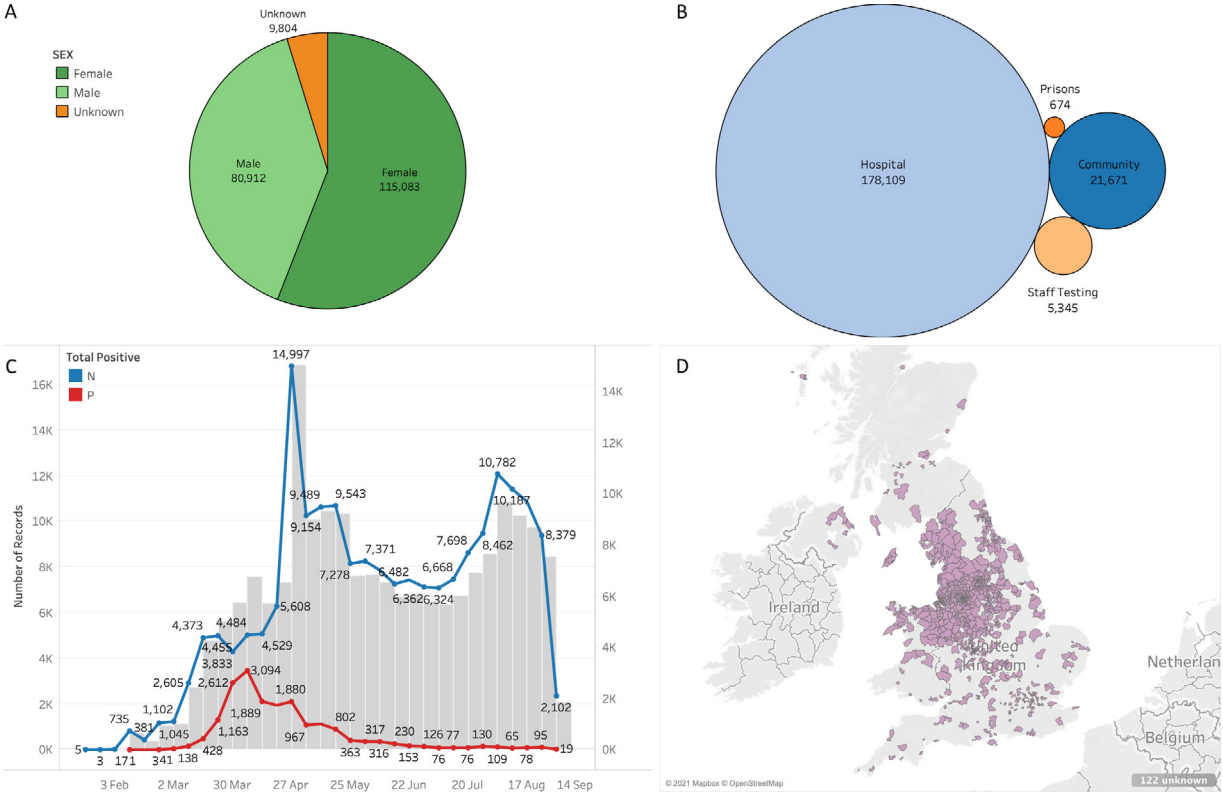

Fig. 2. **A** - Demographics of all patients referred for SARS-CoV-2 testing.
B - Public health referring locations for SARS-CoV-2 samples.
C - Number of samples received per week for SARS-CoV-2 testing with Positive (P) and Negative (N) results.
D - Local district of patients referred for SARS-CoV-2 testing.

cidence of positivity in various samples types in the first UK wave of the coronavirus pandemic.

Methods

From 1st February 2020 to 10th March 2020, returning travellers presenting to any hospital in the North-West region of England with respiratory symptoms from South-Asia were risk assessed for potential SARS-CoV-2 infection.[10] This was subsequently expanded on 10th March 2020 for all patients admitted with a fever, respiratory symptoms, anosmia or ageusia.[10]

Initially all tests were referred to the primary PHE reference laboratory until the availability of the polymerase chain reaction (PCR) test for SARS-CoV-2. PHE Manchester commenced SARS-CoV-2 testing from 11th February 2020 for all patients fitting the aforementioned criteria.

