COVID-19 INFECTIVITY OF PATIENTS WHO HAVE RECOVERED FROM DISEASE

A Rapid Guidance Summary from the Penn Medicine Center for Evidence-based Practice
Last updated June 26, 2020. All links rechecked June 26 unless otherwise noted.

This Rapid Guidance Summary is a description of existing guidance and evidence reviews from a variety of sources that was in effect at the time of publication. It should not be used or interpreted as a clinical practice guideline, but instead can be used in development of local recommendations and policies.

Key questions answered in this summary

- At what point after recovery are special precautions no longer necessary for health care providers treating patients with a history of COVID-19 disease?

  Procedures for patients who are still symptomatic or otherwise ill with COVID-19 disease are outside the scope of this report. Procedures for patients whose COVID-19 status is "suspected" or uncertain are outside the scope of this report.

Summary of major recommendations

- We found no specific guidance from public health agencies or professional societies regarding medical procedures for patients who have recovered from COVID-19 disease.
- There is considerable uncertainty about how long a patient remains infectious after onset of COVID-19 disease or the end of the symptoms. Medical center guidance varies and is context specific without further public health agency or professional society guidance.
- Medical centers use both time-based and test-based strategies for determining when a patient who has had COVID-19 disease no longer requires special precautions during care.
- Most medical centers specify a test-based strategy for hospitalized patients. Two tests should be completed at least 24 hours apart. For patients who are intubated, one of those tests should be done on a tracheal or bronchoalveolar sample.
- Time-based strategies are necessary for asymptomatic patients, but there is considerable variation in how medical centers implement them.
- Some medical centers now recommend against re-testing patients who have recovered from COVID-19 disease and are presenting for subsequent inpatient or outpatient care.

Public health agency and professional society guidelines on medical procedures

Source	Recommendations
UK Surgery May 13	No recommendations for management of patients with prior COVID-19 disease. If patient scheduled for surgery has a positive throat swab, surgery should be postponed by at least 14 days and a repeat test should be done within 72 hours of rescheduled surgery.

UK Surgery–intercollegiate guidelines for elective cancer surgery jointly issued by 8 UK surgery societies

Public health agency and professional society guidelines on lifting isolation and other precautions

Source	Recommendations
Guidelines with reference to patients returning for health care	
NHS Scotland June 4	Based on the available limited evidence: IPC precautions should continue for 14 days (minimum) from symptom onset (or first positive test if symptoms onset undetermined) with absence of fever for 48 hours (without use of antipyretics). This includes hospitalized patients requiring ongoing inpatient care and patients attending outpatient departments.
Guidelines that do not specifically address patients returning for care	
PHE May 20	Infection prevention and control (IPC) measures should continue for COVID-19 patients until 14 days have elapsed since their first positive SARS-CoV-2 test. This is due to uncertainties about the duration of infectiousness for patients with more severe illness or underlying immune problems that may delay them clearing the virus. Once the 14 days since the test have elapsed IPC measures for hospitalized patients can be stopped if there is: • Clinical improvement with at least some respiratory recovery • Absence of fever (> 37.8°C) for 48 hours without the use of medication • No underlying severe immunosuppression If SARS-CoV-2 testing has not been done, then isolation periods for hospitalized patients with presumed COVID-19 should be measured from the day of admission.
CDC April 30	Symptomatic patients with COVID-19 should remain in Transmission-Based Precautions until either: Symptom-based strategy At least 3 days (72 hours) have passed since recovery defined as resolution of fever without the use of fever-reducing medications and improvement in respiratory symptoms (e.g., cough, shortness of breath); and at least 10 days have passed since symptoms first appeared Test-based strategy Resolution of fever without the use of fever-reducing medications and Improvement in respiratory symptoms (e.g., cough, shortness of breath), and Negative results of an FDA Emergency Use Authorized COVID-19 molecular assay for detection of SARS-CoV-2 RNA from at least two consecutive respiratory specimens collected ≥24 hours apart (total of two negative specimens) [1]. See Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens for 2019 Novel Coronavirus (2019-nCoV). Of note, there have been reports of prolonged detection of RNA without direct correlation to viral culture. Patients with laboratory-confirmed COVID-19 who have not had any symptoms should remain in transmission-based precautions until either: Time-based strategy 10 days have passed since the date of their first positive COVID-19 diagnostic test, assuming they have not subsequently developed symptoms since their positive test. Note, because symptoms cannot be used to gauge where these individuals are in the course of their illness, it is possible that the duration of viral shedding could be longer or shorter than 10 days after their first positive test. Test-based strategy Negative results of an FDA Emergency Use Authorized COVID-19 molecular assay for detection of SARS-CoV-2 RNA from at least two consecutive respiratory specimens collected ≥24 hours apart (total of two negative specimens). Note, because of the absence of symptoms, it is not possible to gauge where these individuals are in the course of their illness. There have been reports of prolonged detection of RNA without direct correlation to viral culture. Note that detecting viral RNA via PCR does not necessarily mean that infectious virus is present. Consider consulting with local infectious disease experts when making decisions about discontinuing Transmission-Based Precautions for patients who might remain infectious longer than 10 days (e.g., severely immunocompromised).

