Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
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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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RECOMMENDATIONS

For asymptomatic, not severely immunocompromised fully vaccinated adults, we suggest the use of the following symptom-based criteria for return to work clearance:
(Very low certainty of evidence; Weak recommendation)

a. At least 8 days have passed since the first positive COVID-19 RT-PCR test; AND
b. No symptoms have developed during this period.

For asymptomatic, not severely immunocompromised not fully vaccinated adults, we suggest the use of the following symptom-based criteria for return to work clearance:
(Very low certainty of evidence; Weak recommendation)

a. At least 10 days have passed since the first positive COVID-19 RT-PCR test; AND
b. No symptoms have developed during this period.

For symptomatic, not severely immunocompromised adults with mild-to-moderate COVID-19 diagnosis and any vaccination status, we suggest the use of the following symptom-based criteria for return to work clearance:
(Very low certainty of evidence; Weak recommendation)

a. At least 10 days have passed since the onset of symptoms; AND
b. No fever during the previous 24 hours; AND
c. There has been substantial improvement in respiratory symptoms of the acute illness.

For symptomatic, not severely immunocompromised adults with severe-to-critical COVID-19 diagnosis and any vaccination status, we suggest the use of the following symptom-based criteria for return to work clearance:
(Very low certainty of evidence; Weak recommendation)

a. At least 21 days have passed since the onset of symptoms; AND
b. No fever during the previous 24 hours; AND
c. There has been substantial improvement in respiratory symptoms of the acute illness.

For symptomatic, severely immunocompromised adults with any vaccination status, we suggest the use of the following for return to work clearance:
(Very low certainty of evidence; Weak recommendation)

a. At least 22 days have passed since the onset of symptoms; AND
b. No fever during the previous 24 hours; AND

c. There has been substantial improvement in respiratory symptoms of the acute illness; AND
d. PCR test results are negative on at least 1 respiratory specimen.

Note:
Severely immunocompromised individuals include the following:

- Individuals receiving active chemotherapy for cancer
- Being within one year out from receiving a hematopoietic stem cell or solid organ transplant
- Untreated HIV infection with CD4 <200
- Primary immunodeficiency
- Taking immunosuppressive medications (e.g., drugs to suppress rejection of transplanted organs or to treat rheumatologic conditions such as mycophenolate and rituximab)
- Taking more than 20mg a day of prednisone for more than 14 days

Consensus Issues
The evidence base included studies that investigated the clearance of COVID-19 infection in relation to vaccination status, symptom presentation (i.e., asymptomatic versus symptomatic), and immunocompromised state (i.e., non-, moderately, or severely immunocompromised). These factors were taken into consideration in recommending the criteria for allowing workers who were previously infected with COVID-19 to return to work.

Despite studies including non, moderately, and severely immunocompromised individuals, the panelists decided to make recommendations that only distinguished severely versus non-severely immunocompromised individuals due to insufficiency of evidence among moderately immunocompromised individuals.

Among asymptomatic, not severely immunocompromised individuals, separate recommendations were made depending on vaccination status. Evidence base including one study showed faster viral clearance and shorter infection duration by two days among fully vaccinated compared to not fully vaccinated individuals. The panelists unanimously voted for a weak recommendation due to indirectness of the evidence, wherein the reference standard used was time to RT-PCR clearance instead of viral culture positivity.

Among severely immunocompromised individuals, the evidence on prolonged viral shedding was an important consideration for the panelists. However, data remains lacking on the duration of infectivity of the virus among this subgroup. The evidence base included only one study on this subgroup and the reference standard for infectivity was RT-PCR instead of viral culture. For this reason, a panelist opined that a test-based criteria for clearance to work would be a more prudent strategy compared to a symptom-based criteria. However, concern on the impracticality of a test-based approach was raised as this may lead to prolonged isolation of patients who continue to shed detectable SARS-CoV-2 RNA on RT-PCR but are no longer infectious. A weak recommendation was made mainly due to the very low certainty of evidence.

PREVIOUS RECOMMENDATION

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

a. Asymptomatic adults who are not severely immunocompromised if they fulfill the following: *(Very low certainty 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)

b. Adults who had mild to moderate COVID-19 who are not severely immunocompromised if they fulfill the following: *(Very low certainty 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

c. Adults who had severe to critical COVID-19 who are not severely immunocompromised if they fulfill the following: *(Very low certainty 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.

Test-based strategy
We suggest the use of test-based strategy using RT-PCR for the discontinuation of isolation and return to work clearance of the following: *(Very low quality of evidence; Conditional recommendation)*

a. Severely immunocompromised adults
b. 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

<u>Severely immunocompromised:</u> 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.

c. Severely immunocompromised adults
d. 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

[a]*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.*

What's New in This Version?

- Updated search to include studies evaluating relationship of vaccination status on various outcomes related to infectivity or transmissibility

Key Findings

- This version includes six observational studies that explored the relationship of vaccination status on various outcomes related to infectivity. From this data, the review provides additional recommendations related to duration of isolation for return-to-work clearance.
- One study found no significant difference (p=0.16) in the proportion of culture-positive results between fully vaccinated and not fully vaccinated individuals (OR 0.67, 95% CI 0.38, 1.18). The duration of viral culture positivity between the two groups were comparable (median of 5 days for both) and suggested no significant difference in terms of duration of infectivity (mean difference=0 days). Another study concluded that vaccinated individuals had faster viral clearance by 2 days (5.5 days, 95% credible intervals [CrI] 4.6, 6.5) vs. 7.5 days for unvaccinated (95% CrI 6.8, 8.2 days) and shorter infection duration by 2.3 days (8.7 days, 95% CrI 7.6, 9.9) vs 11.0 days (95% CrI 10.3, 11.8) for unvaccinated).
- Based on three observational studies, the secondary attack rate was lower by 8.43% (95% CI -18.03%, 1.17%) for fully vaccinated compared to not fully vaccinated individuals, but this difference was not statistically significant (P=0.09).
- Compared to immunocompetent individuals, time to PCR clearance was not significantly different for severely (adjusted hazards ratios [aHR] 0.98, 95% CI 0.84, 1.15) and moderately immunocompromised patients (aHR 0.86; 95% CI 0.71, 1.05). Delayed time to PCR clearance was seen for specific subgroups of patients: solid organ transplant (aHR 0.64, 95% CI 0.42, 0.97), diabetes (aHR 0.82, 95% CI 0.73-0.93), obesity (aHR 0.90, 95% CI 0.83-0.98), rheumatologic disease (aHR 0.90, 95% CI 0.83-0.98), ≥3 comorbidities (aHR 0.73, 95% CI0.60-0.88), older age (aHR 0.996, 95% CI 0.993-0.999).
- The overall certainty of evidence for each of the outcomes was rated very low. Downgrading occurred due to risk of bias issues across the included studies, imprecision related to wide confidence intervals and small sample sizes, and inconsistency.

