PHILIPPINE COVID-19 LIVING CLINICAL PRACTICE GUIDELINES

As of January 2022

Disclaimer

As a living guideline, the recommendations will be updated, and new recommendations will be added as the evidence evolves. The living recommendations are based on the best evidence available in scientific literature at the time of its formulation. However, this living CPG is not a comprehensive guide to all practice questions and management options on COVID-19. This is not meant to restrict the practitioner in using sound clinical judgement and sharing the decision with the patient, and from considering other management options according to the patient's particular needs and preferences. This CPG can serve to inform policy, but it is not meant to serve as a basis for approving or denying financial coverage or insurance claims merely because of nonconformance with recommendations. Neither are the recommendations supposed to be considered as legal rules for dictating certain modes of action to the exclusion of others.

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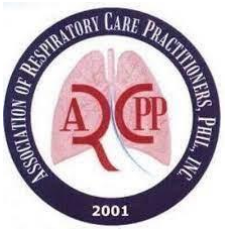
This project was implemented under the Institute of Clinical Epidemiology, National Institutes of Health (NIH), University of the Philippines Manila (UPM). It was completed with the valuable contribution of 190 people representing the different stakeholders

The Philippine COVID-19 Living CPG team dedicates this work to the patients braving their journey with this disease; to all Filipinos who are equally affected physically, emotionally, socially, economically, among others, and to all healthcare professionals contributing to this fight against COVID-19 through patient care and research.

Contact Us

Send us an email at covidcpg.ph@gmail.com for any questions or clarifications on the outputs and process of this Living CPG. You may also suggest a clinical question for the consideration of the Living Clinical Practice Guidelines COVID-19 Taskforce.

Participating Professional Societies and Institutions



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Executive Summary

Coronavirus disease 2019 (COVID-19) has grown into a pandemic and global crisis affecting multiple sectors of society. Over 180 million confirmed COVID-19 cases have been reported globally, with 2.8 million of these cases from the Philippines as of December 2021. Despite the national strategies implemented to curtail the health and economic impact of COVID-19 in the country, epidemiologic projections have yet to point to a foreseeable end to the pandemic, especially with the recent rise of variants with increased transmissibility. Thus, the Philippine COVID-19 Living CPG aimed to provide up-to-date, evidence-based recommendations on the management of COVID-19 among adults with or at risk for COVID-19. Thematic areas included in this CPG were screening and diagnosis, treatment, critical care and respiratory management, non-pharmacologic interventions, vaccines and prophylactic interventions, and adjunct interventions for COVID-19. This document also serves as an update of the PSMID-PCP-PCCP-PCHTM-PRA July 2020 Interim Guidance.

Following the standard CPG development process outlined in the DOH Manual for CPG Development and the GRADE methodology, 90 evidence summaries and 136 recommendations were generated by 47 consensus panelists representing 20 health organizations and institutions. 11 evidence summaries were updated within the first 6 months. The second phase of the project was conducted in the last quarter of 2021 wherein 73 evidence summaries were generated (32 new topics and 41 updated from the first phase). A summary of the latest recommendations is presented here.

The CPG recommendations were used in constructing management algorithms for COVID-19. Process evaluation using website analytics revealed that the CPG recommendations were mostly accessed in regions with the greatest number of new cases and active cases. Furthermore, a list of top evidence summaries accessed reflected topics that CPG users needed the most guidance on, or that remain to be contentious as of the present date.

Severity Classification of COVID-19

The Philippine COVID-19 Living CPG used the following definitions for the spectrum of severity of COVID-19 (as of October 28, 2021):

Mild COVID-19 – no pneumonia or desaturation, acute onset of fever and cough or any three (3) or more of the following: fever, cough, coryza, sore throat, diarrhea, anorexia/nausea/vomiting, loss of sense of smell or taste, general weakness/body malaise/fatigue, headache, myalgia

Moderate COVID-19 – with pneumonia*, BUT no difficulty of breathing or shortness of breath, RR < 30 breaths/min, oxygen saturation# >/= 94% at room air; **OR** without pneumonia but with risk factors for progression: elderly (≥60 years old) and/or with comorbidities