Evidence reviews on viral shedding and duration of infectivity

Reviewer	Findings
HIQA June 9	A total of 113 studies conducted in 17 countries were included in this updated evidence summary. In general, SARS-CoV-2 viral ribonucleic acid (RNA) levels peak around symptom onset or a few days after, and become undetectable (from upper respiratory tract samples) about two weeks after symptom onset. Some evidence suggests that viral RNA levels from lower respiratory tract samples may be higher, peak later and persist for longer than those from upper respiratory tract samples. There is evidence of prolonged viral shedding in stool samples. However, the clinical significance of this finding is uncertain. There may be an association between higher viral loads, detection of the virus in blood, longer duration of virus detection and poorer patient outcomes such as increased disease severity. However, these relationships were not consistently found. Based on a limited number of studies which have compared findings between children and adults, there appears to be no difference between children and adults in terms of viral load or duration of virus detection. The precise duration of infectivity has not yet been established; the presence of viral RNA may not represent transmissible live virus, hence patients may not be infectious for the entire duration of viral RNA detection. However, there are limited reports of live virus isolated up to six days before and up to 13 days (from upper respiratory tract samples) and 18 days (from lower respiratory tract samples) after symptom onset. Limited evidence suggests that infectivity may be related to the viral load. Given that the majority of these studies comprised case series and case reports, these findings should be viewed with caution and will require confirmation using larger, more robust study designs.
Penn Medicine June 8	To date, studies have consistently demonstrated that SARS-CoV-2 virus can no longer be cultured from respiratory tract specimens after approximately 10 days from COVID-19 illness onset. These studies demonstrate that while viral RNA may still be detectable, infectious virus is not. In addition, epidemiologic studies confirm that secondary transmission does not occur beyond 10 days after illness onset. On the basis of these studies, the U.S. Centers for Disease Control and Prevention, the Korean CDC, and several other governing public health bodies have each concluded that the duration of infectivity and timeframe during which persons may transmit virus ends 10 days after illness onset. Duration of infectivity for severely immunocompromised patients is not well-described.
NHS Scotland June 4	It is known that viral RNA can persist for at least 1 week after symptom onset in mild cases and for longer in those more severely affected. It is important to distinguish persistence of viral RNA from that of intact and infectious virus, as the viral RNA may be detected in the absence of viable and infectious virus. Studies of shedding of live virus are limited. One study in patients with mild symptoms could not detect live virus in respiratory secretions beyond 8 days after symptom onset despite ongoing high viral loads. Uncertainties remain regarding the duration of infectiousness of patients with more severe illness and in those with underlying immune problems.
FLARE May 22	Antibody testing cannot speak to infectivity and contagiousness. Individuals with SARS-CoV-2 seropositivity may nevertheless shed contagious virus and, conversely, seronegativity does not rule out acute infection.
ECDC April 8	Incubation period: The median incubation period is considered to be five to six days for COVID-19, with a range from one to 14 days. According to modelling data it remains prudent to consider a period of at least 14 days as an upper limit of the incubation period. Viral shedding: Over the course of the infection, viral RNA has been identified in respiratory tract specimens up to 1–2 days before the onset of symptoms. Viral load persists up to eight days after the onset of symptoms in mild cases and peaks in day 11 in more severe cases. The current update reflects these findings. However, more research is needed on the level and duration of viral shedding in the various patient groups and in the context of asymptomatic and pre-symptomatic infections. There is no evidence on the duration of viral shedding after resolution of fever. In terms of viral load profile, SARS-CoV-2 is similar to that of influenza, which peaks at around the time of symptom onset, but contrasts with that of SARS-CoV-1 and MERS-CoV, which peak in the second week after symptom onset. Older age and more severe infections have been associated with higher viral loads [5,6]. Viral RNA has been detected in feces from day five after symptom onset and up to four to five weeks in moderate cases, as well as in whole blood, serum, saliva, and urine. Prolonged viral RNA shedding has been reported from nasopharyngeal swabs (up to 37 days after onset of symptoms among adult patients) and in feces (more than one month after infection in pediatric patients)]. The