Respiratory tract, tissue, fluid, faecal and cerebrospinal (CSF) samples were tested for SARS-CoV-2 by a semi-quantitative real time reverse transcription PCR (rRT-PCR). For respiratory tract specimens, samples were either taken as naso-pharyngeal aspirates (NPA), nasal swabs (NS), sputum, throat swabs (TS), nose and throat swabs (NTS) or pleural fluids as per PHE guidelines.[11] Due to inter-operator variability in technique, “nasal swab” was allocated as the broad term for the combination of anterior nasal swabs, mid-turbinate swabs and nasopharyngeal swabs. Additionally, this was deemed necessary from a practical perspective as PHE Manchester received numerous nasal swab samples from referring laboratories throughout the UK which do not identify the type of nasal

swab as this was not defined by UK PHE guidelines.[11] Samples were collected in viral transport medium (VTM) during the first wave at PHE Manchester and transported as Category B (UN3373) specimens to the laboratory.[11, 12]

Multiple assays and platforms were utilized due to mass-testing requirements (Supplementary Appendix 1). Initial testing was performed using a laboratory developed RdRp assay[13] alongside a B2M human endogenous control assay. As commercial solutions became available testing was switched to a combination of the Roche 6800/8800 Cobas®, Cepheid Xpert and the Integrated Design Technologies (IDT) CDC assay. The Roche and Cepheid assays were performed as per manufacturer's instructions with the IDT assay being run as a single well N1, N2, B2M reaction. The IDT N gene assay was performed using either a MagNAPure 96, Qiagen MDx or QIAsymphony extraction with Thermal cycling on an LC480 II or ThermoFisher ABI 7500 Fast instrument using the manufacturers cycling parameters (Supplementary Appendix 1).[13–16]

All assays utilised within the laboratory had extensive local validation to allow their use for testing of lower respiratory tract samples including sputum, BAL, NPA and tracheal aspirates in addition to the manufacturers validation of naso/oropharyngeal swabs (Supplementary Appendix 1). Due to a lack of availability of positive clinical material for faeces, tissue and CSF, these samples have not undergone a local validation and therefore were tested off-label. All reports were issued with an interpretive comment that these samples are not validated for testing and a negative result does not rule out infection.

Due to the need to rapidly expand testing, all platforms and assays were utilized immediately post extensive local validation. This resulted in the sequential use of the RdRp (ceased 31st March 2020), Roche Cobas, Cepheid and IDT CDC assays with all running in parallel from 11th May 2020 after local validation and verification **(Fig. 1).** All assays were rolled out for all clinical settings, hospital departments and for community outbreaks.

Data were extracted from the laboratory information management system into MS Excel. After initial screening with removal of patient duplicates, data were extracted and analysed in SPSS. Utilising SPSS and Tableau Desktop, results and figures were produced.

Results

During the study period of 11th February to 31st August 2020, PHE Manchester received 206,009 samples for 205,799 patients for SARS-CoV-2 testing. Of these, 1721 samples were deemed inappropriate (incorrect sample type such as blood, referral for other investigations); 205 were environmental and quality assurance samples and thus were removed from the primary analysis. Due to invalid results, some patient samples were tested on a secondary platform, resulting in a total of 204,083 tests for SARS-CoV-2 being performed 198,339 patients who fulfilled the criteria of SARS-CoV-2 testing under the PHE case definition algorithm **(Fig. 2** and Tables 1 and 2**).**

Table 1
Demographics of referred patients.

	Referred patients	Tested patients	Positive patients
Total patients	205,799	198,339	17,993
Male	115,083 (58.7%)	80,912 (41.3%)	7772 (45.3%)
Female	80,912 (41.3%)	115,083 (58.7%)	9403 (54.7%)
Unknown sex	9804	2344	818
Mean	–	51.8	60.50
Median	–	53.67	64.31
Range	–	0 days–120 years	0 days–104 years

Table 2
Results of SARS-CoV-2 testing.