Severe COVID-19 – with pneumonia and ANY one of the following: signs of respiratory distress, oxygen saturation < 94% at room air, RR ≥30 breaths/minute, requiring oxygen supplementation

Critical COVID-19 – with pneumonia and ANY one of the following: impending respiratory failure requiring high flow oxygen, non-invasive or invasive ventilation, acute respiratory distress syndrome, sepsis or shock, deteriorating sensorium, multi-organ failure, acute thrombosis

*Pneumonia – evidence of lower respiratory disease during clinical assessment (e.g. cough, fever plus crackles) and/or imaging (CXR, ultrasound, CT scan)
#Proper recording of the O2 saturation: finger should be inserted in the oximeter for about 10-20 seconds, patient should be still and not talking

Summary of Recommendations on Screening and Diagnosis

Recommendation	Strength of Recommendation	Certainty of Evidence
We suggest doing an initial screening for ANY influenza-like illness, typical and atypical COVID-19 symptoms* within the past 14 days in apparently healthy adults and children, especially for individuals with known exposure to a laboratory-confirmed case of COVID-19 *Symptoms include but not limited to: fever/chills, cough, shortness of breath/dyspnea, sore throat, runny nose, myalgia, headache, fatigue/malaise, diarrhea, nausea/vomiting, abdominal pain, anosmia, ageusia, wheezing, chest pain, altered mental status, seizures, rash, pink eye*	Weak	Very Low
We suggest pulse oximetry with close clinical monitoring by qualified medical personnel in suspected and confirmed COVID-19 patients especially those who are at high risk for deterioration.	Weak	Very Low
We recommend the use of the following specimens as alternative specimens to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 among symptomatic and asymptomatic patients suspected of COVID-19 in hospital and outpatient settings: • oropharyngeal swab • saliva drool/spit and oral saliva • nasal swab/wash • throat swab **SARS COV-2 RT-PCR of nasopharyngeal swabs remains the diagnostic test of choice to confirm the diagnosis of COVID-19 among suspected individuals.*	Strong	Moderate Moderate Moderate Low
We suggest the use of saliva swab and posterior oropharyngeal saliva specimens as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 among symptomatic and asymptomatic patients with suspected COVID-19 in hospital and community/outpatient settings.	Weak	Low
We recommend against the use of sputum as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19.	Strong	Very Low
There is no evidence to recommend the use of bronchoalveolar lavage as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19.	-	-

Recommendation	Strength of Recommendation	Certainty of Evidence
We suggest the use of rapid antigen test for the diagnosis of symptomatic individuals suspected of COVID-19 as an alternative to RT-PCR if all the following conditions are met: ○ Individuals are in the early phase of illness (less than or equal to 7 days from onset of symptoms) ○ Testing kits demonstrated sensitivity of more than or equal to 80% AND have very high specificity of more than or equal to 97%	Weak	Low
We suggest against the use of rapid antigen test for screening purposes	Weak	Low
We suggest against the use of saliva as specimen for rapid antigen test in patients suspected of COVID-19 infection.	Weak	Low
We suggest against the use of rapid antigen tests alone in asymptomatic patients suspected of COVID-19 infection	Weak	Low
We suggest the use of rapid antigen tests for the diagnosis of individuals suspected of COVID-19 during the setting of an outbreak provided that all the following conditions are met: ○ Individuals are in the early phase of illness (less than or equal to 7 days from onset of symptoms); AND ○ Testing kits demonstrated sensitivity of more than or equal to 80% AND have very high specificity of more than or equal to 97%.	Weak	Very Low
There is insufficient evidence to recommend for or against the use of repeat antigen testing for screening or diagnosis of COVID-19.	-	Very Low
We suggest the use of self-administered rapid antigen test for the diagnosis of COVID-19 in symptomatic individuals, provided that ALL OF THE FOLLOWING conditions are met: 1. Ease of collecting samples is ensured; 2. Ease of interpretation is ensured; 3. Test kits have passed flex studies; AND 4. Individuals present with symptoms for less than 7 days.	Weak	Low
We suggest against the use of self-administered rapid antigen test for routine screening of COVID-19	Weak	Low
There is insufficient evidence to recommend the use of breath test in detecting COVID-19 infection.	-	Low
We suggest the use of pooled RT-PCR testing in targeted* low-risk and low-prevalence populations using a pool size of 5 in individuals suspected of COVID-19 infection. **Target population refer to the list of PSP and DOH*	Weak	Moderate

