RETURN TO WORK

RECOMMENDATIONS

We recommend the use of **symptom-based strategy** for the discontinuation of isolation and return to work clearance of the following:

1. **Asymptomatic adults who are not severely immunocompromised if they fulfill the following *(Very low quality of evidence; Strong recommendation):***
   - remained asymptomatic throughout their infection
   - 10 days have passed from the first positive viral diagnostic test (RT-PCR or rapid antigen)
2. **Adults who had mild to moderate COVID-19 who are not severely immunocompromised if they fulfill the following *(Very low quality of evidence; Strong recommendation):***
   - Afebrile for at least 24 hours without use of antipyretic medications
   - Respiratory symptoms have improved (cough, shortness of breath)
   - 10 days have passed from symptom onset
3. **Adults who had severe to critical COVID-19 who are not severely immunocompromised if they fulfill the following *(Very low quality of evidence; Strong recommendation):***
   - Afebrile for at least 24 hours without use of antipyretic medications
   - Respiratory symptoms have improved (cough, shortness of breath)
   - 21 days have passed from symptom onset

A repeat negative RT-PCR test is no longer needed for discharge of immunocompetent patients with probable or confirmed COVID-19 regardless of severity, *because, in most cases, it results in prolonged isolation of patients who continue to shed detectable SARS-CoV-2 RNA but are no longer infectious.*

We suggest the use of **test-based strategy** using RT-PCR for the discontinuation of isolation and return to work clearance of the following:

1. **Severely immunocompromised adults**
2. **Health care workers**

if they fulfill the following:

- Afebrile for at least 24 hours without use of antipyretic medications
- Respiratory symptoms have improved (cough, shortness of breath)
- With at least 1 negative RT-PCR test of a respiratory specimen

(Very low quality of evidence; Conditional recommendation)

Severely immunocompromised: Ongoing chemotherapy for cancer, or within one year from receiving a hematopoietic stem cell or solid organ transplant; untreated HIV infection with CD4 count < 200, combined primary immunodeficiency disorder, and receipt of prednisone >20mg/day for more than 14 days, may cause a higher degree of immunocompromised and require actions such as lengthening the duration of work restrictions. Other less immunocompromising conditions include advanced old age, DM, CKD. The degree of immunocompromise is determined by the health care provider, and preventive actions are adapted to each individual and situation.

Consensus Issues

Considerations related to resource implications, cost-effectiveness, and the perceived balance of benefits and harms of test-based strategies were the main reasons for recommending the use of symptom-based strategy as a method to guide decisions on return to work. These recommendations were made despite the very low quality of evidence presented.

EVIDENCE SUMMARY

What criteria should be used for allowing workers who were previously infected with COVID-19 to return to work?

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Key Findings

Evidence for this review question came from 5 observational studies and 2 case series. Very low certainty of evidence suggests that a test-based strategy is associated with higher false negative rates after 9 days from symptom onset, higher excess costs and length of stay for hospitalized patients, and greater lost work days. For workers who have recovered from mild-to-moderate COVID-19, a symptom-based strategy may be indicated as replication competent virus has not been recovered among these groups after 10 days following symptom onset. Test-based strategies may be appropriate for workers who have recovered from severe COVID-19 and/or with immunocompromised states, as data on infectivity show prolonged viral shedding that can last for several months from symptom onset.

Introduction

Patients recovering from COVID-19 may remain infectious for a certain period of time. Thus, it is paramount that we allow them to return to work after they have ceased being contagious. Symptom-based strategy has been suggested as a potentially more cost-effective alternative than test-based strategies (e.g., RT-PCR or viral culture) for identifying COVID-19 patients who are no longer infectious and can be allowed to discontinue isolation and return to work [1].

Review Methods

A comprehensive search for published articles was conducted on March 22, 2021 in MEDLINE, Cochrane Library, UptoDate, and medrxiv.org. Free text and keywords related to “COVID-19”, “symptom-based strategy”, and “test-based strategy” were used. The authors included any observational studies or clinical trials that investigated the effectiveness of symptom-based and/or test-based strategies (e.g., RT-PCR or viral culture) as criteria for allowing workers who have been previously infected with COVID-19 to return to work. There were no restrictions on age, sex, race, language and co-morbidities.