Introduction

Patients recovering from COVID-19 may remain infectious for a certain period. Thus, it is paramount that they are allowed to return to work only 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]

In the advent of vaccination and emergence of new and more transmissible variants (e.g., delta variant), recommendations on return-to-work criteria need to be updated. The Department of Health (DOH) of the Philippines has already recommended mass vaccination especially among the vulnerable and working population as the safety and efficacy of COVID vaccines in reducing the risk of severe illness became more established. As of December 9, 2021, at least 39.5 million Filipinos have been fully vaccinated, with 2.8 million healthcare workers and 17.9 million front liners in essential sectors.[2,3]

Fully vaccinated individuals may still contract breakthrough infections and transmit the disease at the same level as unvaccinated individuals.[4] Whether vaccinated individuals spread the virus for a shorter duration compared to unvaccinated individuals remains uncertain. This review aimed to update recommendations on return-to-work clearance in relation to symptom- versus test-based strategies and duration of isolation, with particular focus on an individuals' vaccination status, COVID-19 symptom presentation, and immunocompromised state.

Review Methods

A comprehensive search for published articles was conducted on November 25, 2021 in MEDLINE, Cochrane Library, UptoDate, medrxiv.org, WHO trial registry, and ClinicalTrial.gov databases. Free text and keywords related to "COVID-19", "COVID Vaccination", "Delta Variant" and "Transmission" were used. There were no restrictions on the type of vaccine received, number of doses given, age, sex, race, language, and co-morbidities.

The following studies were included: (a) observational studies, non-randomized or randomized clinical trials that investigated the effect of COVID vaccination status on return-to-work guidance for workers previously infected with COVID-19; and (b) observational studies that assessed the difference in disease transmission between vaccinated and unvaccinated individuals, as these would provide evidence that the probability of recovering replication-competent viruses declines faster among vaccinated individuals. These studies would justify shortening the isolation days required before clearing a recovered COVID-19 patient to return to work.

Results

Characteristics of included studies

Evidence from the initial version of this review was obtained from three cohort studies [5-7], two cross-sectional studies [8,9], and two case series.[10,11] In this update, six prospective cohort studies [12-17] were added to the existing evidence base. Of these, one preprint study and one published study from the USA evaluated the difference in viral transmission dynamics between vaccinated and vaccinated individuals. Both were conducted during the delta variant outbreak (up to August 2021). Three studies provided data on secondary attack rates. One study assessed the time to PCR clearance among severely immunocompromised adults.

Six cohort studies were conducted among the general population. All studies involved vaccinated and unvaccinated patients who tested positive for COVID-19 via RT-PCR. The characteristics of these studies are summarized in Appendix 3. The following outcomes were evaluated among

vaccinated and unvaccinated individuals: (1) infectivity assessed by viral culture positivity, (2) duration of infectivity (assessed by culture or positive PCR), (3) duration of viral clearance assessed by PCR, (4) difference in cycle threshold levels and viral load, (5) viral load (via cycle threshold values), and (6) secondary attack rates.

Overall summary of methodological quality
The overall certainty of evidence for each of the outcomes was rated very low. Downgrading occurred due to risk of bias issues across the included studies, imprecision related to wide confidence intervals and small sample sizes, and inconsistency.

Summary of results of included studies
A. Duration of infectivity (according to COVID-19 severity)
The likelihood of recovering a viable virus generally declined after the onset of symptoms. 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). For patients with mild to moderate COVID-19, replication competent virus has not been recovered after 10 days following symptom onset.[2] 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 the onset of symptoms, with one patient remaining infectious up to 20 days after symptom onset.[4]

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

B. Duration of infectivity (according to vaccination status)
The study by Salvatore et al. included 95 eligible incarcerated persons with PCR-confirmed COVID-19 infection, among which 78 (82%) were fully vaccinated and 17 (18%) were partially vaccinated or unvaccinated. Majority of the vaccinated received the Pfizer vaccine (73%), followed by Moderna (18%), and Janssen (9%) vaccines. Viral culture results were available for 842/978 (86.6%) specimens collected.

In the study by Kissler et al. 2021 involving 173 people (90% male) affiliated with the National Basketball Association (NBA), 37 (21.4%) had breakthrough infections or positive PCR results at least two weeks from the receipt of the final dose. Of these 37 breakthrough infections, 25 or 67.6% occurred in delta variant cases and 4 or 10.8% in alpha variant cases. Most breakthrough infections were seen in recipients of the Pfizer vaccine (23-62%), followed by the Janssen vaccine (8-22%). The study assessed viral clearance duration (i.e., time from peak viral concentration to clearance of acute infection) and duration of acute infection (i.e., time from detection to clearance of acute infection).

<u>Viral culture positivity as outcome measure</u>
The study by Salvatore et al. found no significant difference (p=0.16) in the proportion of culture-positive results between fully vaccinated (57/690 or 8%) and not fully vaccinated (18/152 or 12%) individuals (OR 0.67, 95% CI 0.38, 1.18). Likewise, the two groups had comparable viral culture positivity (median [MD] 5 days for both) and shortened duration of infection (MD 0 days).