Sample Type	Cepheid							Cobas							IDT CDC							Sample Type Positives	Sample Type Negatives	All Samples	Total Samples P/N	ST Positivity
	E	ER	I	N	P	Y	Total	Positivity	I	N	P	X	Y	Total	Positivity	Hyper	I	N	P	X	Z	Total	Positivity					
VAS	0	0	0	54	1	0	55	1.82%	2	58	2	0	4	66	3.33%	0	0	24	3	0	0	27	11.11%	6	136	148	142	4.23%
VBAL	0	0	0	0	1	0	1	100.00%	2	55	4	0	1	62	6.78%	0	0	36	8	0	0	44	18.18%	13	91	107	104	12.50%
VCSF	0	0	0	0	0	0	0	0.00%	1	10	0	0	0	11	0.00%	0	0	6	0	1	0	7	0.00%	0	16	18	16	0.00%
VF	0	0	0	0	0	0	0	0.00%	0	9	0	0	0	9	0.00%	0	0	8	0	0	0	8	0.00%	0	17	17	17	0.00%
VFL	0	0	0	0	0	0	0	0.00%	0	2	0	0	1	3	0.00%	0	1	3	0	0	0	4	0.00%	0	5	7	5	0.00%
VNPA	0	0	0	17	1	0	18	5.56%	1	171	2	0	0	174	1.16%	0	1	103	4	1	0	109	3.74%	7	291	301	298	2.35%
VNS	0	0	0	8	2	0	10	20.00%	44	2351	734	2	3	3134	23.79%	0	10	1807	371	0	0	2188	17.03%	1107	4166	5332	5273	20.99%
VNT	17	2	5	10961	324	0	11309	3.02%	752	114125	12491	68	71	127507	9.87%	0	74	40820	3060	21	1	43976	6.97%	15892	165906	182792	181798	8.74%
VSP	0	0	0	25	8	1	34	24.24%	268	3881	448	2	233	4832	10.35%	1	43	1638	257	2	0	1941	13.61%	714	5544	6807	6258	11.41%
VSW	1	0	1	27	3	0	32	12.90%	4	1518	158	0	1	1681	9.43%	0	3	1001	36	0	0	1040	3.47%	198	2546	2753	2744	7.22%
VT	0	0	0	0	0	0	0	0.00%	0	47	1	0	0	48	2.08%	0	0	23	2	0	0	25	8.00%	3	70	73	73	4.11%
VTS	0	0	0	12	0	0	12	0.00%	15	4431	51	22	4	4523	1.14%	0	1	1170	20	1	0	1192	1.68%	71	5613	5727	5684	1.25%
WS	0	0	0	0	0	0	0	0.00%	0	0	0	0	0	0	0.00%	0	0	1	0	0	0	1	0.00%	0	1	1	1	0.00%
Total	18	2	6	11104	340	1	11471	3.12%	1089	126658	13891	94	318	142050	9.88%	1	133	46640	3761	26	1	50562	7.46%	18011	184402	204083	202413	8.90%

Legend - VNT: Nose and throat swab, VAS: Tracheal aspirate, VSP: Sputum, VSW: Undefined swab, VNPA: Naso-pharyngeal aspirate, VTS: Throat swab, VNS: Nasal swab, WS: Wound swab, VBAL: Broncho-alveolar lavage, VT: Tissue, VF: Faecal, VCSF: Cerebrospinal fluid, VB: Blood, ST: Sample type, E: Presumptive, ER: Error, Y: Invalid, X: Not tested, Z: Inhibitory, I: Insufficient, H:Hyper*.
NB: Negative fluids: 1 = Vitreous fluid, 1 = Saliva, 3 = Pleural fluid.
*Hyper – One sample was strongly positive at a low CT value which reflexed onto the LIMS system as a "Hyper" positive result. This has been included in the positive total.