Recommendation	Strength of Recommendation	Certainty of Evidence
We suggest repeating RT-PCR testing when the initial RT-PCR test is negative among symptomatic patients highly suspected to have COVID-19 infection.	Weak	Low
There is insufficient evidence to recommend an RT-PCR cycle threshold cut-off value* to determine infectivity among COVID-19 confirmed patients * *Interpretation of RT-PCR cycle threshold values may vary and is dependent on the PCR assay used, gene target, sample type, and timing of sample collection*	-	Very Low
We suggest using antibody tests that accurately measure IgG or total antibodies to determine COVID-19 seroprevalence among adults when needed for public health purposes.	Weak	Very Low
We suggest against using antibody tests detecting IgM to determine COVID-19 seroprevalence among adults	Weak	Very Low
We suggest against using lateral flow immunoassay (LFIA) tests to determine COVID-19 seroprevalence among adults	Weak	Very Low
We recommend against routine measurement of SARS-CoV-2 antibody titers after vaccination.	Strong	-
We recommend against the use of SARS-CoV-2 antibody testing to diagnose presumptive COVID-19 reinfection among symptomatic patients previously diagnosed with COVID-19.	Strong	Very Low
We recommend the use of both clinical risk assessment and RT-PCR* to screen for COVID-19 among asymptomatic individuals scheduled for non-emergency surgery. **Use high-risk PPE regardless of RT-PCR or Ag-RDT test results in areas with prevalence of 1% or higher.*	Strong	Very Low
We recommend the use of both clinical risk assessment and Antigen-Rapid Diagnostic Test (Ag-RDT)** to screen for COVID-19 among asymptomatic individuals scheduled for non-emergency surgery when RT-PCR testing is not available or when turnaround time of results is prolonged. ***Ag-RDT should have a Sn of 80% and Sp of 97%*	Strong	Very Low
For asymptomatic, not severely immunocompromised fully vaccinated adults, we suggest the use of the following symptom-based criteria for return-to-work clearance: a. At least 8 days have passed since the first positive COVID-19 RT-PCR test; AND a. No symptoms have developed during this period.	Weak	Very Low
For asymptomatic, not severely immunocompromised not fully vaccinated adults, we suggest the use of the following symptom-based criteria for return to work clearance:	Weak	Very Low

Recommendation	Strength of Recommendation	Certainty of Evidence
a. At least 10 days have passed since the first positive COVID-19 RT-PCR test; AND 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: 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.	Weak	Very Low
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.	Weak	Very Low
For symptomatic, severely immunocompromised adults* with any vaccination status, we suggest the use of the following for return to work clearance: b. At least 22 days have passed since the onset of symptoms; AND c. No fever during the previous 24 hours; AND d. There has been substantial improvement in respiratory symptoms of the acute illness; AND a. PCR test results are negative on at least 1 respiratory specimen	Weak	Very Low
We suggest against the use of chest x-ray to diagnose COVID 19 infection among asymptomatic individuals.	Weak	Very Low
We suggest chest x-ray to facilitate rapid triage, infection control and clinical management among any of the following: a. patients with mild features of COVID 19 at risk for progression b. patients with moderate to severe features of COVID 19 patients with symptoms of at least 5 days duration	Weak	Very Low
We suggest against the routine use of CT scan for diagnosing COVID-19 among suspected patients with COVID-19 presenting at the emergency department if RT-PCR testing is readily available with timely results.	Weak	Very Low