Shorter culture positivity was seen for fully vaccinated participants who received Moderna than those who received Pfizer (p=0.048) or Janssen vaccines (p=0.003). No significant difference was seen between Pfizer and Janssen vaccines (p=0.12).

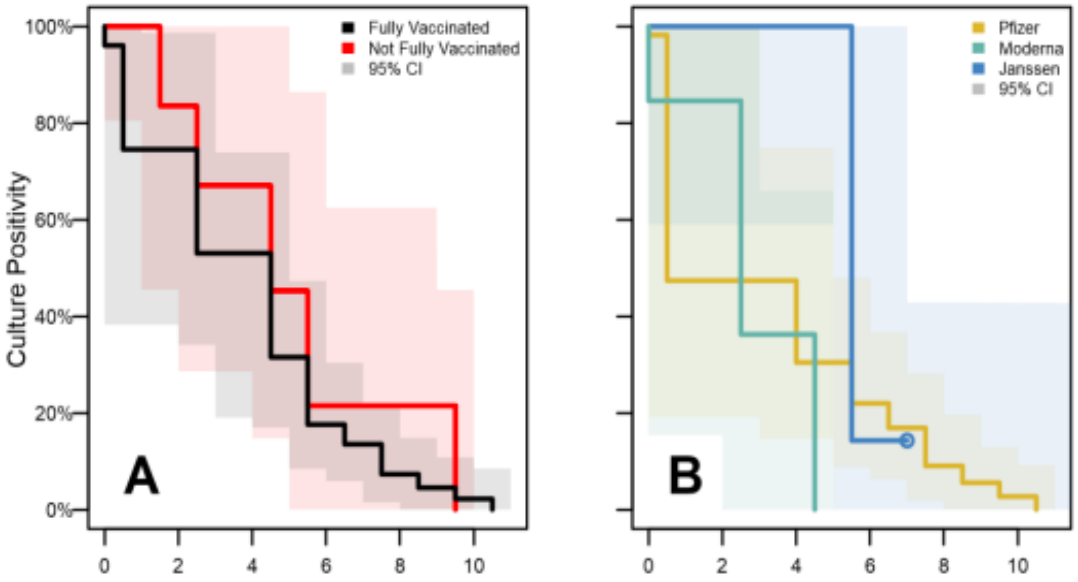

Figure 1. SARS-CoV-2 viral culture test positivity survival curves according to (A) vaccination status and (B) vaccine type received (Salvatore et al., 2021)

In contrast, the Kissler 2021 study concluded that vaccinated individuals had faster viral clearance by 2 days (5.5 days, 95% CrI 4.6, 6.5) compared to those unvaccinated (7.5 days, 95% CrI 6.8, 8.2 days). Vaccinated individuals also had shorter infection duration by 2.3 days (8.7 days, 95% CrI 7.6, 9.9] compared to the unvaccinated (11.0 days, 95% CrI 10.3, 11.8). Viral clearance was measured with longitudinal quantitative RT-PCR tests using anterior nares or oropharyngeal samples. The certainty of the effect estimates for this study was affected by several factors including imprecision (a small sample size preventing sufficient subgroup analysis according to variant or vaccination status) and risk of bias (most participants were healthy young men athletes, no systematic tracking of symptoms, and no testing for the presence of infectious virus).

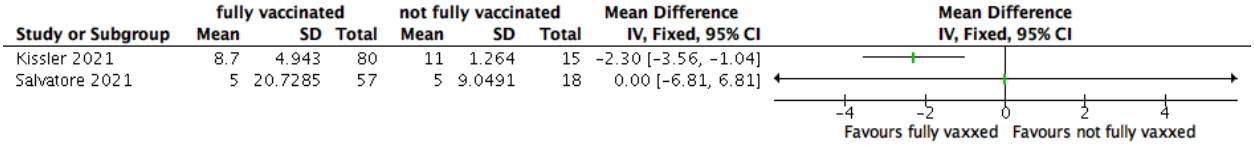

Figure 2. Duration of infectivity between vaccinated and unvaccinated individuals

C. Secondary attack rate for vaccinated and unvaccinated individuals

Secondary attack rate refers to the probability that an infection occurs among susceptible people within a specific group (i.e., household or close contacts). This metric reflects how likely it is for vaccinated and unvaccinated COVID-19 patients to transmit the disease to their household contacts.[18]

Three observational studies (n=249,036) showed lower secondary attack rates for vaccinated individuals (MD -8.43%, 95% CI -18.03%, 1.17%). However, interval estimates for all three studies were imprecise and crossed the unity line. Likewise, the pooled effect estimate was also imprecise, suggesting that this difference is not statistically significant between the two groups.[12,13,16]

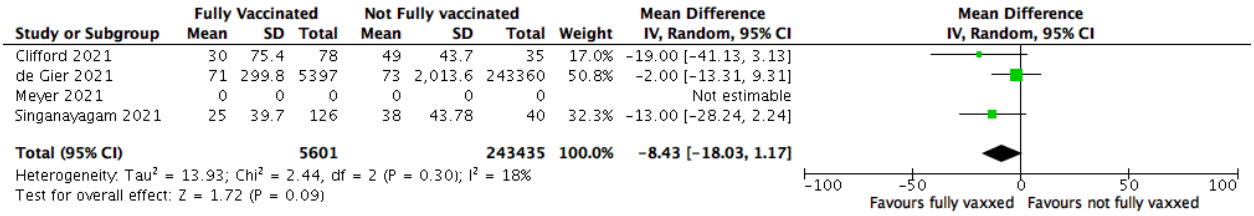

Figure. 3 Secondary attack rate between vaccinated and unvaccinated individuals

D. Duration of infectivity: immunocompromised individuals

A March 2021 prospective cohort study in the USA by Epstein et al. provided data related to the time to achieve SARS-CoV-2 PCR clearance among 3,758 severely immunocompromised adults. On average, patients were tested at least three times with PCR. Certainty of evidence for this outcome was low as the study had sampling issues and did not use viral culture studies to assess infectivity.