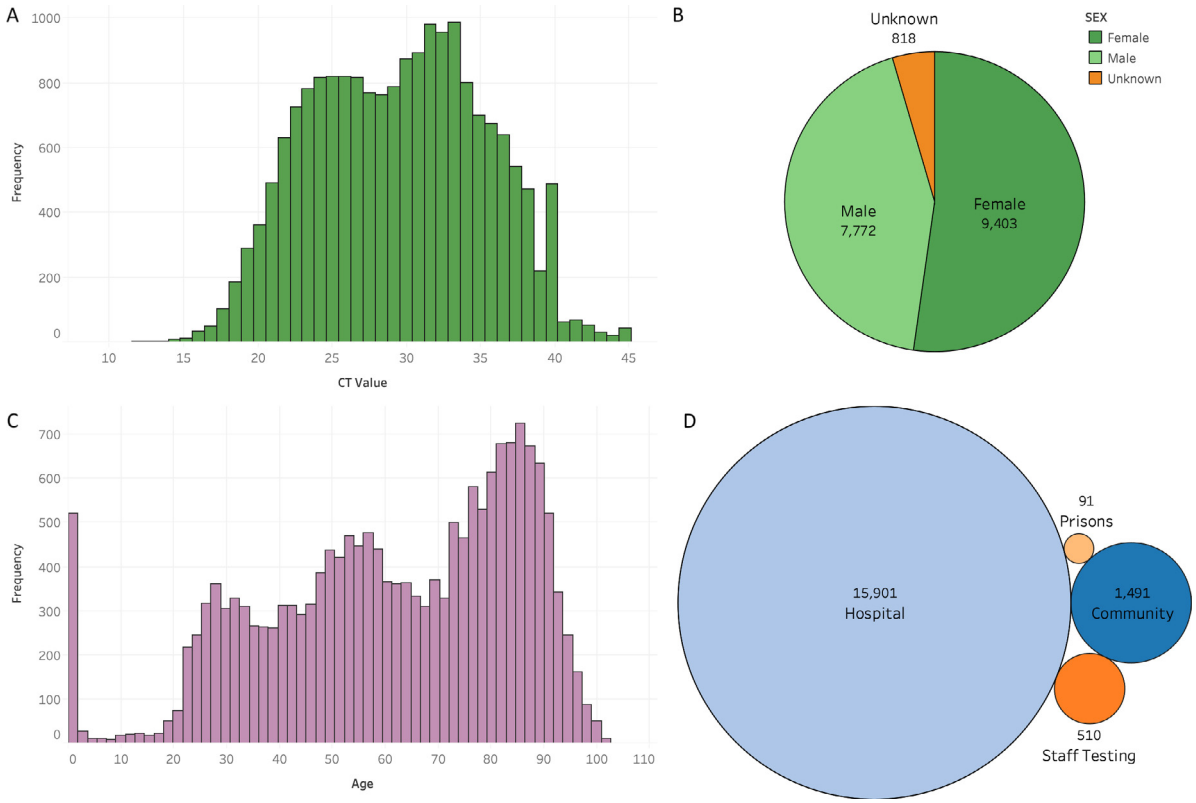

Fig. 3. **A** - Histogram of all positive CT values.
B - Demographics of patients positive for SARS-CoV-2.
C - Histogram of age of all positive SARS-CoV-2 patients.
D - Public health referring locations for positive SARS-CoV-2 samples.

A weekly average of 7152 samples were sent from locations throughout the North-West of England with the majority sent from the university teaching hospitals (**Fig. 2**).

Patients age ranged from 1-day to 112-years with a mean age of 51.8 and female preponderance (58.7%). COVID-positive patients ranged in age from 1-day to 104-years with a mean age of 60.50 (**Fig. 3**) Patient demographic characteristics are shown in **Table 1**.

Of the 204,083 tests for SARS-CoV-2, 202,413 specimens demonstrated a conclusive (positive/negative) result. 1670 samples failed to demonstrate a positive or negative result due to the reasons illustrated in **Table 2**

Of these 202,413 tests, 18,011 were positive demonstrating a positivity of 8.90%. A total 11,471 samples were tested on the Cepheid platform of which 340 were positive (3.12% positive); 142,050 on the Roche Cobas (13,891/9.88% positive) and 50,562 on the IDT CDC assay (3761/7.46% positive).

The majority of samples received were nose and throat swabs (182,792), sputum (6807) and throat swabs (5727). Other respiratory sample types tested were nasal swabs (5332), undefined upper-respiratory viral swabs (VSW – 2753), nasopharyngeal aspirates (NPA – 301), tracheal aspirates (VAS – 148) and broncheoalveolar lavage (BAL – 107). Non-respiratory samples consisted of tissue (73), faecal (17), CSF (18), fluids (7) and one rectal swab.

The highest positivity was in nasal swabs at 20.99% followed by BAL samples (12.50%) (**Table 2**) and correspondingly had the lowest median CT-value (**Fig. 4**).

The majority of the positive nasal swabs were from hospital settings (880) followed by the community (28) Only two nasal swabs from prison settings and one from staff testing was positive, indicating the likelihood of hospitalized and care-home patients having a higher burden of disease as upper respiratory samples are less sensitive and their positivity correspondingly indicates this (**Fig. 5**).[17–19]

None of the faecal (17), fluid (5) or cerebrospinal fluid specimens (16) tested were positive for SARS-CoV-2, in contrast to their respiratory positive samples which was a criteria for acceptance for COVID testing. However, only 41 specimens in total were received for these specimen types. A total of 73 post mortem lung tissues were tested with a 4.11% positivity rate.