We included studies that assessed the duration of infectivity as these are the studies that prove that the probability of recovering replication-competent viruses declines after onset of symptoms--justifying the use of symptom-based strategies over test-based strategies. However, since these studies did not directly compare symptom-based and test-based strategies, these studies were considered as indirect evidence. Studies that looked at excess costs, excess length of stay and days of work lost were also considered as indirect evidence.

Results

Characteristics of included studies

We found 3 cohort studies [2,7,8], 2 cross-sectional studies [3,4], and 2 case series [5,6] considered eligible for inclusion in this review. The characteristics of these studies are summarized in Appendix 2.

One cohort study estimated the excess acute-care length of stay and extra cost under a testing-based rather than symptom-based isolation strategy among 11 hospitalized veterans in the US [7]. One cohort study assessed the days of work lost and median time to work clearance associated with a test and symptom-based return to work criteria used among COVID-19 positive healthcare workers in the USA [8]. One cross-sectional study investigated the false negative rate of symptom-based strategy combined with CT-scan and/or antibody level vs. RT-PCR for among asymptomatic healthcare and non-healthcare workers [9].

Five studies provided data on duration of infectivity [2-6]. Outcomes of the first study included the following: cumulative frequency of PCR Cycle threshold (Ct) value and viral culture, Kaplan Meier plot of time to cessation of viral shedding by duration of illness stratified by disease severity, IgG and IgM readings stratified by disease severity, and time to first positive antibody level [2]. On the other hand, the second study investigated duration of infectivity, CT values and symptoms to test and comparison of symptom onset to test the probability of successful cultivation on Vero cells [3]. A third study included patients with severe and critical COVID-19 with or without severe immunosuppression, and investigated the viral loads and duration of symptoms for infectious virus shedding, key determinants for infectious virus shedding. and the probability of isolating a virus based on the levels of antibody titer [4]. On the other hand, two case series measured the duration of viability of SARS-CoV-2 on immunocompromised patients [5,6].

Overall summary of methodological quality

The overall quality of evidence was rated very low across outcomes; downgrading occurred due to indirectness, serious risk of bias concerns, and/or imprecision [2,3,4,5,6,7,8].

Summary of results of included studies

Duration of infectivity

The likelihood of recovering a viable virus generally declined after onset of symptoms. For patients with mild to moderate COVID-19, replication competent virus has not been recovered after 10 days following symptom onset [1]. A prospective cohort study with 100 COVID-19 patients with different severities by Young et al., estimated the mean duration of viral shedding via RT-PCR at 16.7 days (95% CI 15.2-18.3) [2]. A retrospective cross-sectional study by Bullard et al., analyzed 90 samples and successfully cultivated SARS-CoV-2 from 26 (28.9%) of the samples. The samples included in this study included those positive for SARS-CoV-2 by RT-PCR from day of symptom onset (day 0) up to 21 days after symptom onset. Within this follow-up period, positive cultures were only observed up to day 8 after symptom onset [3].

Importantly, the recovery of replication-competent virus between 10 and 20 days from symptom onset has been reported in some adults with severe COVID-19 including some immunocompromised patients [1]. The cross-sectional study by van Kampen et al found that patients that had severe or critical COVID-19 had detectable and viable virus eight days or more since onset of symptoms, with one patient remaining infectious up to 20 days after symptom onset [4]. Case series data from 20 immunocompromised patients detected viral RNA for up to 78 [IQR 24-64] days after the symptom onset [5]. Another case series study including 3

immunocompromised patients noted infectious viral shedding even up to 4 months after post-symptom onset [6].

For this outcome of duration of infectivity, the quality of evidence was further lowered down to very low due to imprecision from small sample sizes as well as very serious risk of bias concerns from the inclusion of case series designs and variable methods for measuring infectivity [5,6].

