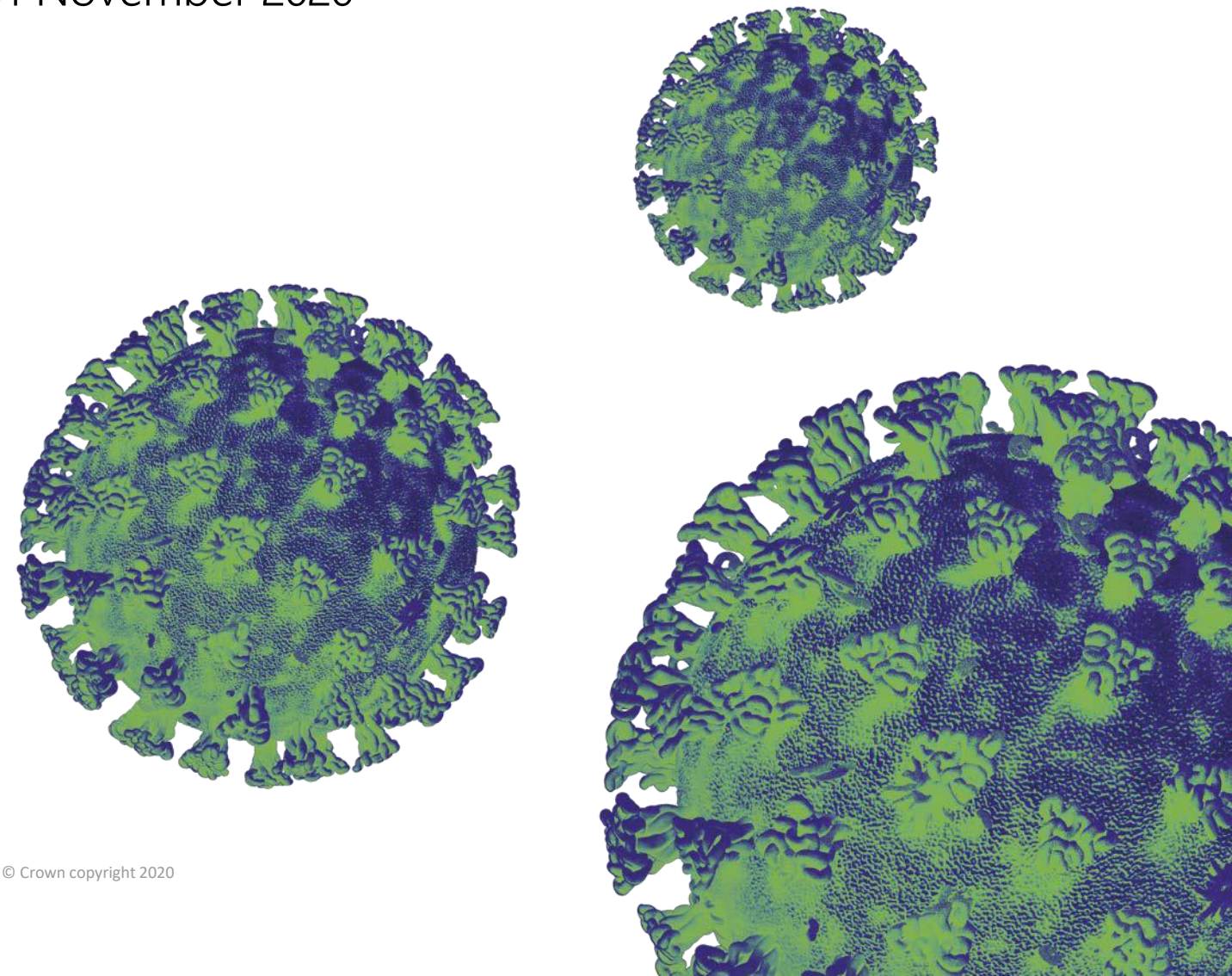
Llywodraeth Cymru
Welsh Government

Technical Advisory Group

Briefing paper- Infectivity of Covid-19

01 November 2020



Technical Advisory Group – Testing Subgroup

Briefing paper - Infectivity of Covid-19 – 1st November 2020

Introduction

A key element for the control of the spread of SARS-CoV-2 is the identification and isolation of people who are infectious.

The virus can be detected in a number of different body compartments during the course of infection (upper respiratory tract, lower respiratory tract, stool, serum).[1] However the respiratory tract is by far the main source of transmissible virus and is the focus of this paper.

Infectivity is determined by combination of viral load in the upper respiratory tract and a range of behavioural factors such as coughing or social mixing. Information on infectivity comes from studies of viral load & shedding, and transmission studies.