Reviewer	Findings
	viral load can be a potentially useful marker for assessing disease severity and prognosis: a recent study indicated that viral loads in severe cases were up to 60 times higher than in mild cases. Although there is no specific evidence for COVID-19, immunocompromised patients may shed SARS-CoV-2 virus for prolonged periods similar to other respiratory viruses. Viral RNA shedding of SARS-CoV-2 does not equate with infectivity, unless there is proof that the virus can be isolated and cultured from the particular samples. On the other hand, the infectious dose has not been determined; therefore, it is unclear how much virus is needed to infect humans. *CEP NOTE: sections on asymptomatic and pre-symptomatic patients are not included here* Immunity: Based on the currently available data, the IgM and IgG antibodies to SARS-CoV-2 develop between 6-15 days post-disease onset. However, clinically validated laboratory assays for detection of antibodies are still lacking and therefore these results need to be considered cautiously. In addition, correlates of protection are still to be defined which is necessary to be able to comment on the possibility of re-infection and the duration of immunity. In summary, and based on limited evidence from one study indicating that viral load persists up to eight days after the onset of symptoms in mild cases and longer in more severe cases (peaking in the second week), patients should continue self-isolation at home or in a safe place if they are discharged from hospital before this period. Immunocompromised and patients with severe illness, as well as healthcare workers, should be prioritized for testing to exclude the possibility of prolonged shedding.

Medical center guidance on procedures for patients who have had COVID-19

Center	Recommendation
Mass General June 22	For inpatients who are intubated: resolution of fever without antipyretic medication, resolution of respiratory status, reduction of supplemental oxygen need, at least 10 days since onset of symptoms, at least one negative swab test (all criteria must be met). For inpatients who are not intubated: resolution of fever without antipyretic medication, improvement of respiratory status, at least 10 days since onset of symptoms, at least one negative swab test and at least one negative test of endotracheal aspirate or bronchial lavage (all criteria must be met). Non-hospitalized patients (time-based criteria can supersede test-based criteria if time-based criteria met): Test-based criteria: resolution of fever without antipyretic medication, resolution of all respiratory symptoms, at least 10 days since first positive tests, and two negative nasal swab tests at least 24 hours apart with the first test at least 10 days since first posiitive test (all criteria must be met). Time-based criteria (discharged inpatient): at least 72 hours since resolution of fever without antipyretic medication and resolution of all respiratory symptoms, and at least 14 days since discharge. Time-based criteria (symptomatic case managed as outpatient): at least 72 hours since resolution of fever without antipyretic medication, resolution of all respiratory symptoms, and at least 14 days since symptoms first appeared. Time-based criteria (asymptomatic case): at least 72 hours since resolution of fever without antipyretic medication and resolution of all respiratory symptoms, and at least 10 days since first positive test.
Nebraska June 16	Persons diagnosed with COVID-19 who are immunologically normal appear to cease shedding transmissible virus around day 10 of illness, but current information is limited and the duration of shedding in immuno-compromised persons may be longer. Based on this information we chose to be conservative with our recommendations: • We consider all patients to no longer be infectious 21 days after illness onset and they should be cared for as any other patient • Outpatients who meet the criteria for exiting home isolation can do so before 21 days but should maintain extra caution when entering healthcare settings for the 21 days after symptom onset (see guidance below) o Generally, avoid healthcare settings and defer appointments for 21 days after symptom onset if medically possible. o Patients who need to attend an appointment or have additional testing (lab, imaging, etc.) or procedures before the 21-day period is complete, must contact the location they will be visiting and discuss beforehand.