The median time to PCR clearance (interquartile range) was 22 days (4–34) for the severely immunocompromised, 20 days (8–33) for the moderately immunocompromised, and 16 days (6–29) for the non-immunocompromised. Adjust hazards ratios (aHR) showed a delayed time to PCR clearance for the following subset of patients: solid organ transplant (aHR 0.64, 95% CI 0.42, 0.97), diabetes (aHR 0.82, 95% CI 0.73, 0.93), obesity (aHR 0.90, 95% CI 0.83, 0.98), rheumatologic disease (aHR 0.90, 95% CI 0.83, 0.98), ≥3 comorbidities (aHR 0.73, 95% CI 0.60, 0.88), and older age (aHR 0.996, 95% CI 0.993, 0.999). Compared to immunocompetent individuals, time to PCR clearance was similar for severely (aHR 0.98, 95% CI 0.84, 1.15) and moderately immunocompromised patients (aHR 0.86, 95% CI 0.71, 1.05).

E. Impact of a test-based strategy on costs and acute care length of stay

Low-quality evidence from a cohort study [6] 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 test-based rather than symptom-based isolation strategy. Median excess acute-care length of stay was eight days (range 0–27 days). Among ten 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.[6] The certainty of this estimate was rated very low due to indirectness from using data only on severe, elderly patients.

F. Impact of symptom-based strategy on days of work lost

Low quality evidence from one cohort study [7] 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.[7] 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.

Recommendations from Other Groups

Department of Health of the Philippines
As of October 7, 2021, DOH has released an IATF Resolution No. 142 s.2021 outlining return to work guidelines for employees infected with COVID-19.[19] A ***symptom-based strategy is currently used***, with different duration of isolation days prescribed for individuals with varying vaccination status (e.g., 7 days for fully vaccinated close contacts, 14 days for unknown vaccine status).

US Centers for Disease Control and Prevention (CDC)
As of September 10, 2021, the US CDC has updated their Interim Guidance for Managing Healthcare Personnel (HCP) with SARS-CoV-2 Infection or Exposure to SARS-CoV-2.[20] A ***symptom-based strategy is still preferred in most clinical situations*** for determining when HCP with SARS-CoV-2 infection could return to work. No guidelines specific for vaccinated individuals are currently made.

As of December 23, 2021, this guidance by CDC was updated due to SARS-CoV-2 Omicron variant. In this update, asymptomatic HCP with higher-risk exposures will be allowed to return to work if they have received all COVID-19 vaccine doses including booster dose and remain asymptomatic or test negative for SARS-CoV-2. For HCP who test positive for SARS-CoV-2, they are required to quarantine for 10 days regardless of vaccination status. Quarantine duration may be reduced to 7 days if HCPs have a negative test (taken within 48 hrs before return to work), if asymptomatic or mildly symptomatic (with improving symptoms).

UK Health Department
As of November 30, 2021, the United Kingdom Health Department has released a guideline for management of staff and exposed patients/residents in health and social care settings. [21] Return to work criteria is based on a ***combination of both test-based and symptom-based strategies***. No distinction was made based on vaccination status.

Australian Health Department
As of November 2021, Health Direct, a government funded service of Australian Health Department, has published the following recommendation.[22] A ***symptom-based strategy is generally used***, with a provision for shortening the required isolation days for PCR-confirmed asymptomatic cases (10 to 7 days for fully vaccinated, 14 to 10 days for other vaccine status) and symptomatic cases (14 to 10 days for fully vaccinated, 20 to 14 days for other vaccine status). A test-based strategy with ***two repeat PCR tests is recommended for significantly immunocompromised individuals*** regardless of vaccination status.

Research Gaps
Currently, there are no ongoing studies about the effect of vaccination on outbreak infection and how it may affect the strategy on the criteria for allowing workers to return to work listed in the NIH-U.S. NLM's *ClinicalTrials.gov* and Cochrane Library. However, some studies can indirectly support earlier return to work through decrease in transmission. These studies are listed in Appendix 6.

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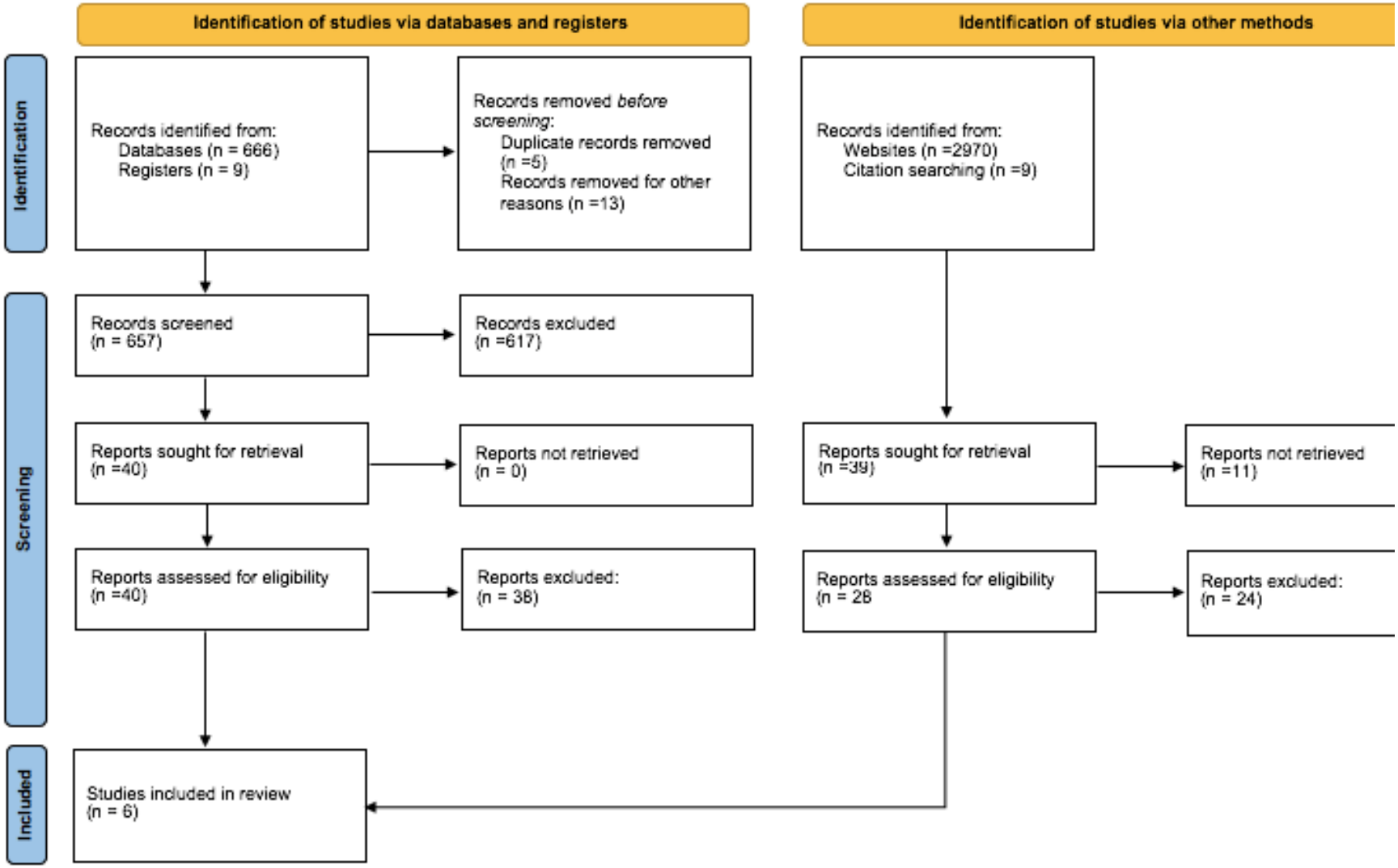
[22] https://www.healthdirect.gov.au/coronavirus-covid-19-self-isolation-faqs Accessed: December 3, 2021 10:45.

