Repeat SARS-CoV-2 PCR positivity – Interim infection control management in health and social care settings

1.0 Background and purpose of this paper

This paper summarises issues relating to the management, in health and social care settings, of recurrent SARS-CoV-2 PCR positive results. Key questions not addressed by current guidance are posed along with suggested answers together with rationale derived from available evidence. Proposed answers would form the basis for PHE guidance to support: (i) management of staff who repeatedly test PCR positive and (ii) patients being transferred from one care setting to another. This interim guidance can be reviewed as new evidence emerges.

2.0 Issues

In the health and social care settings there are increasing detections of repeatedly SARS-CoV-2 PCR positive (both asymptomatic[1] and post-symptomatic) individuals. This is predominately an issue among health and social care staff but also in patients transferring from one setting to another.

Current guidance provides recommendations on isolation and return to work policy for asymptomatic SARS-CoV-2 PCR positive cases. However, it does not cover repeat-testing or the management of staff with subsequent positive PCR results.

Whilst it is anticipated guidance will shortly be finalised recommending against routine testing of asymptomatic people, testing will continue to be indicated in certain circumstances, including in the context of outbreaks and for management of high risk environments such as health and social care settings containing vulnerable individuals. Testing in these settings will detect individuals (including staff) returning a second/subsequent positive PCR test. Health Protection Teams are required to advise on their management. Best practice has not yet been developed in this rapidly evolving situation.

It is important to highlight that for practical purposes a positive PCR result does not mean that an individual is infectious (and conversely a negative result does not necessarily mean that an individual does not have infection).

[1] Whilst asymptomatic testing is assumed to happen in health and social care settings, this paper this does not imply a recommendation for wider use. Asymptomatic testing has only been approved by the Chief Medical Officer in specific circumstances and not for whole population screening. Asymptomatic testing can help to manage risk in particular high-risk groups and outbreaks in health and social care settings. Under certain conditions, including where there are particularly vulnerable populations, 'group testing may have a useful role to play in providing reassurance – not to an individual that they are 'safe' - but rather to groups, to demonstrate that overall risk levels are low. One-off asymptomatic testing should not be used as a tool for action on an individual basis because it does not guarantee that someone does not have the virus. This paper therefore considers one of the consequences of asymptomatic 'group testing' for either staff or patients.

3.0 Outstanding questions and proposed answers

Question 1: Should asymptomatic SARS-CoV-2 PCR positive cases be managed differently to symptomatic COVID-19 cases in terms of duration of isolation?

Proposed answer: No

Question 2: Should confirmed symptomatic COVID-19 cases and asymptomatic SARS-CoV-2 PCR positive cases be excluded from subsequent 'group testing' activities and if so for how long?

Proposed answer: Yes. For a period of at least 4 weeks up to a maximum of 6 weeks.

Question 3: If previously SARS-CoV-2 PCR positive cases have a subsequent positive PCR test how should they be managed and what are the criteria for determining whether a repeat positive result should be managed as a new infection?

Proposed answer: The default position should be not to take a repeat swab within a four to six-week window period; however if a swab is taken, the management of a positive result should be individualised. Factors to consider will include: presence of any immune deficiency; severity of initial illness; presence of ongoing symptoms; time elapsed since original positive result; Ct level (both of initial and current test); presence and level of antibodies both previously (if available) and current, and consideration of potential risk to vulnerable patients/residents.

4.0 Rationale for proposed answers - summary of evidence review relating to questions

This paper predominantly draws from evidence summarised and presented in the NERVTAG paper "Duration of infectiousness of SARS-CoV-2 infection" produced on 10/06/2020:

4a. NERVTAG paper - viral dynamics of infec

Q1 - Should asymptomatic SARS-CoV-2 PCR positive cases be managed differently to symptomatic COVID-19 cases in terms of duration of isolation?

Current position

Currently, 'COVID-19: management of staff and exposed patients or residents in health and social care settings' guidance recommends 7-day isolation of asymptomatic SARS-CoV-2 PCR positive staff cases from the sample date, with return to work on day 8 providing no symptoms have developed. This is considered to have equivalence with the management of symptomatic COVID-19 cases (return to work 7 days from symptom onset, provided clinical improvement and afebrile for 48 hours). For staff working with extremely vulnerable people, evidence of viral clearance prior to working may be required and is subject to local policy. Further advice on return to work of staff with complex health needs, including immunosuppression, should be sought according to local arrangements.

All care home residents who are asymptomatic SARS-CoV-2 PCR positive are currently isolated for 14 days while they remain in care settings. If they are discharged from hospital to standalone residences, they are also isolated for 14 days if they are immunocompromised or were critically unwell (otherwise they are to complete 7 days) 'COVID-19: guidance for stepdown of infection

control precautions within hospitals and discharging COVID-19 patients from hospital to home settings'.

