Public Health England

Protecting and improving the nation's health

Duration of infectiousness following COVID-19: data from England

WHO call 30/09/2020

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Content

Data from Virus Reference Department at Public Health England:

- Analysis of SARS-CoV-2 RT-PCR Ct values in symptomatic cases
- Analysis of SARS-CoV-2 virus isolation from upper respiratory tract samples
- Analysis of Ct values and virus isolation from pre-symptomatic and asymptomatic cases
- Comparison of virus detection by age group

Background and Aims

RT-PCR does not distinguish between infectious and non-infectious virus

UK guidance on self-isolation updated on 30th July 2020 from 7 to 10 days, in line with WHO guidance

Prolonged PCR positivity after COVID-19 has been reported

Propagation in cell culture can confirm presence of infectious virus in clinical samples and may be a better proxy for infectiousness

Aim: Analysis of data from England to understand how SARS-CoV-2 RT-PCR detection relates to cultivable virus to support decision-making on isolation / infection control

Previous studies on duration of infectiousness

- 4 studies (Germany[1], USA[2], Hong Kong[3], Canada[4]) and one care home outbreak investigation (USA[5]) – cultivable virus detectable up to **8/9 days** after symptom onset (mild-to-moderate COVID-19).

- Dutch study[6] isolated virus up to **20 days** from hospitalised cases with a more severe spectrum of illness, including immunocompromised

- Cultivable virus from 17 pre-symptomatic and 1 asymptomatic case (Arons et al[5])

- Summary of culture based studies [7]

1. Wolfel et al. Nature 2020. 2. Kujawski et al. Nature Medicine 2020. 3. Ranawaka et al. EID 2020. 4. Bullard et al. CID 2020. 5. Arons et al. NEJM 2020. 6. Van Kampen et al. medRxiv 2020 7 Jefferson et all, medRxiv Sept 2020

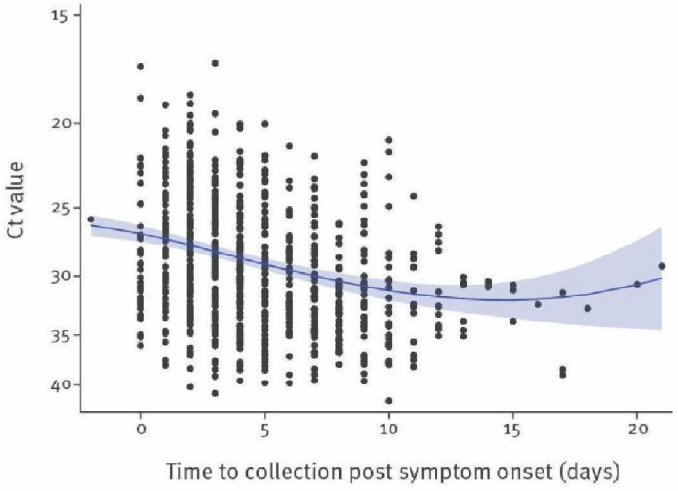
Kinetics of viral RNA detection in upper respiratory tract

n=754 URT samples (from 425 symptomatic cases)

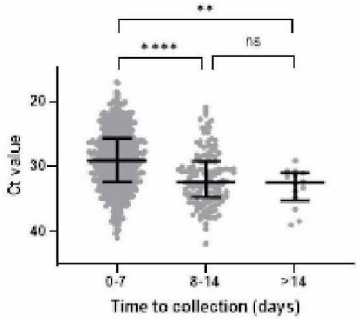
Tested in first 2-3 months of pandemic (late Jan to early April 2020)

All tested at Virus Reference Department, Public Health England (RT-PCR targeting RdRp)[7]

Linked to clinical data from GB FF100 surveillance study (Boddington *et al*[8])



Fractional polynomial model fitted to random intercept regression model



7. Corman et al Eurosurveillance 2020. 8. Boddington et al medRxiv 2020

Propagation of virus from clinical samples

Vero E6 cells inoculated with clinical specimen, inspected for cytopathic effect for up to 14 days, confirmed by nucleoprotein staining by EIA on infected cells
All work performed in CL3 laboratory inside a class 3 cabinet.