Excess costs[1] and acute care length of stay
Low-quality evidence from a cohort study [7] involving 11 hospitalized veterans concluded that testing-based isolation practices generated a cumulative 123 excess bed days of care and $454,669 (~Php 22,069,633) in additional cost under a testing-based rather than symptom-based isolation strategy. Median excess acute-care length of stay was 8 days (range: 0–27 days). Among 10 patients with Allocation Resource Center (ARC) financial data, median excess cost was $39,067 (range, $0–$111,505 or Php 0-5,412,452) and cost per additional inpatient day was $3,645 (range, $2,998–$5,335 or Php 145,523- 258,961). In total, 275 bed days and $952,983 (Php 46,257,794) were spent in acute care, of which >40% could have been avoided using new symptom-based recommendations [7]. The certainty of this estimate is very low due to indirectness from using data only on severe, elderly patients.

Days of work lost
Low quality evidence from one cohort study [8] by Shenoy et al. estimated that time plus symptom–based criteria would have resulted in 4,097 fewer lost workdays, or an average of 7.2 fewer days of work lost per employee [8]. In this study, healthcare workers (n=425) diagnosed and treated for COVID-19 had prolonged recovery of viral RNA. The average interval between first positive to first negative RT-PCR tests was 17 days, while the average interval between first positive to second negative RT-PCR test was 19.5 (SD 6.1) days. Median time to work clearance was 29 days (95% CI, 28–31). Using a test-based strategy resulted in a median time to return to work of 19 days. The quality of evidence for this outcome was downgraded due to indirectness.

False negative rates of RT-PCR
A cross-sectional study [9] in China including both healthcare and other workers found that RT-PCR may have false negative results for COVID-19 infection under certain conditions, especially for asymptomatic infections. Among 172 people with abnormal first physical examination results, the authors observed that 170 cases (98.8%) were negative in the first SARS-CoV-2 nucleic acid test, but one was positive by RT-PCR at the time of reexamination. On the other hand, 120 (70%) of the population with abnormal first physical examination results were antibody positive, but only seven were classified as at risk of infection, and the remaining 113 (65.70%) were considered to have protective antibodies in vivo, and were speculated to have been infected with SARS-CoV-2 [9]. The quality of evidence for this outcome was rated very low because of risk of bias concerns coming from the inclusion of other diagnostic tests such as CT Scan and serologic testing as part of the return to work clearance strategy. Moreover, not all the participants had COVID-19 and not all were subjected to CT Scan and RT-PCR [9]

Recommendations from Other Groups

As of February 16, 2021, CDC [1] stated that a test-based strategy is generally not recommended for clearing healthcare personnel (HCP) to return to work clearing staff who are no longer infectious but continue to shed detectable SARS-CoV-2 RNA. However, CDC also stated that a test-based strategy could be considered to allow HCP to return to work earlier than if the

[1] **Note: Conversion rate used: 1 USD= Php 48.54**

symptom-based strategy were to be used. Furthermore, a test-based strategy could also be considered together with a consultation with local infectious disease experts for some HCPs suspected to be still infectious beyond 20 days (e.g., those who are severely immunocompromised). The symptom and test-based strategy recommendations by CDC are summarized in Tables 1-2 [1].

Table 1. Symptom Based Strategy

Severity of the disease	When to return to work?
Mild to moderate COVID-19 who are not severely immunocompromised	● At least 10 days have passed since symptoms first appeared ● At least 24 hours have passed since last fever without the use of fever-reducing medications ● Symptoms (e.g., cough, shortness of breath) have improved
Not severely immunocompromised and were asymptomatic throughout their infection	● At least 10 days have passed since the date of their first positive viral diagnostic test
Severe to critical illness or who are severely immunocompromised	● At least 10 days and up to 20 days have passed since symptoms first appeared ● At least 24 hours have passed since last fever without the use of fever-reducing medications ● Symptoms (e.g., cough, shortness of breath) have improved ● Consider consultation with infection control experts

Table 2. Test Based Strategy

Clinical Presentation	When to return to work?
Symptomatic	● Resolution of fever without the use of fever-reducing medications and ● Improvement in symptoms (e.g., cough, shortness of breath), and ● Results are negative from at least two consecutive respiratory specimens collected ≥24 hours apart (total of two negative specimens) tested using an FDA-authorized molecular viral assay to detect SARS-CoV-2 RNA.
NOT symptomatic	● Results are negative from at least two consecutive respiratory specimens collected ≥24 hours apart (total of two negative specimens) tested using an FDA-authorized molecular viral assay to detect SARS-CoV-2 RNA.