Virus Shedding and Infectivity

It is now known that viral RNA may be detected by RT-PCR in upper respiratory samples for prolonged periods, in some cases more than 120 days, following initial infection. [2] However, the presence of viral RNA does not appear to correlate with either the presence of live virus or indeed infectivity.

Intuitively, the presence of culturable virus should correlate with infectivity, and this has been confirmed in a hamster model of COVID infection; Although viral RNA was continuously detected in the nasal washes of inoculated hamsters for 14 days, the communicable period was short and correlated with the detection of infectious virus but not viral RNA.[3]

Although the presence of viral RNA does not correlate with the presence of culturable virus, the RT-PCR cycle threshold (Ct) values correlate strongly with cultivable virus. In one study, the probability of culturing virus declined to 8% in samples with Ct > 35.[4]

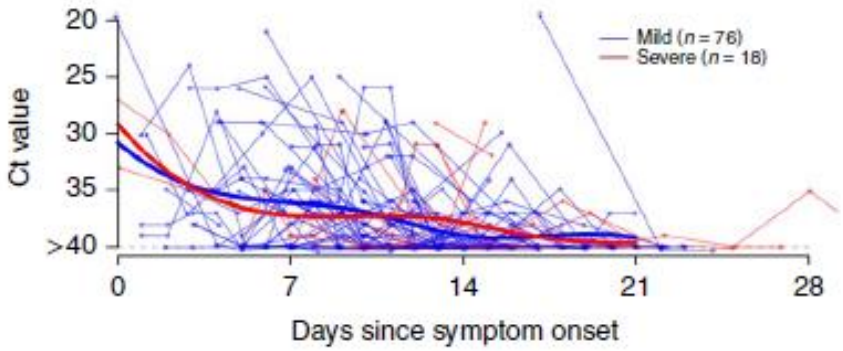
A number of studies have reported on the time course of shedding of culturable virus.

In a study of 90 patients, RT-PCR SARS-CoV-2–positive samples were incubated on Vero cells. Twenty-six samples (28.9%) demonstrated viral growth. There was no growth in samples with a Ct > 24 or symptom onset to test > 8 days. [5]

Clinical and virological data were obtained from 129 hospitalized COVID-19 patients (89 intensive care, 40 medium care). Infectious virus shedding (identified by culture) was detected in 23 of the 129 patients (17.8%). The median duration of shedding

was 8 days post onset of symptoms (IQR 5 – 11) and the probability of detecting infectious virus dropped below 5% after 15.2 days post onset of symptoms.**Error! Bookmark not defined.**

In a report of temporal patterns of viral shedding in 94 patients with laboratory-confirmed COVID-19, viral load was inferred from RT-PCR Ct value. The highest viral load in throat swabs was seen at the time of symptom onset, and inferred that infectiousness peaked on or before symptom onset. Viral load was not impacted by age, gender or severity of illness.[6]



In a UK study, virus culture was attempted from 324 upper respiratory samples (from 253 cases) that tested positive for SARS-CoV-2 by RT-PCR. This study confirmed the relationship between Ct value and the recovery of culturable virus. Median duration of virus shedding as measured by culture was 4 days (IQR: 1–8). The culture positivity rate was significantly higher during week 1 than week 2 (74% vs 20%; p = 0.002). Ten days after symptom onset, the probability of culturing virus declined to 6.0% (95% CI: 0.9–31.2%). [4]

FIGURE 2

Relationship between RT-PCR Ct value and culture positivity in mixed effects logistic regression analysis, SARS-CoV-2, England, January–May 2020 (n = 324)

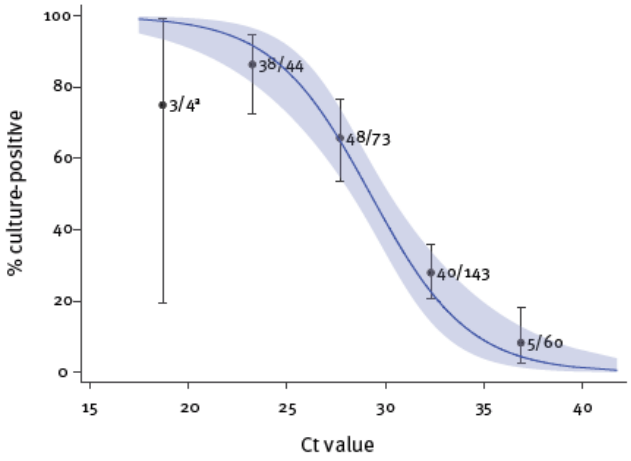


TABLE 1

Estimated percentage of SARS-CoV-2 samples culture-positive 7–15 days after symptom onset, England, January–May 2020 (n = 121)

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

CI: confidence interval.
[a] From mixed effects logistic regression model.