For detection of SARS-CoV-2 via the Cepheid N-gene target, the mean CT value was 33.90 (range 15.5–44.8) whilst for the E-Gene, the mean CT value was 29.40 (range 14.4–44.4). Comparatively, the mean CT for the IDT N gene assay was 28.91 (range 9.46–44.8); 30.51 (range 13.4–43.31) for the Cobas Generic and 28.17 (range 13.09–37.68) for the Cobas Specific **(Fig. 6).** The specimens spanned a wide range of cycle threshold values reflecting ranging viral loads.[16] The utilization of the dual-target assays (Cepheid and Cobas) assisted in reducing the risk of false-negative results associated with generic variants (**Fig. 6**).

Discussion

Testing for SARS-CoV-2 is vital to diagnose active cases, isolate infected cases to reduce the transmission of the virus and control the COVID-19 pandemic. To further this aim, PHE Manchester expanded and expediated SARS-CoV-2 testing rapidly during the first wave with 204,083 tests performed.

During the study period, 17,993 patients were diagnosed with SARS-CoV-2 at PHE Manchester demonstrating a positivity of 9.1% with sample positivity correspondingly lower at 8.90% (Tables 1 and 2). This demonstrates a high burden of COVID-19 patients in the North-West of England during the first UK wave of the pandemic.

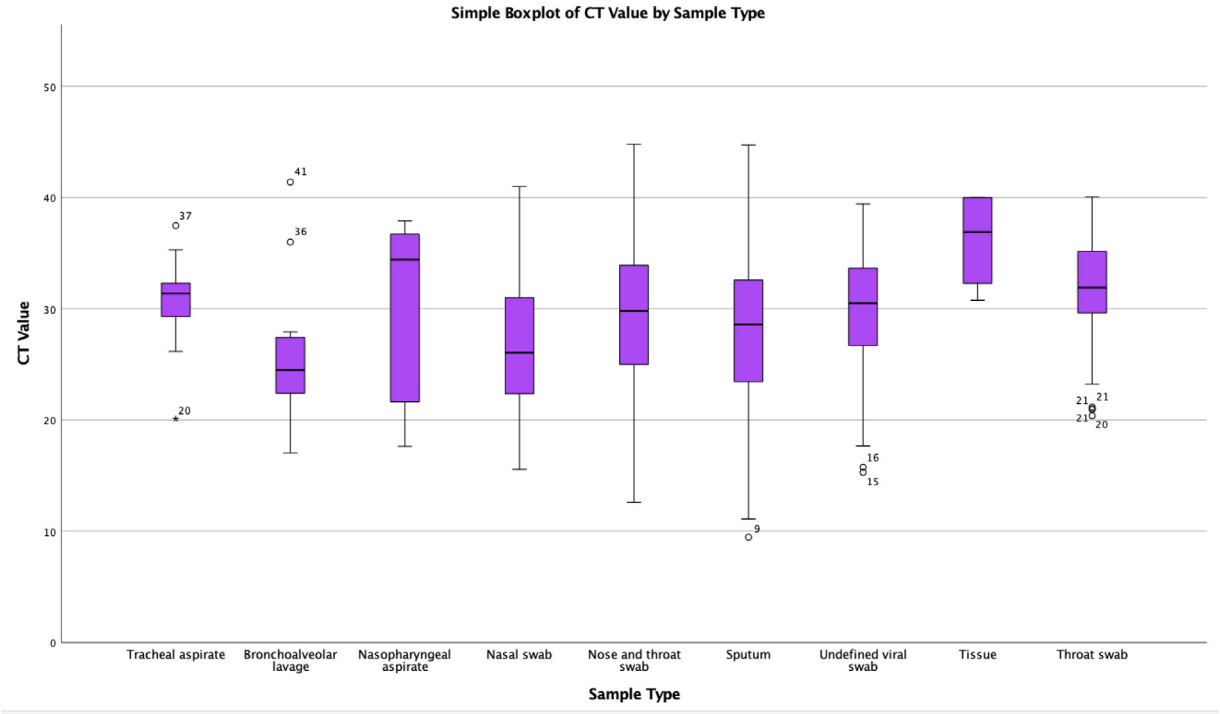

Fig. 4. Inter-quartile range, median CT-values and range for samples positive with the real-time PCR assays by sample type.