As of January 28, 2021, the UK government has recommended that workers who have tested positive for SARS-CoV-2 by PCR should self-isolate for at least 10 days after symptom onset. Additionally, asymptomatic workers who have not been hospitalized but tested positive should also undergo the 10-day isolation after their first positive diagnostic test. Conversely, if the worker has been admitted to hospital it is recommended that this worker should be isolated in hospital (or continue to self-isolate on discharge) for 14 days from their first positive PCR test result. This is because COVID-19 cases admitted to hospital will have more severe disease and are more

likely to have pre-existing conditions, such as severe immunosuppression. For the same reasons, the 14-day isolation rule also applies to other (non-staff) COVID-19 cases admitted to hospital [10].

As of September 10, 2020, the Australian government recommends that all staff, whether or not they have patient contact, should not come to work if they have fever or respiratory symptoms. It was also recommended that the staff should isolate for 14 days while waiting for the result of a COVID-19 test and/or after testing positive for COVID-19. If the result is negative, the employee should remain at home until they are well enough to return to work. If the result is positive, the staff member should follow the advice of their doctor and isolate themselves in their home or in a hospital until they are well. Lastly, it was recommended that staff who do not develop COVID-19 symptoms while in quarantine can return to work without a medical clearance and that testing for COVID-19 is not necessary [11].

Research Gaps

Currently, there are no ongoing studies about symptom and test-based strategy as criteria for allowing workers to return to work listed in the NIH- U.S NLM's *ClinicalTrials.gov* and Cochrane Library.

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Appendix 1. Characteristics of Included Studies

First Author- Year- Setting	Type of Study	Population Characteristics	Sample Size	Intervention		Outcome
				Reference	Index	
Young, Barnaby 2020 Singapore	Prospective Cohort	COVID-19 patients, mean age was 46 years (95% confidence interval [CI] 43-49), males comprised 56 (56%) and 38 (38%) had comorbidities. Median time from symptom onset to hospital admission was 5.3 days (interquartile range (IQR) 1.3-8).	100	Viral Culture	RT-PCR	Cumulative frequency of PCR Cycle threshold (Ct) value and viral culture, Kaplan Meier plot of time to cessation of viral shedding by duration of illness stratified by disease severity, IgG and IgM readings stratified by disease severity and time to first positive antibody level.
Bullard, Jared 2020 Canada	Retrospective cross sectional study	90 COVID-19 RT-PCR positive samples	90 samples	Viral Culture	RT-PCR	Infectivity, CT values and symptom to test, comparison of symptom onset to test to the probability of successful cultivation on Vero cells
Van Kampen, Jeroen 2021 Netherlands	Cross sectional study	129 hospitalized individuals with COVID-19, for whom at least one virus culture from a respiratory tract sample was available. Of these, 89 patients (69.0%) had been admitted to intensive care and the remaining 40 patients (31.0%) were admitted to the medium care. Thirty patients were immunosuppressed (23%) of whom 19 (14.7%) were non-severely immunocompromised and 11 (8.5%) were severely	129	Viral Culture	RT-PCR, Antibody titers	Duration of symptoms for infectious virus shedding, key determinants for infectious virus shedding and the probability of isolating a virus based on the levels of antibody titer