In a detailed analysis of 9 cases, pharyngeal virus shedding was very high during the first week of symptoms (peak at 7.11×10^8 RNA copies per throat swab, day 4). Shedding of viral RNA from sputum as detected by RT-PCR outlasted the end of symptoms. However virus was not cultured after day 8 from symptom onset. [7]

In a review of 79 studies on SARS-CoV-2, pooled mean duration of SARS-CoV-2 RNA shedding was positively associated with age (p=0.002), but not gender (p = 0.277). At that time, no study had detected live virus beyond day nine of illness despite persistently high viral loads. SARS-CoV-2 viral load in the upper respiratory tract appears to peak in the first week of illness. [1]

A systematic literature review of 113 studies from 17 countries concluded that the evidence suggests that the viral load of SARS-CoV-2 peaks from upper respiratory tract samples around the time of symptom onset or a few days after, and becomes undetectable within about two weeks. [8]

Information from transmission studies

In a report of the temporal patterns of viral shedding in 94 patients with laboratory-confirmed COVID-19 and modeled COVID-19 infectiousness profiles from a separate sample of 77 infector–infectee transmission pairs, it was estimated that 44% (95% confidence interval, 30–57%) of secondary cases were infected during the index cases' presymptomatic stage. [6]

In a transmission study in Wuhan, examining 124 cases in 50 infection clusters, the infectious curve showed that in 73.0% of the secondary cases, their date of getting infected was before symptom onset of the first-generation cases, particularly in the last three days of the incubation period. [9]

In a prospective study conducted in Taiwan, 100 confirmed Covid-19 cases and their contacts were identified and the secondary clinical attack rate was measured for different time intervals from symptom-onset. There were 2761 close contacts of the 100 cases; the secondary attack rate was 0.7% amongst the 1818 people with

contact with case patients within 5 days of symptom onset and 0% amongst the 852 people with contact >5 days after symptom onset.[10]

A South Korean study inferred transmission onset time from 72 infector-infectee pairs, either with known or inferred contact dates, utilizing the incubation period. The median transmission onset was estimated to be 1.31 days (standard deviation, 2.64 days) after symptom onset with a peak at 0.72 days before symptom onset. The pre-symptomatic transmission proportion was 37% (95% credible interval [CI], 16–52%). [11]

The first 243 confirmed cases in Singapore, including 157 locally acquired cases were reviewed to determine whether presymptomatic transmission might have occurred. Presymptomatic transmission was defined as the transmission of SARS-CoV-2 from an infected person (source patient) to a secondary patient before the source patient developed symptoms, as ascertained by exposure and symptom onset dates, with no evidence that the secondary patient had been exposed to anyone else with COVID-19. Seven COVID-19 epidemiologic clusters in which presymptomatic transmission likely occurred were identified, and 10 such cases within these clusters accounted for 6.4% of the 157 locally acquired cases. In the four clusters for which the date of exposure could be determined, presymptomatic transmission occurred 1–3 days before symptom onset in the presymptomatic source patient. [12]

In a study in Guangzhou, a total of 195 unrelated clusters with 212 primary cases, 137 non-primary (secondary or tertiary) cases and 1938 uninfected close contacts were traced. Modelling suggested that the daily transmission probability during the incubation period was similar to that during the illness period, with an estimated odds ratio (OR) of 1.13 (0.59-2.18). [13]

In a Korean case series of repeat-PCR-positive COVID-19 cases, there was a clinical and epidemiological investigation of 285 of a total of 447 repeat-PCR-positive cases. Following meeting discharge criteria or release from isolation, the average interval to a repeat-PCR-positive test in cases (45% of whom still had symptoms such as coughs or sore throats) was 14.3 days (range 1-37 days). Virus was not cultured from any of the 108 repeat-PCR-positive cases examined, and in the 93 of these with Ct value reported, 8 were between 25 and 30 and the rest over 30. During the repeat-PCR-positive exposure period of the 285 index cases for whom contact management was complete, none of the 790 contacts (351 family and 439 others) acquired infection.[14]

In a study in Brunei, there were 27 repeat-PCR-positive cases in 138 discharged COVID-19 patients. All 27 were re-admitted, their average Ct value was 35, and only 6 had mild symptoms. Contact tracing was repeated, and no new cases were linked to these 27 patients. [15]

In Summary

Whereas there remains some uncertainty about the length of infectious period the evidence that the peak of infectivity is in the pre-symptomatic, early symptomatic stages is consistent within the literature reviewed. (High Confidence)