Virus culture attempted from **324 URT samples** (from 253 cases)

Cultivable virus from **133 URT samples (41%)** (from 111 cases)

92% of cases were non-severe (asymptomatic or mild-to-moderate disease)
8% of cases were severe (required intensive care admission and/or fatal)

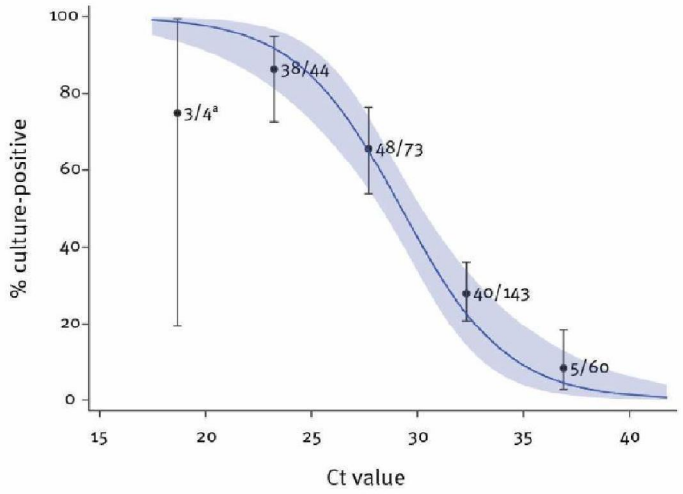
"Real-world" samples - from community surveillance, healthcare worker surveillance, early pandemic response, outbreak investigations

Relationship between Ct value and virus isolation

Median Ct value of all samples = 31.15 (IQR 27.50-33.86; range 17.47-41.78)

Strong relationship between Ct value and ability to recover infectious virus

Estimated odds ratio of recovering infectious virus decreases by 0.67 for each unit increase in Ct value (95%CI 0.58-0.77)



Mixed effects regression analysis

Cultivable virus from 5/60 with Ct>35
None had severe illness, none were asymptomatic

Est. probability of recovery of virus where Ct>35 was **8.3% (95%CI 2.8-18.4%)**

Singanayagam et al. Eurosurveillance, 2020

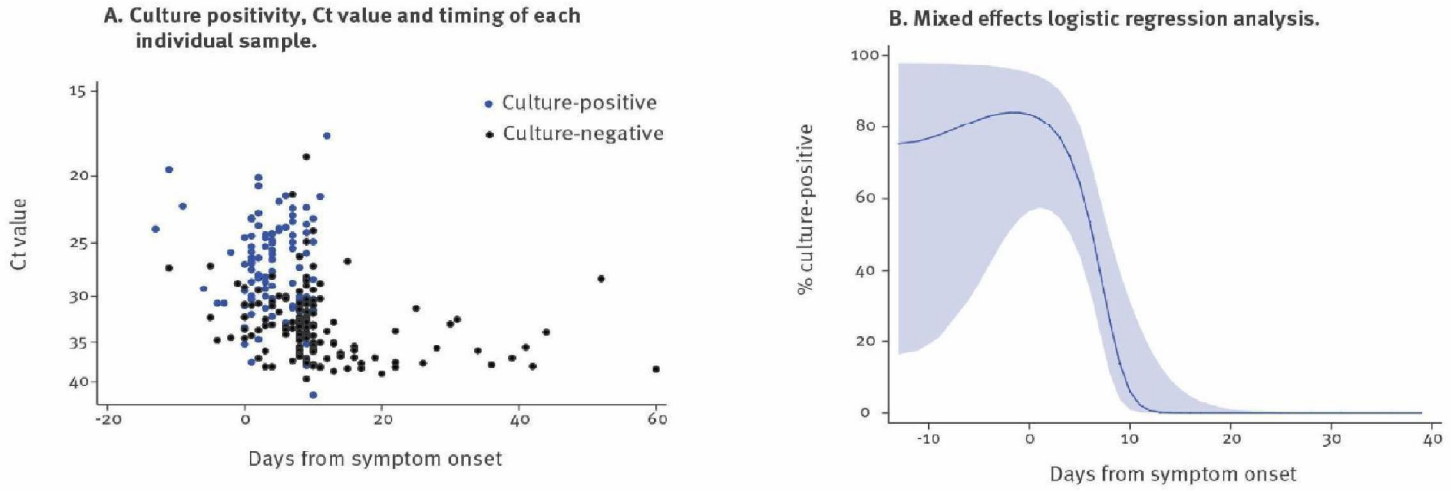
Relationship between time from symptom onset and virus isolation

246 URT samples (from 176 symptomatic cases) where record of date of symptom onset available

Cultivable virus from 103 URT samples (**42%**) (from 81 cases)

Median duration of virus shedding as measured by culture = 4 days (IQR 1-8, range -13 to 12)

Culture positivity rate significantly higher in week 1 than week 2 (74% vs 20%, p=0.002)



Late culture positive samples

More than half of samples tested (n=130 samples, 53%) were taken >7 days after symptom onset