First Author- Year- Setting	Type of Study	Population Characteristics	Sample Size	Intervention		Outcome
				Reference	Index	
		immunocompromised				
Aydillo, Teresa 2020 New York	Case Series	20 immunocompromised patients with COVID-19. Of the 20 patients, 15 were receiving active treatment or chemotherapy. Eleven had severe Covid-19.	20	Viral Culture	RT-PCR	Viability of virus, variant identification
Tarhini, Hassan 2021 United States	Case Series	3 deeply immunocompromised patients with COVID-19	3	Viral Culture	RT-PCR	Viability and duration of viral shedding
Wu, Chenwei 2020 Washington	Cohort	70 veterans diagnosed with COVID-19 with 29 (41.4%) requiring hospitalization. All were male, with a median age of 74 years (range, 68–100). In addition, 9 (81.8%) had severe illness and 1 (9.1%) was immunocompromised due to solid- organ transplantation	11	Test based strategy	Symptom based strategy	Estimated excess acute-care length of stay and extra cost **Note:** Excess acute-care length of stay was defined as the difference between the true discharge date and the discharge eligibility date. Excess cost of care was determined by multiplying the "excess" fraction of a patient's stay by the total acute-care cost reported by the Veterans Health Administration (VHA) Allocation Resource Center

First Author- Year- Setting	Type of Study	Population Characteristics	Sample Size	Intervention		Outcome
				Reference	Index	
						(ARC). ARC costs are based on the managerial cost accounting system used widely in VHA cost-effectiveness research, adjusted for administrative overhead and special fees. Emergency department and intensive care costs were excluded.
Shenoy, Erica 2020 Massachusetts	Cohort	1049 COVID-19 positive health care workers	1049	Test based strategy	Symptom based + time based strategy	mean and median number of days from first positive to first negative test, Kaplan-Meier estimate of median time to clearance, test-based clearance, additional days of work lost per employee than would have been accrued using the time plus symptom-based clearance method. **Note:** Lost work days were calculated comparing a time plus symptom–based clearance to the test-based protocol. For the former, it was assumed that the day the employee was tested under test-based clearance indicated the resolution of symptoms.

First Author- Year- Setting	Type of Study	Population Characteristics	Sample Size	Intervention		Outcome
				Reference	Index	
Duan, Ping 2020 China	Cross sectional study	4729 asymptomatic subjects were included in the study. The male-to-female ratio in the total population is about 1:2, with a centralised age distribution between 18.0 and 60.0 years, with a median age of 33.0 (IQR: 28.0–47.0) years. Medical staff (62.93%) accounted for the largest proportion, followed by rear-service personnel (30.73%) and administrative staff (6.34%).	4729	RT-PCR	Symptom based CT Scan Antibody levels	% abnormal initial physical examination, false negative rate

Appendix 2. GRADE Evidence Profile

Question: What criteria should be used for allowing workers who were previously infected with COVID-19 to return to work?

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect estimate	Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias		
Duration of infectivity	5 studies (342 patients)	cross-sectional (cohort type accuracy study), case series	very serious [a,b]	serious	not serious	not serious	none	**Mild-moderate**: virus cannot be cultured after day **10** **Severe**: virus can be cultured at day **10-20** **Immunocompromised**: prolonged viral shedding up to 4 months	⨁◯◯◯ very LOW
Excess costs	1 study (11 patients)	cross-sectional (cohort type accuracy study)	very serious [b,c]	serious	not serious	not serious	none	**$454,669 (~Php 22,069,633)** excess cost under a testing-based rather than symptom-based isolation strategy	⨁◯◯◯ very LOW
Excess acute care length of stay	1 study (11 patients)	cross-sectional (cohort type accuracy study)	very serious [b,c]	serious	not serious	not serious	none	Median: **8 days** (range: 0-27)	⨁◯◯◯ very LOW
Days of work lost	1 study (1049 patients)	cross-sectional (cohort type accuracy study)	very serious [c,d,e]	serious	not serious	not serious	none	average of **7.2** fewer days of work lost per employee	⨁◯◯◯ very LOW
False negative rates of RT-PCR	1 study (4729 patients)	cross-sectional (cohort type accuracy study)	very serious [d,f]	serious	not serious	not serious	none	170/72 **(98.8%)**	⨁◯◯◯ very LOW

[a] study design
[b] small sample size
[c] theoretical assumptions
[d] selection bias
[e] unclear index test
[f] problem with interpretation of index test