Infectivity may be prolonged in patients with severe disease or who remain symptomatic, but is still likely to be significantly reduced from 14 days after symptom onset. (Medium Confidence)

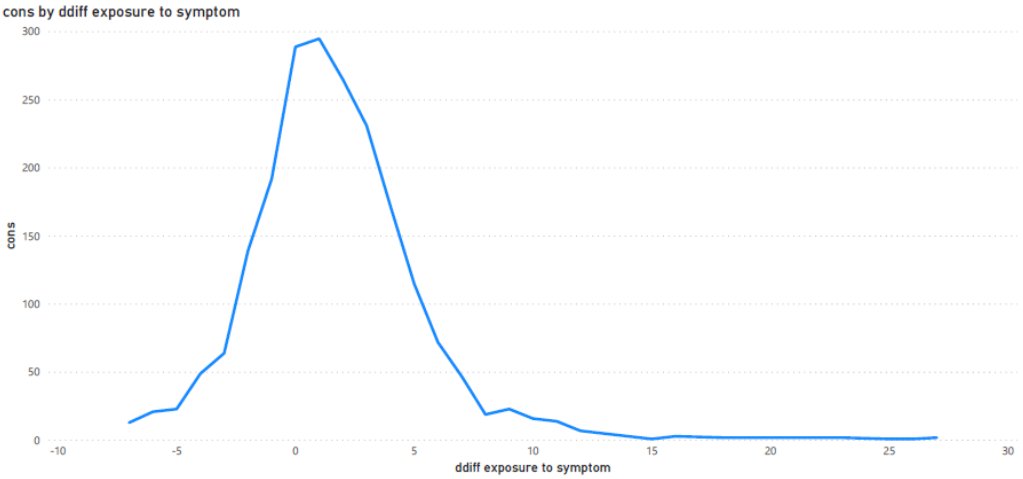
In order to reduce transmission within the population effort should be focused on reducing the number of individuals circulating within the community when in their highly infectious period (within 5-7 days of symptom onset or first week of infection). (High Confidence)

The evidence presented supports the fact that individuals (excluding those that are severely immunocompromised) are highly unlikely to be infectious 14 days after onset of symptoms particularly when symptoms have resolved and they have been afebrile for at least 48 hours. (Very High Confidence)

Appendix

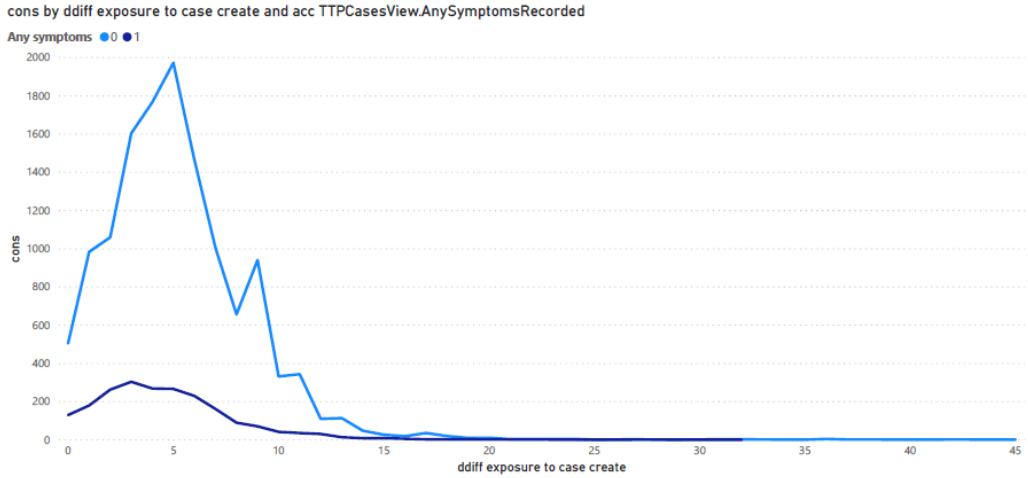
Further information from an initial analysis of data from the Welsh CRM system.

Graph 1 shows Time in days between contact between an index case and their contact, and the development of symptoms by the contact (secondary case). The Median is approx. 2 days, and the Mode approx. 1 day.



Graph 2 shows the time in days between contact between an index case and their contact, and the finding of a positive result in the contact (secondary case). The Mean is approx. 10 days, and the Median approx. 5 days.

The light blue line shows data where the index case denied symptoms, and the dark blue line where the index case had symptoms at the time of positive test.



Taken together the data suggests that:

- many secondary cases are infected at the same time by an index case (otherwise median time of exposure to symptoms would be 5 days).
- contacts (who become secondary cases) are likely highly infectious for three days before confirmation is made by testing.

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