

## De-isolation and return to work

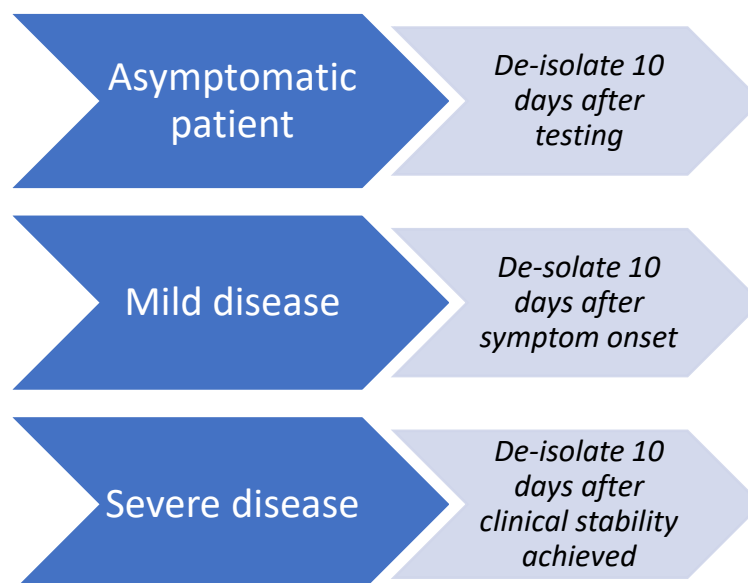
### Version 5 – what's new?

- Reduction in the time to de-isolate the patient from 14 days to 10 days.

### Recommendations:

- i** Symptomatic patients with mild disease (not requiring hospitalisation for COVID-19) can be de-isolated 10 days after the onset of their symptoms, provided their fever has resolved and their other symptoms are improving.
- i** Hospitalised patients with moderate-severe disease (who require hospitalisation due to COVID-19) can be de-isolated 10 days after achievement of clinical stability (i.e. from when they are not requiring supplemental oxygen and are otherwise clinically stable).
- i** Asymptomatic patients can be de-isolated 10 days after their test.
- i** Repeat PCR testing is NOT required in order to de-isolate a patient and is not recommended.

It is common for patients to continue to have symptoms for longer than the above time periods. Full recovery may take several weeks for some patients, especially for symptoms such as fatigue, cough and anosmia. Patients who are still symptomatic at the end of their isolation period can be de-isolated provided that their fever has resolved and their other symptoms have shown improvement. Patients admitted to hospital can continue their isolation period at home or at an isolation facility once clinical stability has been achieved.



### **Distinction between isolation period and returning to work**

The recommended isolation time is the period during which a patient is still considered infectious. This should be distinguished from the point at which a patient is medically well enough to return to work. Some patients, especially those who have had severe disease, may require to be booked off sick for longer than the above isolation periods.

#### ***Rationale for recommendations:***

##### **Duration of viral shedding**

Most patients with mild COVID-19 infection continue to shed SARS-CoV-2 nucleic acid from their upper airways for a median of approximately 7-12 days.<sup>1-3</sup> The duration of shedding is longer in severe cases, though in both mild and severe cases, significant variation is seen.<sup>1,3,4</sup> Prolonged viral shedding for over a month has been described in cases of both mild and severe disease.<sup>5</sup>

##### **Viral shedding does not equate to infectiousness**

The presence of detectable virus nucleic acid by RT-PCR does not necessarily imply infectiousness. The virus may be detectable by PCR assays at a level below the threshold required to infect someone, or the virus may not be replication competent. A better proxy for infectiousness is the ability to successfully culture the virus from a sample. The measure is imperfect in that it is still theoretically possible to successfully culture a virus at an inoculum below the infectious dose, or the infectious dose may be lower than the quantity capable of being cultured. However, the successful culture of a virus at a minimum implies both that the virus is replication competent and that the inoculum is not trivially small.