Appendix 1. Evidence to Decision

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (3)					In the advent of vaccination and emergence of new and more transmissible variants (e.g., delta variant), recommendations on return-to-work criteria need to be updated.
Benefits	Large (1)	Moderate (1)	Small	Uncertain (1)			Fully vaccinated individuals showed shorter duration of infection (2.26 days) using RT-PCR positivity as the outcome measure. No difference in duration of culture positivity was noted between fully vaccinated and unvaccinated /partially vaccinated groups.No significant differences were also noted in terms of average Ct values [MD 1.98, 95% CI -1.27, 5.23]), viral load, secondary attack rate (MD 8.4, 95% CI -18.0, 1.17).
Harms	Large	Moderate (1)	Small	Uncertain			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 workdays.
Balance of Benefits and Harms	Favors the use of criteria (1)	Probably favors the use of criteria (1)	Does not favor the use of criteria (1)				
Certainty of Evidence	High	Moderate (1)	Low	Very low (3)			For CT level, the overall certainty of evidence is very low because of its indirectness as it is just a surrogate marker for viral load. For days of infectivity, the overall certainty is very low due to insufficient follow up. For secondary attack rate, the overall certainty is very low due to imprecision. 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
Accuracy	Very Accurate	Accurate (1)	Inaccurate (1)	Very Inaccurate	Uncertain (1)		

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
							costs and length of stay for hospitalized patients, and greater lost workdays.
Values	Important uncertainty or variability	Possibly important uncertainty or variability (2)	Possibly NO important uncertainty or variability	No important uncertainty or variability (1)			No research evidence found.
Resources Required	Uncertain (1)	Large cost	Moderate Cost	Negligible cost or savings	Moderate savings (1)	Large savings (1)	RT-PCR costs Php 3800-4500. Days in isolation: 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.
Certainty of evidence of required resources	No included studies (2)	Very low	Low (1)	Moderate	High		
Cost effectiveness	No included studies (2)	Favors using comparator	Does not favor either using the criteria or the comparator	Favors the criteria (1)			No local data on economic evaluation of RT PCR. No data as well on the cost of isolation facility and days of income lost.
Equity	Uncertain (2)	Reduced	Probably no impact	Increased (1)			
Acceptability	Uncertain (2)	No	Yes (1)				
Feasibility	Uncertain (1)	No	Yes (2)				

Appendix 2. Search Yield and Results



Appendix 3. Characteristics of Included Studies

Table 1. Characteristics of included studies in updated review

First Author- Year- Setting	Type of Study	Population Characteristics	Sample Size	Control	Intervention	Outcome
Clifford, Samuel 2021 United Kingdom	Prospective Cohort	213 index samples and 312 contacts	525	Unvaccinated	Vaccinated	Vaccine effectiveness, Vaccine effectiveness to infection, vaccine effectiveness to transmission, Secondary attack rate
De Gier, Brechje 2021 Netherlands	Retrospective Cohort	7,771 contacts of 4,921 index cases. Of the index cases 1,740 were fully vaccinated (35.4%) and 2,641 (53.7%) were unvaccinated. Of the contacts 4,189 (53.9%) were fully vaccinated and 2,941 were unvaccinated (37.8%)	12,692	Unvaccinated	Vaccinated	Vaccine effectiveness against transmission Vaccine effectiveness against infection
Kissler, Stephen 2021 Boston, USA	Retrospective Cohort	173 with acute SARS COV 2 from National Basketball Association	173	Unvaccinated	Vaccinated	Mean viral trajectories among alpha and delta infection Viral dynamics between vaccinated and unvaccinated
Salvatore, Phillip 2021 USA	Prospective cohort	95 participants from Texas Federal prison, 78 fully vaccinated, 17 partially vaccinated	95	Partially vaccinated	Vaccinated	RT PCR positivity, Viral culture positivity
Singana-yagam, Anika 2021 United Kingdom	Prospective cohort	471 index case, 602 community contact	1,073	Unvaccinated	Vaccinated	Secondary attack rate, Vaccine effectiveness