Evidence review

The evidence for duration of PCR detection for asymptomatic cases is considered relative to symptomatic cases. Evidence summarised in the NERVTAG paper (with one additional) is presented in Table 1. The balance of evidence does not consistently indicate prolonged viral detection for asymptomatic SARS-CoV-2 PCR positive cases compared to symptomatic COVID-19 cases. Rather, the available evidence generally suggests lower or equivalent duration of detection.

Recommended position

It is considered there is insufficient evidence to extend duration of isolation of asymptomatic SARS-CoV-2 PCR positive cases *compared to symptomatic COVID-19 cases*.

Table 1. Direct comparison of duration of PCR positivity asymptomatic vs symptomatic cases

Main finding	Brief description of study	Author/ reference
Asymptomatic cases demonstrated faster viral clearance c.f. symptomatic cases (P<0.001 for difference over first 19 days).	Prospective cohort, 30 quarantined subjects, Vietnam	Chau et al. (Nervtag #4) The natural history and transmission potential of asymptomatic SARS-CoV-2 infection. *CID* 04/06/2020 https://doi.org/10.1093/cid/ciaa711
Virus was resolved faster in the asymptomatic group by 4 days (9.6 days to negative vs 13.6 for the pre-symptomatic group).	Prospective cohort, 56 infected people, 23 asymptomatic and 33 symptomatic, Shenzen	Xiao et al. (Nervtag #16) Early viral clearance and antibody kinetics of COVID-19 among asymptomatic carriers. *MedRix* 02/05/2020 https://doi.org/10.1101/2020.04.28.20083139
No difference in time to clearing virus between asymptomatic and pre-symptomatic (both 7 or 8 days) but viral load lower in asymptomatic group, significant in a small subset measured at 7-13 days.	Not provided	Not provided
Initial Ct values similar both groups. Median duration shedding in asymptomatic group was 19 d (IQR 15–26; range 6 - 45d) - significantly longer duration than symptomatic group (median 14d) (log-rank *P* = 0.028).	37 asymptomatic and 37 symptomatic individuals, PCR-confirmed.	Long, Q., Tang, X., Shi, Q. *et al.* Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med* 18/06/2020 https://doi.org/10.1038/s41591-020-0965-6 (paper published since NERVTAG review)
No observed difference in Ct values across samples received between asymptomatic, pre-symptomatic and symptomatic cases.	PHE data presented to NERVTAG ('Supplementary data 9th June 2020-Analysis of virus isolation data'), n=328 samples	PHE data

Q2 - Should confirmed symptomatic COVID-19 cases and asymptomatic SARS-CoV-2 PCR positive cases be excluded from subsequent group testing activities and if so for how long?

Current position

No recommendation.

Evidence review

The suggested duration of exclusion of PCR positive cases from 'group testing' activities in health and care settings is dependent on duration of PCR positivity. Evidence from multiple studies was summarised in the paper presented to NERVTAG and is summarised in Table 2.

Authors of the NERVTAG submission concluded that "re-testing or screening patients or staff who have recovered from COVID-19 is likely to detect RT-PCR positivity until 21 days for those who have had mild symptoms, but at values below which virus is likely to be cultured and until 28 days for those with severe symptoms but at values below which virus is likely to be cultured". Importantly, positivity does not correspond with isolation of viable virus. The latest time point virus has been isolated by PHE was 12 days post symptom onset; unpublished data [*now in preprint*] provided to NERTAG from van Kampen et al on infectiousness of 129 hospitalised patients concluded a ≤5% probability of culturable virus if ≥15 days from symptom onset.

Routine re-testing of asymptomatic cases therefore *would be expected to return positive RT-PCR tests commonly within the 3-4 week timeframe without indicating infectivity*. Selected studies (Table 2) suggest PCR detection may occur until around day 40. Therefore, evidence does not suggest utility of routine re-testing or benefit from including these individuals in any group testing activity within this timeframe.

It is anticipated that healthcare workers and care workers working in social care settings where there are extremely vulnerable individuals will be more likely to be subject to 'group testing' or screening for SARS-CoV-2. In these settings, risk mitigation is based primarily on mandatory wearing of PPE for all interactions with both patients and residents and other staff.

Recommended position

It is recommended that previously identified asymptomatic or post-symptomatic PCR positive cases should be exempt from routine re-screening or 'group testing' activities for 6 weeks. Any positive PCR tests in this period should be disregarded except if new symptoms have developed.