##### **In mild cases, cultures are generally only positive for 8-9 days after symptom onset**

In a small cohort of 9 mild COVID-19 cases from Germany by Wölfel et al., viral loads and viral cultures were performed on a variety of specimens simultaneously.<sup>6</sup> The virus was readily culturable from specimens taken during the first week of symptoms (17% from swabs, 83% from sputum), but no positive cultures were obtained from samples taken after 8 days from symptom onset. This was despite ongoing high viral loads being detected at the time. The paper estimated that the likelihood of recovering replication-competent virus would approach zero by day 10. This paper informed previous version of the guidelines, but due to concerns about generalizing from a very small sample that was limited to mild cases only, a precautionary buffer of 14 days of isolation was recommended.

In a much larger cohort, published after the release of the version 4 of the clinical management guidelines, ninety SARS-CoV-2 RT-PCR positive samples from patients in Manitoba, Canada were incubated for culture.<sup>7</sup> Virus was successfully isolated from 26 of these (28.9%). Notably, there was no culturable virus in samples with a real-time PCR cycle threshold value of >24, or in samples obtained later than 7 days after symptom onset. It is unclear from the manuscript what proportions of the samples came from patients with asymptomatic, mild, and severe disease.

Lastly, in a cohort study in the United States, SARS-CoV-2 RT-PCR positive samples from residents of a skilled nursing facility underwent viral culture (n=48).<sup>8</sup> Positive cultures were obtained from samples taken up to 9 days after the onset of typical symptoms (fever, cough, or shortness of breath). Patients in this cohort ultimately displayed a range of severity, from asymptomatic through to severe disease.

##### **Variations for asymptomatic and severely ill patients**

The duration of infectiousness in patients with severe disease (i.e. requiring admission due to clinical instability) less well established. In general, patients with severe disease may continue to shed virus

at higher levels for longer periods than patients with mild disease. One study of 129 severely-ill hospitalised patients did indeed find viable virus for a median of 8 days, with an interquartile range of 5-11 days.<sup>9</sup> The probability of a positive culture in this cohort dropped below 5% after 15 days from the onset of symptoms. To provide a safe buffer, we therefore suggest de-isolating such patients 10 days after clinical stability has been achieved (e.g. after supplemental oxygen was discontinued), rather than 10 days after symptom onset.

Asymptomatic patients represent a conceptual challenge, since unlike symptomatic patients it is not possible to easily estimate where in the course of viral shedding they are at the timepoint at which they test positive. For simplicity, and to err on the side of caution, the guidelines committee recommends that asymptomatic patients be isolated for 10 days following their test date.

#### **Staff in healthcare and laboratory settings**

For a guide to the management of staff in healthcare and lab settings with COVID-19 illness and exposure, please consult the latest version of the **Guideline for symptom monitoring and management of essential workers for COVID-19 related infection**.

## References

1. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)2020. Available from: <https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf>.
2. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. *JAMA*. 2020.
3. Liu Y, Yan LM, Wan L, Xiang TX, Le A, Liu JM, et al. Viral dynamics in mild and severe cases of COVID-19. *Lancet Infect Dis*. 2020;20(6):656-7.
4. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020.
5. Qi L, Yang Y, Jiang D, Tu C, Wan L, Chen X, et al. Factors associated with duration of viral shedding in adults with COVID-19 outside of Wuhan, China: A retrospective cohort study. *Int J Infect Dis*. 2020.
6. Wolfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Muller MA, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature*. 2020.
7. Bullard J, Dust K, Funk D, Strong JE, Alexander D, Garnett L, et al. Predicting infectious SARS-CoV-2 from diagnostic samples. *Clin Infect Dis*. 2020.
8. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. *N Engl J Med*. 2020;382(22):2081-90.
9. van Kampen JJA, van de Vijver DAMC, Fraaij PLA, Haagmans BL, Lamers MM, Okba N, et al. Shedding of infectious virus in hospitalized patients with coronavirus disease-2019 (COVID-19): duration and key determinants. *medRxiv*. 2020:2020.06.08.20125310.