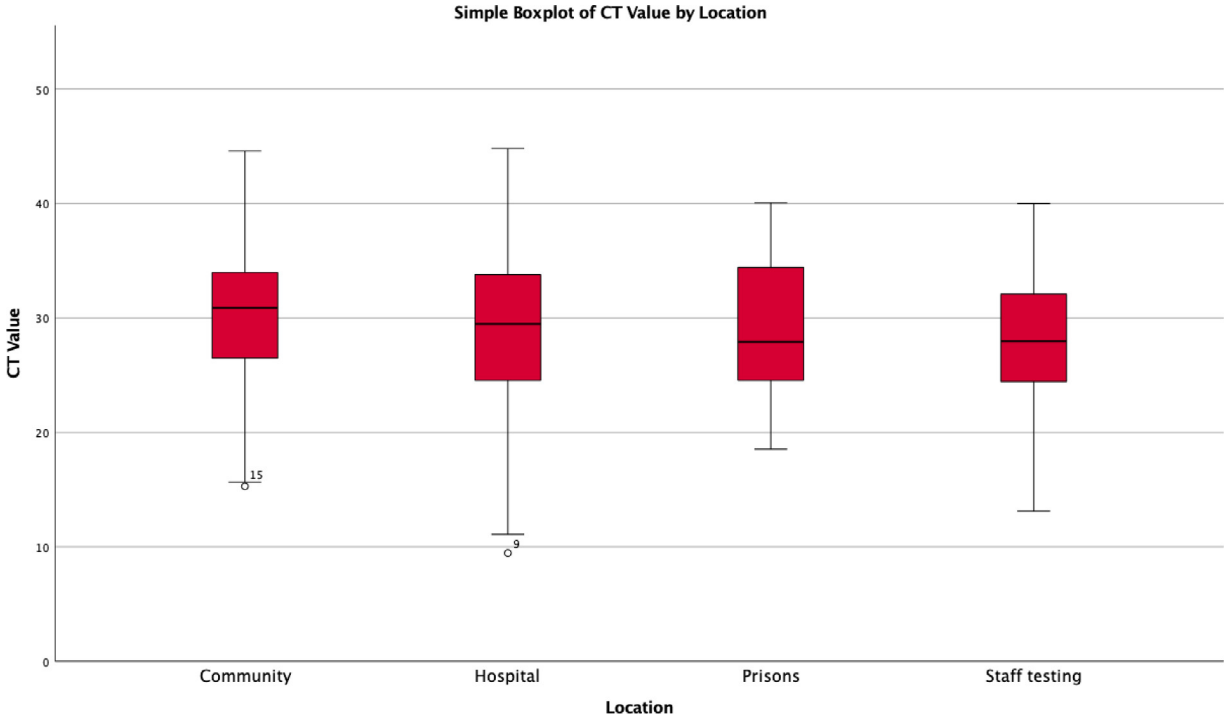

Fig. 5. Inter-quartile range, median CT-values and range for samples positive with the real-time PCR assays by location of sample.

The average age of referred COVID patients samples is 51.8 years however, our data show a higher mean age of COVID -positive patients (60.5 years) with the highest age of 104, corresponding with previous studies **(Fig. 3C).**[20] There is no observationally significant difference between the CT values of positive patients stratified by sex (Fig. 7).

From an assay perspective, the highest positivity is demonstrated by the dual-target Roche assay (9.88%). Correspondingly, the mean CT values for the Cobas Specific and Cepheid N-gene targets are 28.18 and 29.41 respectively, showing a high burden of disease[21–28] **(Table 3 and Supplementary Appendix 1).** The utilization of the dual-target assays (Cepheid and Cobas) may assist in the future of reducing the risk of false-negative results associated with generic variants due to their range **(Fig. 6).** RdRp was a single target assay with the IDT N gene utilised two targets (N1 and N2) on a single dye layer to report a single output. However, this still had the advantage of being able to minimize the risk missing positives associated with genetic variants (Fig. 6).