Recommendation	Strength of Recommendation	Certainty of Evidence
If RT-PCR test is not available, we suggest using non-contrast chest CT scan for symptomatic patients suspected of having COVID-19 to guide early triage and management under the following conditions: • Patients with mild COVID-19 who are at risk for progression (elderly, with comorbidities) • Patients with moderate to severe COVID-19	Weak	Very Low
We suggest against the use of lung ultrasound alone in diagnosing patients with suspected COVID-19 infection.	Weak	Low
<u>To guide the decision to admit patients with COVID-19 to the hospital:</u> We suggest the use of the following scoring systems: a. Age, BUN, number of Comorbidities, CRP, SpO2/FiO2 ratio, Platelet count, Heart rate (ABC2-SPH) risk score, b. Confusion Urea Respiration Blood Pressure (CURB-65) severity score, c. Risk Stratification in the Emergency Department in Acutely Ill Older Patients (RISE-UP) score, and d. Rapid Emergency Medicine Score (REMS) There is insufficient evidence to recommend the use of the 4C Mortality Score, COVID Outcome Prediction in the Emergency Department (COPE) model, and Quick Sepsis-related Organ Failure Assessment (qSOFA) score. *(Very low certainty of evidence)*	Weak -	Low Very Low
<u>To guide in the expectant monitoring of hospitalized patients:</u> We suggest the use of the 4C Deterioration model. There is insufficient evidence to recommend the use of the Modified Early Warning Score (MEWS) and National Early Warning Score 2 (NEWS2) scoring systems.	Weak -	Low Very low
There is insufficient evidence to recommend the use of specific cut-off values of CRP, LDH and Ferritin to guide immunotherapy in COVID-19.	-	Very Low
We suggest the use of D-dimer to guide anticoagulation of patients with COVID-19, because of its significant association with mortality, thromboembolism, and worsening severity of disease.	Weak	Low
There is insufficient evidence in using symptoms*, biologic factors or severity of acute COVID-19 in predicting the development of long COVID-19 symptoms. **The most common symptoms of long COVID-19 identified were fatigue, dyspnea, sleep disturbance, anxiety or depression, and memory impairment*	-	Very Low

Recommendation	Strength of Recommendation	Certainty of Evidence
We suggest against the use of procalcitonin alone as a basis for initiating antibiotic therapy among COVID-19 confirmed patients	Weak	Very Low
If available, we recommend using a procalcitonin level of less than or equal to 0.25ng/ml for discontinuing antibiotic therapy among COVID-19 confirmed patients.	Strong	Very Low
We suggest against the use of PF4 antibody ELISA Heparin Induced Thrombocytopenia (HIT) test kits and non-ELISA rapid HIT test kits for COVID-19 Vaccine Induced Thrombosis and Thrombocytopenia (VITT).	Weak	Low
We suggest against using serum tryptase for patients who had anaphylaxis after receiving COVID-19 vaccine.	Weak	Very Low

Summary of Recommendations on Treatment

Recommendation	Strength of Recommendation	Certainty of Evidence
We recommend against the use of hydroxychloroquine/chloroquine, with or without azithromycin among patients with COVID-19 infection.	Strong	Moderate
We recommend against the use of azithromycin among patients with COVID-19 infection.	Strong	Moderate
There is insufficient evidence to recommend the use of favipiravir among patients with COVID-19.	-	Low
We suggest against the use of remdesivir in patients with COVID-19 infection who have O2 saturation ≥94% and do not require oxygen supplementation. We suggest the addition of remdesivir to dexamethasone in patients with COVID-19 infection who have O2 saturation < 94% and/or requiring oxygen supplementation. We suggest against the use of remdesivir in patients with COVID-19 infection who are already on invasive mechanical ventilation or ECMO. **For patients who progress to invasive mechanical ventilation while on remdesivir, the drug can be continued.*	Weak Weak Weak	Low Low Low
We suggest the use of molnupiravir within 5 days of symptom onset among non-hospitalized adult patients (18 years old and older) with mild to moderate COVID-19 infection with at least one risk factor* for progression.	Weak	Low
We suggest against the use of baloxavir as treatment for patients with COVID-19 infection.	Weak	Very low
We recommend against the use of oseltamivir as treatment for patients with COVID-19 infection.	Strong	Very low
We recommend against the use of lopinavir/ritonavir as treatment for COVID-19 infection.	Strong	Moderate
We recommend the addition of tocilizumab to systemic steroids in patients showing rapid respiratory deterioration and/or requiring high doses of oxygen (high-flow nasal cannula, noninvasive or invasive mechanical ventilation) and with elevated biomarkers of inflammation (CRP). We recommend against the use of tocilizumab among patients with COVID-19 infection who do not require oxygen.	Strong Strong	Moderate Very low