First Author-Year- Setting	Type of Study	Population Characteristics	Sample Size	Control	Intervention	Outcome
Epstein, Rachel 2021 Boston, USA	Prospective cohort	433 immunocompromised 3322 immunocompetent	3,758	Unvaccinated	Vaccinated	PCR clearance

Table 2. Characteristics of included studies from previous review

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 immunocompromised	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	
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 (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-

First Author- Year- Setting	Type of Study	Population Characteristics	Sample Size	Intervention		Outcome
				Reference	Index	
						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.
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 4. GRADE Evidence Profile

Table 1. Decreasing Days of Infectiousness

Vaccination compared to none in decreasing the duration of isolation among COVID-confirmed

Certainty assessment							Summary of findings				
Participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							Without vaccination	With vaccination		Risk without vaccination	Risk difference with vaccination
Secondary Attack Rate											
249,036 (3 observational studies)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ Very low	243,435	5,601	-	The mean secondary attack rate was 0	MD **8.43 lower** (18.03 lower to 1.17 higher)
Days of Infectivity											
170 (2 observational studies)	serious[b]	serious[c]	not serious	Serious[d]	none	⨁◯◯◯ Very low	Kissler 2021 study concluded that vaccinated individuals had faster viral clearance by 2 days (5.5 days, 95% CrI 4.6, 6.5) compared to those unvaccinated (7.5 days, 95% CrI 6.8, 8.2 days). Vaccinated individuals also had shorter infection duration by 2.3 days (8.7 days, 95% CrI 7.6, 9.9] compared to the unvaccinated (11.0 days, 95% CrI 10.3, 11.8). Salvatore et al. found no significant difference (p=0.16) in the proportion of culture-positive results between fully vaccinated (57/690 or 8%) and not fully vaccinated (18/152 or 12%) individuals (OR 0.67, 95% CI 0.38, 1.18). Likewise, the two groups had comparable viral culture positivity (median [MD] 5 days for both) and shortened duration of infection (MD 0 days).				

CI: confidence interval; **MD**: mean difference

Explanations

a. the confidence interval crosses the line of unity

b. the study of Salvatorre was graded with fair quality based on New Castle Ottawa due to short follow up duration, in the study of Kissler the population is also not comparable to the general population for it consist of healthy young men.

c. the two studies have different outcomes, Salvatore has same duration of infectivity while on Kissler it favored vaccination with less than 2.3 days

d. the studies were imprecise, CI crosses line of unity

Table 2. Duration of Infectivity among Immunocompromised and Immunocompetent

Certainty assessment							Summary of findings				
Participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							Immuno-competent	Immuno-compromized		Risk if immune-competent	Risk if immuno-compromized
Time to PCR clearance											
3,758 (1 observational study)	not serious	not serious	not serious	Not serious	none	⨁⨁◯◯ low	3,222	436	-	The mean time to PCR clearance was 0	MD **0.98 higher** (0.84 higher to 1.15 higher)

CI: confidence interval; **MD**: mean difference

Table 3. Symptom- versus test-based criteria

Outcome	Certainty assessment							Effect estimate	Test accuracy CoE
	№ of studies	Study design	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	Mlild-moderate: virus cannot be cultured day 10 Severe: virus can be cultured at day 10-20 Immunocompromized: prolonged viral shedding up to 4 months	⊕◯◯◯ VERY LOW
Exces 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 (1,049 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 RT-PCR	1 study (4,729 patients)	Cross-sectional (cohort type accuracy study),	very serious[d,f]	serious	not serious	not serious	none	170/72 (98.8%)	⊕◯◯◯ VERY LOW

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Study design
b. Small sample size
c. Theoretical assumptions
d. Selection bias
e. Unclear index test
f. Problem with interpretation of index test

Appendix 5. Detailed Study Appraisal

Table 1. New Castle Ottawa Scale

Study	Selection					Comparability		Outcomes		Total quality score
	Representativeness of exposed Cohort	Selection of non-exposed cohort	Ascertainment of Exposure	Demonstration that outcome of interest was not present at the start of study	Adjust for the most important risk factors	Adjust for other risk factors	Ascertainment of outcome	Follow up length	Loss to follow up rate	
Clifford 2021	1	1	1	1	1	1	1	1	1	9
De Gier 2021	1	1	1	1	1	1	1	1	1	9
Kissler 2021	1	1	0	1	1	1	1	1	1	8
Salvatore 2021	1	1	1	1	1	1	1	0	1	8
Singanayagam 2021	1	1	1	1	1	1	1	1	1	9
Epstein 2021	1	1	1	1	1	1	1	1	1	9

Appendix 6. Characteristic of Ongoing Studies

Question: Can vaccination decrease the duration of infectivity of COVID 19 hence allowing earlier return to work?

Title Identifier Expected Completion Date	Intervention	Comparator/Control	Patients/Population Recruited	Outcomes
A Study of SARS CoV-2 Infection and Potential Transmission in Individuals Immunized With Moderna Vaccine NCT04811664 Match 23, 2021	Experimental: Immediate Vaccination Participants will receive Moderna COVID-19 Vaccine in 100 mcg dose given as 0.5 ml IM into the deltoid muscle on Day 1 and Day 29. Experimental: Immediate Vaccination Participants will receive Moderna COVID-19 Vaccine in 100 mcg dose given as 0.5 ml IM into the deltoid muscle on Day 113 and Day 141.	Control: Vaccine Declined Participants who prefer not to be vaccinated, If requested, participant will be offered vaccine if they have not received vaccine outside of the study	- 12,000 participants randomized 1:1 >Immediate Vaccination -Group 1 (at Months 0 and 1) or Standard of Care -Group 2, with vaccination given at Months 4 and 5 if not received off-study previously. -Up to an additional 6,000 participants will be enrolled into the Vaccine Declined *RECRUITING*	Primary Outcome Measures: - Efficacy of Moderna COVID-19 Vaccine against SARS-CoV-2 infection -Effect of Moderna COVID-19 Vaccine on peak nasal viral load Secondary Outcome Measures: -Impact on secondary transmission -Prevent serologically confirmed infection -Prevent disease confirmed PCR test and symptoms -Magnitude of viral load over time -Efficacy regardless of baseline serostatus -Immunogenicity -Immune response correlating with acquisition, viral load, secondary infection -Efficacy against asymptomatic infection -Efficacy on Viral load -Efficacy on Secondary transmission
Long-Term Experience and Health Effects of COVID-19 NCT04477902 July 2020	None *Observational		• -18 years of age or older • -Any gender specification • -Has consented to proceed with survey • -Is able to complete the survey via email on a regular basis • COMPLETED	Primary Outcome Measures Longitudinal -To gain on-going COVID-19 feedback/data to drive timely action locally and nationally in order to mitigate transmission -looking on Risk reduction and Quality of life
COVID 19 Infection in After Vaccination NCT05033834 September 5, 2021	Fully vaccinated	Partially vaccinated	Patients 18 years old and above of both genders. -Received at least one dose of COVID-19 registered vaccines. -Diagnosed COVID-19 positive after vaccination by real time PCR (confirmed case) or combined	Primary Outcome - assess the prevalence of COVID-19 infection after vaccination Secondary Outcome -evaluate the severity of infection after vaccination