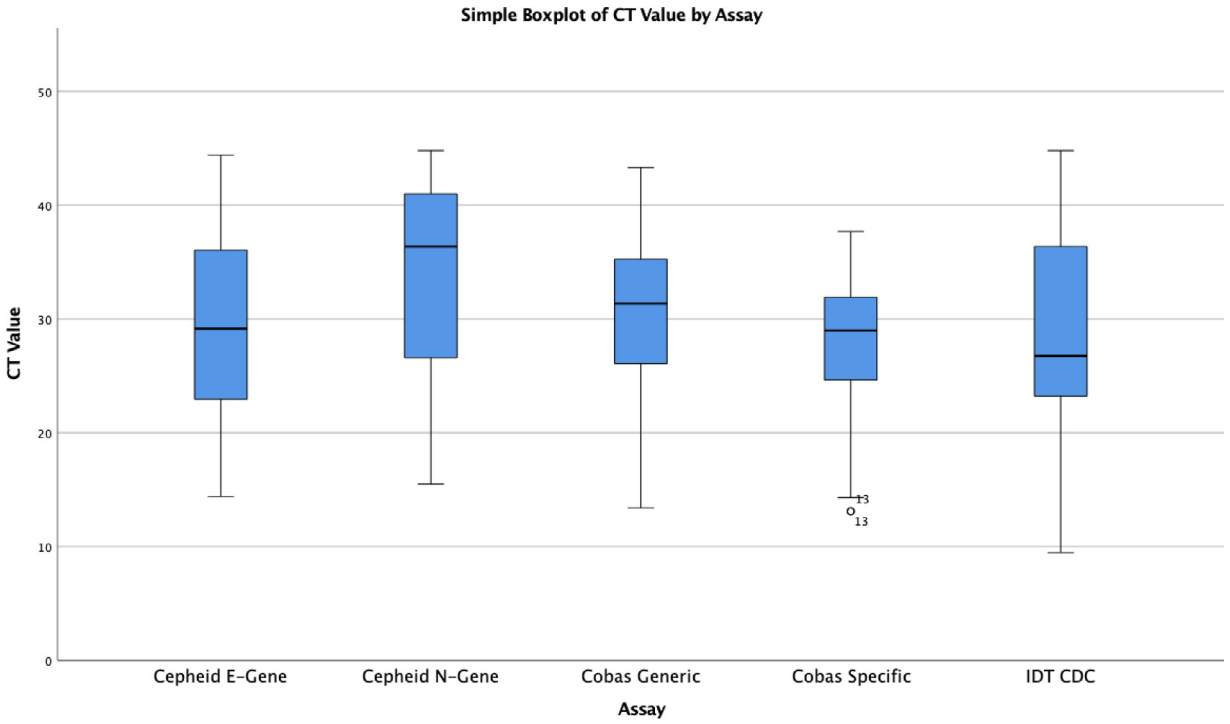

Fig. 6. Inter-quartile range, median CT-values and range for samples positive with the real-time PCR assays by assay type (all sample types).