Recommendation	Strength of Recommendation	Certainty of Evidence
We suggest the use of baricitinib in addition to dexamethasone and remdesivir as treatment for hospitalized COVID-19 patients who require low-flow oxygen, high-flow oxygen, and non-invasive ventilation. There is insufficient evidence to recommend baricitinib as an alternative to tocilizumab as treatment for hospitalized COVID-19 patients.	Weak -	Low Very low
There is insufficient evidence to recommend the use of imatinib among patients with COVID-19 infection	-	Low
We suggest against the use of tofacitinib among hospitalized COVID-19 patients	Weak	Low
We suggest against the use of leronlimab as treatment for COVID-19	Weak	Very low
We suggest against the use of infliximab among patients with COVID-19 infection	Weak	Very Low
We suggest against the use of bevacizumab as treatment for patients with COVID-19 infection	Weak	Very Low
We recommend against the use of ivermectin for the treatment of patients of any severity We suggest against the use of ivermectin combined with doxycycline for the treatment of patients with COVID-19.	Strong Weak	Very low Very low
We suggest against the use of artesunate, artemisinin or pyronaridine tetraphosphate + artesunate in the treatment of COVID-19	Weak	Very Low
We suggest against the use of colchicine in the treatment of COVID-19.	Weak	Low
We suggest against the use of interferon in the treatment of hospitalized patients with moderate to critical COVID-19.	Weak	Very low
There is insufficient evidence to recommend the use of fluvoxamine among COVID-19 patients	-	Low
We suggest the use of bamlanivimab and etesevimab combination therapy as treatment for mild to moderate, non-hospitalized COVID-19 patients with at least 1 risk factor for progression to severe disease.	Weak	Low
We suggest casirivimab + imdevimab as treatment for symptomatic, non-hospitalized patients with at least 1 risk factor for severe COVID-19. We recommend against casirivimab + imdevimab as treatment for hospitalized COVID-19 patients.	Weak Strong	Moderate Low
There is insufficient evidence to recommend casirivimab-imdevimab as treatment for asymptomatic COVID-19 patients	-	Low
We suggest against the use of regdanvimab for the treatment of mild to moderate COVID-19	Weak	Very Low

Recommendation	Strength of Recommendation	Certainty of Evidence
We recommend against the use of convalescent plasma among patients with COVID-19 infection.	Strong	Moderate
We suggest against the use of intravenous immunoglobulin as treatment for moderate to severe COVID-19.	Weak	Very low
There is insufficient evidence to recommend using umbilical cord-derived mesenchymal stem cell therapy among adults with severe COVID-19.	-	Very low
There is insufficient evidence to recommend the use of inhaled corticosteroids as treatment for non-hospitalized patients	-	Very low
We recommend against the use of steam inhalation alone in the treatment of COVID-19.	Strong	Very low
There is no evidence to recommend the use of VCO as treatment among patients with COVID-19 infection.	-	-
There is insufficient evidence to recommend the use of Lianhua in treatment of patients with non-severe COVID-19	-	Very low
We suggest against the use of famotidine in the treatment of COVID-19.	Weak	Very low
We recommend against the use of ibuprofen as treatment among patients with COVID-19 infection.	Strong	Very low