	▯ Those who meet the criteria for symptom subsidence above AND are asymptomatic (or returned to baseline for those with chronic symptoms such a cough) can visit without the need for COVID-19 precautions. Current guidance on mask use for non-COVID-19 patients should be followed. ▯ Those who do not meet the criteria above (not met criteria for exiting home isolation OR still symptomatic) will be cared for using typical COVID-19 precautions and PPE until they reach 21 days post COVID-19 diagnosis. • Outpatient this means entering via a separate entrance and clinic staff utilizing N95 respirators, gowns, gloves, eye protection. • Inpatients will be readmitted to the COVID unit until a negative test is obtained. ▯ Patients inside the 21-day period should avoid aerosol generating procedures (bronchoscopy, etc.) if at all possible. If these must be performed, they should be done using COVID precautions unless they can be tested and proven negative. o The exception to this rule is those who have had 2 negative tests documenting clearance of viral shedding and that they are non-infectious. Those who have documented viral clearance by testing can visit healthcare setting and should follow current guidance on mask use for non-COVID-19 patients. Inpatients diagnosed with COVID-19 will remain in isolation for 21 days after their first positive test unless they meet test-based criteria for exiting isolation. After 21 days we do not consider them infectious. Patients who reach the 21 day milestone should not have any further SARS-CoV-2 testing to document clearance and routine pre-procedural and admission screening should be stopped for 3 months.
Penn Medicine June 8	Current Penn Medicine guidance recommends that inpatients with COVID-19 undergo a test-based strategy for clearance of isolation (2 negative PCR tests performed sequentially). For outpatients, Penn Medicine guidance recommends a time-based strategy. Outpatients who have reached 28 days from symptom onset and who are clinically recovered will have their COVID-19 infection banner resolved. We strongly recommend that a patient who has met either of these clearance criteria should not undergo subsequent SARS-CoV-2 testing. This includes admission-based or pre-procedural testing. Additionally, these patients should not be re-tested for persistent or recurrent symptoms possibly associated with COVID-19. There is no scientific evidence at this time to suggest re- infection is possible within such a short timeframe or that persistent symptoms indicate infectivity. A patient who has recovered from COVID-19 and has met the test-based or time-based criteria for clearance is no longer considered infectious. If a "cleared" patient is re-tested on subsequent admission or pre-procedure and is found to be positive for SARS-CoV-2, the patient does not require admission to a COVID care unit or COVID-19 isolation precautions.
Hopkins June 3	Healthcare settings: the current requirement is 2 sequential negative COVID-19 RT-PCR tests before airborne precautions can be lifted. However, viral RNA may be shed for 2-3 weeks or longer in many patients; unclear if this represents an infectious risk.
Connecticut June 3	If initial positive test or onset of symptoms was within past three weeks, presume that the patient is COVID positive. If initial positive test or onset of symptoms was within 3 to 6 weeks, symptoms are improving or resolved, fever is resolved without antipyretic medication and patient is not immunocompromised, presume that the patient is COVID-negative. If initial positive test or onset of symptoms was more than 6 seeks ago, or if initial positive test or onset of symptoms was within 3 to 6 weeks and patient remains symptomatic, retest for COVID-19 infection.
Cleveland May 28	For hospitalized patients: At least 10 days since onset of symptoms, at least 72 hours since resolution of fever without antipyretic medication, and at least 72 hours with improvement of respiratory symptoms, two negative swab tests at least 24 hours apart (all criteria must be met). *CEP Note: guidance for non-hospitalized patients was on restricted web site.*

Beth Israel May 22	Symptomatic patients: time based strategy (preferred except for hospitalized patients): at least 72 hours since resolution of fever without antipyretic medication, improvement of respiratory symptoms, and at least 14 days since discharge (all criteria must be met). Continue precautions in the healthcare setting for at least 7 days following recovered status if defined using above time-based criteria (negative swab test required in addition for immunocompromised patients). Symptomatic patients: test based strategy (preferred for patients still hospitalized): at least 72 hours since resolution of fever without antipyretic medication, improvement of respiratory symptoms, at least 10 days since initial positive test, and 2 consecutive swab tests at least 24 hours apart (all criteria must be met). Asymptomatic patients: time based strategy: at least 14 days since initial positive test.
UCSF May 8	Non-hospitalized patients: improvement of symptoms and at least 30 days since onset of symptoms or first positive test. If patient must return for care before 30 days, but at least 14 days after onset of symptoms, do not discontinue precautions unless two consecutive swab tests (at least 24 hours apart) are negative. Hospitalized patients: at least 72 hours since resolution of fever without antipyretic medication, improvement of respiratory symptoms, at least 14 days since onset of symptoms or initial positive test, and 2 consecutive swab tests at least 24 hours apart (all criteria must be met). *CEP Note: Please see full document for guidance on care for patients who have been in close contact with a COVID-19-positive person.*
Washington May 5	For planning elective aerosol-generating procedures, either two negative tests within 72 hours of the planned procedure or 6 weeks elapse since initial diagnosis. Patients who meet the CDC criteria for release from transmission-based precautions (see above) may be seen in a health-care setting. Patients do not need a test of cure prior to being seen in clinic.

Guidance sources

ECDC–European Centres for Disease Control and Prevention
FLARE–Massachusetts General Hospital: Fast Literature Analysis and Review
HIQA–Health Information and Quality Authority (Ireland)
PHE–Public Health England

Update history (key additions and changes only)

June 26: New public health agency guidance from NHS Scotland. New evidence reviews added. New medical center guidance added and other medical center guidance updated. Guidance more than one month old deleted. New conclusion that some centers recommend against re-testing.

June 8: Initial report.

About this report

A Rapid Guidance Summary is a focused synopsis of recommendations from selected guideline issuers and health care systems, intended to provide guidance to Penn Medicine providers and administrators during times when latest guidance is urgently needed. It is not based on a complete systematic review of the evidence. Please see the CEP web site (http://www.uphs.upenn.edu/cep) for further details on the methods for developing these reports.

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