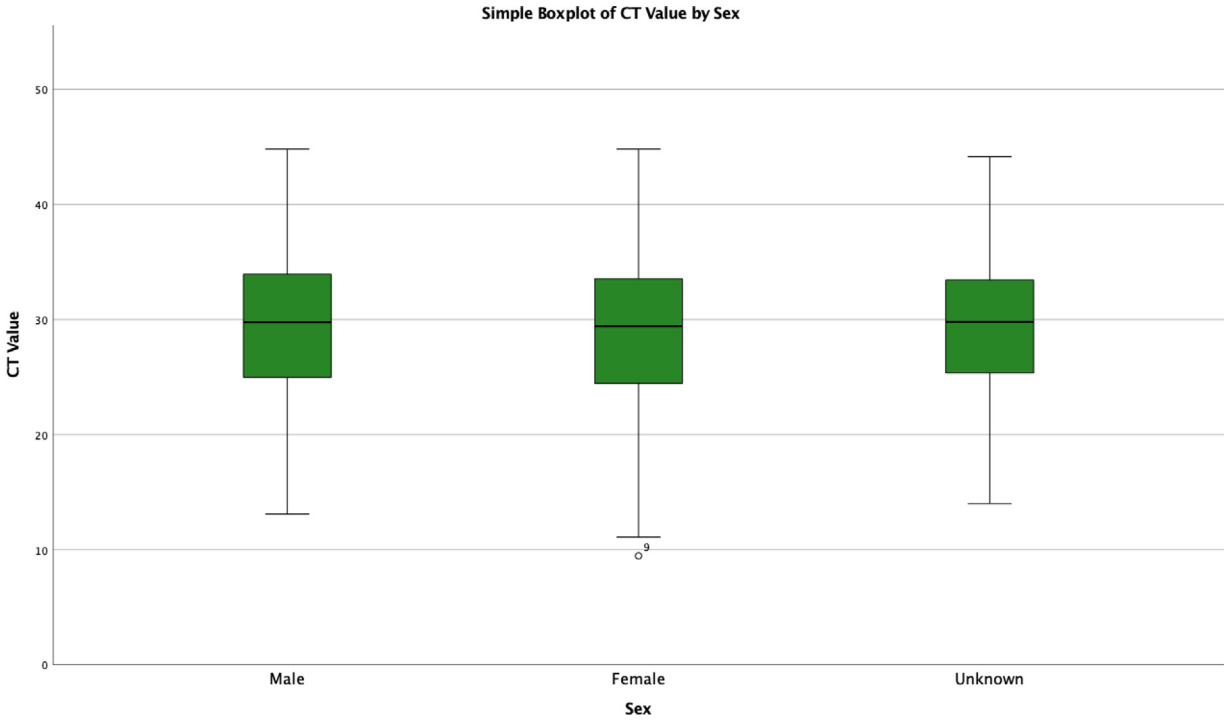

Fig. 7. Inter-quartile range, median CT-values and range for samples positive with the real-time PCR assays by patient sex.

Table 3
CT values of assays.

Assay	Mean	Median	Range
IDT CDC	28.91	26.76	3.46–44.80
Cepheid N-gene	33.91	36.35	15.50–44.80
Cepheid E-gene	29.41	29.15	14.40–44.40
Cobas generic	30.51	31.35	13.40–43.31
Cobas specific	28.18	29.00	13.09–37.68

Although, all platforms and assays were eventually utilized in parallel and rolled out for all clinical departments, there was a predilection for emergency department, surgical, paediatric, haematological and transplant use for urgent Cepheid tests. This may have slightly contributed to influence the positivity rate and sensitivity of the Cepheid platform as a proportion of this patient cohort (transplant, haematology) may have been shielding due to the UK government guidelines[29] and therefore, less likely to acquire COVID-19.

A secondary finding is the high positivity of nasal swabs in this dataset with a positivity of 20.99% followed by BAL samples (12.50%). Of note is the contrasting positivity between nasal swabs and combined NTS (8.74%). This correlates with previous studies which demonstrate combined nasal and throat specimens are more sensitive for SARS-CoV-2 detection than throat specimens with a higher SARS-CoV-2 viral load.[30, 31] This is illustrated briefly by this dataset with gradually reducing positivity with increasing oral secretions by sample type (VNS>VNT>VTS) indicating the oral swab component may decreases the sensitivity of the combined swabs. However, a majority of nasal swabs were performed in hospital settings which may skew the data as these patients had more severe disease compared to asymptomatic staff testing and in prison settings.

None of the faecal, fluid, or CSF specimens were positive for SARS-CoV-2. This contrasts previous studies[32] however, our sample size for non-respiratory specimens is comparatively limited.

This study is a retrospective review of analysis of laboratory surveillance data with no detailed patient outcome denoting data that could not be correlated with symptoms or disease course. The total number of some sample types tested were small which may have biased the data analysis. We also compared CT values across the different assays in use for multiple sample types to demonstrate real-world data for SARS-CoV-2 testing.

Further spatiotemporal studies of patients with symptoms data and consecutively collected specimens from multiple sites is merited. Additionally, further studies are warranted for same sample types tested across multiple assays in a real-world setting.

Conclusion

There was a high incidence of SARS-CoV-2 patients in the North-West of England during the first UK wave of the COVID-19 pandemic. Rapid escalation of testing capacity by utilizing multiple platforms was required to test for multiple sample types to ensure rapid diagnosis, isolate infected cases, to reduce the transmission of the virus and control the COVID-19 pandemic.

Consent for publication

All authors gave their consent for publication.

Availability of data and materials

All the data for this study will be made available upon reasonable request to the corresponding author.

Ethical approval

Ethical approval was not obtained as this study is an analysis of laboratory surveillance data. However, patient identifiable information was anonymised to ensure patient confidentiality during the data analysis with all positive SARS-CoV-2 cases reported via the PHE system.

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Declaration of Competing Interest

All authors declare they have no conflicts of interests or anything to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2021.04.013.

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