21% (27 samples from 18 cases) were culture positive

None had severe illness or were immunosuppressed

Latest culture positive sample at **day 12**

Day post symptom onset	Estimated percentage culture positive (95% CI)	N (observed number tested)	R (observed number culture positive
7	40.1 (22.8 to 60.4)	14	10
8	25.8 (11.0 to 49.4)	33	9
9	13.7 (3.7 to 39.6)	34	10
10	6.0 (0.9 to 31.2)	23	6
11	2.2 (0.2 to 23.9)	6	1
12	0.7 (0.0 to 17.9)	3	1
13	0.2 (0.0 to 13.1)	4	0
14	0.03 (0.0 to 9.4)	2	0
15	0.006 (0.0 to 6.7)	2	0

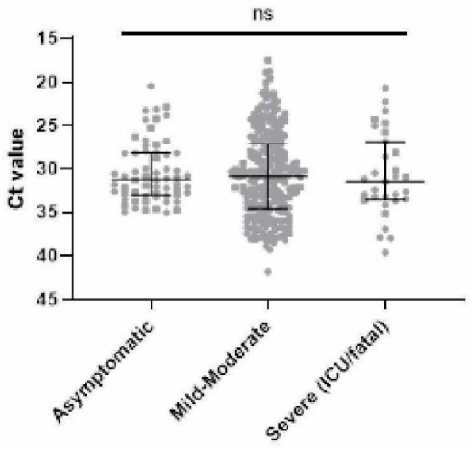
Probability of culturing virus declined to **6.0%** (95% CI: 0.9–31.2%) after day 10

Pre-symptomatics and asymptomatics

No difference in Ct values between those with asymptomatic, mild-to-moderate or severe illness

7/13 (54%) samples were from **pre-symptomatic** cases
- Regression analysis: pre-symptomatic samples as likely to be culture positive as samples taken when symptomatic

62 samples from **asymptomatic** cases
- No difference in culture positivity rate between asymptomatics (21/62) and symptomatics (111/260) – estimated OR 0.66 (95%CI 0.34 to 1.31, p=0.23)
- No difference in proportion of asymptomatic cases between males and females, estimated OR0.86 (95% CI 0.46 to 1.90, p=0.63).



Comparison of virus detection by age group

No difference in Ct values (p=0.12) or culture positivity (p=0.63) from URT samples received across the different age groups

Proportion of asymptomatic cases was similar across age groups, except for 81-100 year olds who were more likely to be asymptomatic than the other age groups (p=0.006)

Age group in years	Ct value Geometric mean (95% CI)			Virus isolation Estimated % culture-positive (95% CI)			Asymptomatic cases % asymptomatic (95% CI)		
	n	mean	95% CI	n	%	95% CI	n	%	95% CI
0–20	14	28.81	26.50–31.33	14	57.8	26.7–83.8	14	14.3	3.0-47.3
21–40	81	30.81	29.77–31.90	81	43.2	30.7–56.5	81	17.5	10.0-28.9
41–60	140	30.83	30.03–31.65	140	37.7	27.8–48.7	140	13.6	8.6-20.8
61–80	40	29.87	28.42–31.38	40	41.3	24.4.–60.5	40	17.5	7.8-34.6
81–100	49	29.09	(27.84–30.41	49	32.1	18.8–49.2	49	40.8	27.4-55.7

Conclusions

In mild-to-moderate COVID-19, infectious virus can persist for a week or more after symptom onset, declining over time

At 10 days after symptom onset, in line with current WHO and UK guidance on release from isolation, probability of culturing virus declines to 6%.

We recommend that infection control measures for persons with mild-to-moderate COVID-19 be particularly focussed immediately after onset of symptoms and retained for 10 days

Ct values and the presence of infectious virus were similar from asymptomatic and pre-symptomatic persons, compared with those who were symptomatic

Asymptomatic and pre-symptomatic persons are likely to be a source of infectious virus.

Limitations

Predominantly cases of mild-to-moderate and asymptomatic COVID-19. More data from immunocompromised persons is required.

Recall bias may affect the interpretation of timing of virus detection in relation to symptom onset

Real-world data, subjects were not sampled systematically

Timing of culture becoming negative related to acquisition of immunity not tested here, but is important to understand

The sensitivity of virus propagation from clinical samples is dependent on laboratory expertise, cell lines and protocols used, and may be affected by sample quality, storage and transport conditions

The significance of low titres of infectious virus for human-to-human transmission remains uncertain.

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Virus culture work

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PCR work

- 5.1.2c

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