Title Identifier Expected Completion Date	Intervention	Comparator/Control	Patients/Population Recruited	Outcomes
			clinical and radiological diagnosis (possible case). NOT YET RECRUITING	-Predict possible risk factors of post vaccination infection (adherence to protective measures)
National Cohort Study of Effectiveness and Safety of SARS-CoV-2 Vaccines (ENFORCE) NCT04760132 February 18, 2021	Cominarty Vaccine Moderna Astra-Zeneca	None	-Male or female eligible for SARS-CoV-2 immunization (as defined by SST in the national vaccination plan) -willing and able to comply with trial protocol (re-visits and biological samples) RECRUITING	Primary Outcome -Assessment of the effectiveness of citizens being vaccinated with one of the SARS-CoV-2 vaccine -minimal protective neutralising antibody titre Secondary Outcome -Number of beakthrough infections in the 24 months period will be used to compare the effectiveness between the vaccines -Assessment of the safety of the vaccines -Assessment of any Adverse Event

Appendix 7. Guidelines from Other Groups

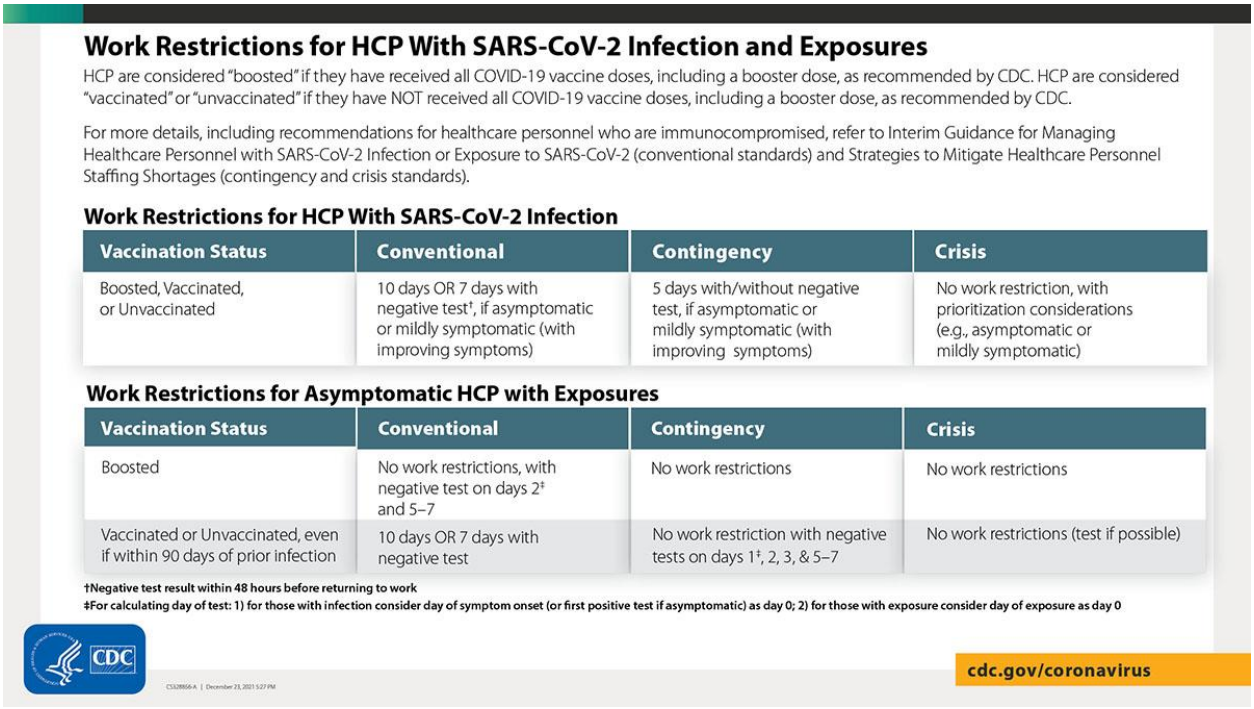
Table 1. DOH Return to Work Criteria (IATF Resolution No. 142; October 7, 2021)

Population	Criteria for Return to Work	
Unknown Vaccine status with Close contacts	Fourteen (14)-day quarantine has been completed regardless of negative test result	
Fully vaccinated individuals with Close Contact	Seven (7) day- quarantine period, provided that the individual remains asymptomatic for the duration of the seven-day period with the first day being the date immediately after the last exposure	
Suspect, probable or confirmed cases, regardless of vaccine status	Asymptomatic	Ten (10)-day isolation have passed from the first viral diagnostic test and remained asymptomatic throughout their infection
	Mild to Moderate COVID-19 confirmed	Ten (10)-day isolation have passed from onset of the first symptom, respiratory symptoms have improved (cough, shortness of breath), AND have been afebrile for at least 24 hours without use of antipyretic medications
	Severe and Critical COVID-19 confirmed	Twenty-one (21)-day isolation has passed from onset of the first symptom, respiratory symptoms have improved (cough, shortness of breath) AND have been afebrile for at least 24 hours without the use of antipyretic medications