Table 2. Duration of PCR positivity (selected studies presented to NERVTAG 10/06/2020)

Main finding (duration of PCR positivity)	Brief description of study	Author/ reference
Range 8-37 days, median 20 days (beyond day 15 Ct>35).	137 hospitalised patients Guangdong, China	Zou et al. (Nervtag #1) SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *NEJM* 19/03/2020 https://www.nejm.org/doi/full/10.1056/NEJMc2001737
Viral RNA remains detectable until day 28 in	Preliminary UK data on 74 HCID COVID positive	Nervtag #2. PHE Paper 2 April 2020.

upper respiratory tract secretions.	patients presented to NERVTAG	
Ct towards the detection limit as defined as a Ct=40, at about day 21. No obvious difference in viral loads across sex, age groups, disease severity.	Total of 414 throat swabs from 94 patients, from symptom onset up to 32 days after onset,	He et al. (Nervtag #3). Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nature Medicine* 15/4/2020 https://doi.org/10.1038/s41591-020-0869-5
33% had viral RNA detected for 20 days or longer after symptom onset. mean viral load >2 log genome copies per ml was detected until day 24 post symptom onset.	Cohort study in Hong Kong including 23 hospitalised patients, viral load in posterior oropharyngeal saliva of the 21 patients.	To et al. (Nervtag #5) Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet* 23/3/2020 https://doi.org/10.1016/S1473-3099(20)30196-1
249 (19%) were RT-PCR positive, the maximum time was 43 days from symptom onset.	Outreach program in New York identified people recovered from COVID in the community with mild disease. In total, 1,343 participants recruited	Wajnberg et al. (Nervtag #6). Humoral immune response and prolonged PCR positivity in a cohort of 1343 SARS-CoV 2 patients in the New York City region. *MedRxiv* 05/05/2020 https://doi.org/10.1101/2020.04.30.20085613
SARS-CoV-2 Vero cell infectivity only observed for RT-PCR Ct < 24 and STT < 8 days. Infectivity of patients with Ct >24 and duration of symptoms >8 days may be low.	Ninety RT-PCR SARS-CoV-2 positive samples incubated on Vero cells. Twenty-six (28.9%) demonstrated viral growth.	Buller et al. (Nervtag #13) Predicting infectious SARS-CoV-2 from diagnostic samples. *CID* 22/05/2020 https://academic.oup.com/cid/article/doi/10.1093/cid/ciaa638/5842165
Mean RNA carriage period, (interval from day of exposure to first day of continuous negative tests) was 22.0 days (SD 7.1). Mean positive RNA test period (interval from first day of positive NA tests to first day of continuous negative tests) was 7.9 days (SD 3.5).	24 asymptomatic carriers, respiratory samples.	(Nervtag #15) Yan *et al.* Duration of SARS-CoV-2 viral RNA in asymptomatic carriers. *Crit Care* 24/05/2020 https://doi.org/10.1186/s13054-020-02952-0
Median duration of viral RNA shedding was 53.5 days (IQR 47.75-60.5). Longest duration of shedding "could be 83 days".	Characteristics of 36 pts with prolonged shedding. 33 mild, 3 severe.	Li et al. Prolonged SARS-CoV-2 RNA shedding: Not a rare phenomenon. *J Med Virol* 29/04/2020 https://doi.org/10.1002/jmv.25952
RNA detected at a maximum of day 32 in NP specimens, day 36 in OP specimens, day 29 in sputum and day 25 in stool.	12 patients with mild to moderate illness.	Kujawski et al. Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the USA. *Nat Med* 23/04/2020 https://doi.org/10.1038/s41591-020-0877-5

Median duration of RNA shedding 12 days (range, 3-38) in NP swabs; 19 days (range, 5-37) in sputum; 18 days (range, 7-26) in stools. Still detectable in any type of sample in 20.9 percent patients exceeding 30 days after symptom onset.	67 patients, 29 severe.	Tan et al. Viral Kinetics and Antibody Responses in Patients with COVID-19. *MedRxiv* 26/03/2020 https://doi.org/10.1101/2020.03.24.20042382

Q3 - If previously SARS-CoV-2 PCR positive cases have a subsequent positive PCR test how should they be managed and what are the criteria for determining whether a repeat positive result should be managed as a new infection?

Current position

No recommendation.

Evidence review

Based on evidence above, it is highly likely that repeat results obtained within the 6-week window will likely represent the tail end of PCR positivity that in the vast majority of cases will not represent infectious virus.

Recommended position

The default position should be to disregard the result within the six-week window period, however if a swab is taken within this period, then the infection control management of any positive result should be individualised. Factors to consider will include the initial clinical picture, presence of any immune deficiency, the severity of initial illness and the resolution of symptoms, presence of any current symptoms, the time elapsed since original positive result, the Ct values if available of the initial and current test, and the presence and level of antibodies both previously (if available) and currently. Here the role of antibody testing will not be to look at immunity per se, but rather length of time since initial exposure, particularly in asymptomatic individuals. This presence of extremely vulnerable patients or residents within the work environment should also be considered.

Factors that may favour extended isolation include:

a. Repeat Ct value <35
b. Lack of development of antibody titre Ab <1:80 (taking into account timing of tests)
c. Immunosuppression
d. New symptoms appearing after complete resolution of symptoms or initial asymptomatic episode

If it is determined that a second infection is likely (or possible) individuals and their households/contacts should be managed the same as those with first episode of confirmed COVID-19 disease. Such Individuals may require further clinical investigation to exclude any underlying clinical immunodeficiency.