Table 2. Interim Guidance for Managing Healthcare Personnel with SARS-CoV-2 Infection or Exposure to SARS-CoV-2 (CDC; Sep 10, 2021)

Population	Criteria
Symptom-based strategy	
Asymptomatic (NOT moderately to severely immunocompromised)	• At least 10 days have passed since the date of their 1st positive viral diagnostic test
Mild to moderate (NOT moderately to severely immunocompromised)	• At least 10 days have passed *since symptoms first appeared* **and** • At least 24 hours have passed *since last fever* without the use of fever-reducing medications **and** • Symptoms (e.g., cough, shortness of breath) have improved
Severe to critical (Moderately to severely immunocompromised)	• At least 10 days and up to 20 days* have passed *since symptoms first appeared* **and** • At least 24 hours have passed *since last fever* without the use of fever-reducing medications **and** • Symptoms (e.g., cough, shortness of breath) have improved • Consider consultation with infection control experts
Test-based strategy	
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 laboratory-based nucleic acid amplification test (NAAT) to detect SARS-CoV-2 RNA
Asymptomatic	• Results are negative from at least two consecutive respiratory specimens collected ≥24 hours apart (total of two negative specimens) tested using an FDA-authorized laboratory-based nucleic acid amplification test (NAAT) to detect SARS-CoV-2 RNA

NOTES:
1. HCP who are moderately to severely immunocompromised may produce replication-competent virus beyond 20 days after symptom onset or, for those who were asymptomatic throughout their infection, the date of their first positive viral test.
2. After returning to work, HCP should self-monitor for symptoms and seek re-evaluation from occupational health if symptoms recur or worsen.



Work Restrictions for HCP With SARS-CoV-2 Infection and Exposures

HCP are considered "boosted" if they have received all COVID-19 vaccine doses, including a booster dose, as recommended by CDC. HCP are considered "vaccinated" or "unvaccinated" if they have NOT received all COVID-19 vaccine doses, including a booster dose, as recommended by CDC.

For more details, including recommendations for healthcare personnel who are immunocompromised, refer to Interim Guidance for Managing Healthcare Personnel with SARS-CoV-2 Infection or Exposure to SARS-CoV-2 (conventional standards) and Strategies to Mitigate Healthcare Personnel Staffing Shortages (contingency and crisis standards).

Work Restrictions for HCP With SARS-CoV-2 Infection

Vaccination Status	Conventional	Contingency	Crisis
Boosted, Vaccinated, or Unvaccinated	10 days OR 7 days with negative test†, if asymptomatic or mildly symptomatic (with improving symptoms)	5 days with/without negative test, if asymptomatic or mildly symptomatic (with improving symptoms)	No work restriction, with prioritization considerations (e.g., asymptomatic or mildly symptomatic)

Work Restrictions for Asymptomatic HCP with Exposures

Vaccination Status	Conventional	Contingency	Crisis
Boosted	No work restrictions, with negative test on days 2‡ and 5–7	No work restrictions	No work restrictions
Vaccinated or Unvaccinated, even if within 90 days of prior infection	10 days OR 7 days with negative test	No work restriction with negative tests on days 1‡, 2, 3, & 5–7	No work restrictions (test if possible)

†Negative test result within 48 hours before returning to work

‡For calculating day of test: 1) for those with infection consider day of symptom onset (or first positive test if asymptomatic) as day 0; 2) for those with exposure consider day of exposure as day 0

CDC

cdc.gov/coronavirus

Table 3. Guideline for Management of Staff and Exposed Patients/Residents in Health and Social Care Settings (UKHD; Nov 30, 2021)

Population	Test Result	Return to Work Criteria
Symptomatic	Negative	• Medically fit to return • Subject to discussion with their line manager or employer and a local risk assessment
	Positive	• Medically fit to return • 10-day isolation period has ended • Afebrile for 48 hours without the use of medication to control fever
	Inconclusive	• Continue to self-isolate • Do another PCR test • Can return to work after isolation period has ended OR if repeat PCR is negative
Asymptomatic	Positive PCR or LFD self-antigen test followed by PCR	• 10-day isolation period has ended • Remain asymptomatic • If symptoms develop during the 10-day isolation period, self-isolate for 10 days form day of symptom onset

Table 4. Australian Health Department

Population	Test Result	Return to Work Criteria
Symptomatic	Fully vaccinated	• 14 days have passed since symptoms began **and** • No fever for past 72 hours **and** • Substantial improvement in respiratory symptoms of acute illness **and** • Patient is not significantly immunocompromised OR • At least 10 days have passed since symptoms began

Population	Test Result	Return to Work Criteria
		• Two consecutive negative PCR tests taken at least 24 hours apart from day 7 from symptom onset
	Unvaccinated, partially vaccinated, or unknown vaccine status	• 20 days have passed since symptoms began **and** • No fever for past 72 hours **and** • Substantial improvement in respiratory symptoms of acute illness **and** • Patient is not significantly immunocompromised OR • At least 14 days have passed since symptoms began • Two consecutive negative PCR tests taken at least 24 hours apart from day 10 from symptom onset
Asymptomatic	Fully vaccinated	• Completed 10 days of isolation since 1st positive PCR test • No symptoms have developed during the isolation period • Earlier release may be supported by some jurisdictions if PCR test is negative on the 7th day and no symptoms have developed throughout the 7-day isolation period
	Unvaccinated, partially vaccinated, or unknown vaccine status	• Completed 14 days of isolation since 1st positive PCR test • No symptoms have developed during the isolation period • Earlier release may be supported by some jurisdictions if PCR test is negative on the 10th day and no symptoms have developed throughout the 10-day isolation period
Significantly immune-compromised	Any vaccination status	• PCR tests are negative on at least 2 consecutive respiratory specimens collected at least 24 hours apart after day 7 from onset of symptoms