Summary of Recommendations on Critical Care and Respiratory Management

Recommendation	Strength of Recommendation	Certainty of Evidence
We recommend the use of dexamethasone for up to 10 days among patients with severe and critical COVID-19.	Strong	High
We recommend the use of 6 mg to 12 mg per day of dexamethasone among patients with severe and critical COVID-19.	Strong	Moderate
We recommend against the use of corticosteroids among mild and moderate (non-oxygen requiring) COVID-19 patients	Strong	Moderate
We suggest that steroid therapy be initiated as soon as diagnosed or categorized as severe or critical COVID-19.	Weak	Very Low
We recommend the use of prophylactic over therapeutic dose anticoagulation among hospitalized patients with moderate, severe or critical COVID-19 disease unless there are any contraindications. We recommend the use of standard dose prophylactic anticoagulation over intermediate dose prophylactic anticoagulation among hospitalized patients with COVID-19 disease unless there are any contraindications.	Strong Strong	Low Moderate
We recommend against the routine use of antibiotics in patients with severe and critical COVID-19 infection, unless with suspicion of secondary bacterial co-infection. For patients on empiric antibiotics, they should be assessed daily for the need for discontinuation, continuation or de-escalation based on clinical and laboratory parameters.	Strong	Very low
There is insufficient evidence on the use of hemoperfusion among patients with COVID-19 infection.	-	Very low
We suggest the use of conservative fluid management rather than liberal fluid management strategy in mechanically ventilated adult COVID-19 patients with acute respiratory distress syndrome who have been adequately resuscitated*. **without tissue hypoperfusion and fluid responsiveness*	Weak	Low
We suggest self-proning in non-intubated patients with severe and critical COVID-19	Weak	Very low
There is insufficient evidence to recommend the use of side lying in non-intubated patients with severe and critical COVID-19	-	Very low
We suggest the use of high-flow nasal cannula oxygenation rather than non-invasive ventilation (e.g., helmet CPAP, mask NIV) in patients with COVID-19 infection and acute	Weak	Very low

Recommendation	Strength of Recommendation	Certainty of Evidence
hypoxemic respiratory failure who do not respond to conventional oxygen therapy.		
We suggest the use of a lung protective ventilation strategy (tidal volume 4-8 mL/kg predicted body weight and plateau pressure less than 30 cmH2O) in patients with COVID-19 infection and ARDS.	Weak	Very low
There is insufficient evidence to recommend the use of a higher PEEP strategy. We suggest individualizing PEEP or employ a PEEP strategy based on respiratory mechanics (i.e., compliance) in patients with COVID-19 infection.	Weak	Low
There is insufficient evidence to recommend a driving pressure limited strategy in patients with COVID-19 infection. We suggest keeping the driving pressure ≤ 14 cmH2O.	Weak	Low
We suggest the use of rapid sequence intubation for COVID-19 patients to reduce infection among healthcare workers performing the procedure.	Weak	Very low
We suggest the use of Venovenous Extracorporeal Membrane Oxygenation (ECMO) for judiciously selected COVID-19 patients with severe ARDS based on the Extracorporeal Life Support Organization (ELSO) criteria.	Weak	Very low
There is insufficient evidence to recommend the use of hyperbaric oxygen therapy for the management of COVID-19 patients.	-	Very low
We suggest light over deep sedation in COVID-19 patients who are mechanically ventilated and who are anxious or agitated.	Weak	Very low
We recommend against the use of nitric oxide among patients with COVID-19	Strong	Low
We recommend against the use of etoposide among patients with COVID-19 pneumonia in cytokine storm.	Strong	Very low
We recommend individualized pulmonary rehabilitation with pre-intervention medical clearance for long COVID patients who show residual respiratory symptoms.	Strong	Moderate
There is insufficient evidence to recommend the use of pirfenidone or nintedanib among patients with post COVID-19 pulmonary fibrosis	-	Very low

Summary of Recommendations on Non-Pharmacologic Interventions

Recommendation	Strength of Recommendation	Certainty of Evidence
We recommend that healthcare workers not directly taking care of COVID-19 patients, and other persons with high risk of exposure to COVID-19 should use properly fitted surgical masks instead of cloth masks.	Strong	Moderate
We suggest using a cloth mask that fits snugly on the face and made of at least two layers of cotton (e.g., t-shirt fabric) or non-woven nylon with aluminum nose bridge for the general public with low risk of exposure to COVID-19 in outdoor or indoor areas to prevent COVID-19 infections.	Weak	Low
We suggest against requiring the use of face shields in addition to face masks among the general public in non-healthcare settings.	Weak	Very low
We recommend the addition of face shields to face masks among the general public in areas with sustained community transmission of SARS-CoV-2.	Strong	Very low
We recommend using medical face mask plus face shield and standard personal protective equipment among health care workers not directly involved in the care of COVID-19 patients in areas with sustained community transmission of SARS-COV2.	Strong	Very low
There is no evidence to recommend the use of copper-containing over non-copper-containing masks to decrease COVID-19 transmission	-	-
We recommend the use of appropriate PPE to include mask (N95 or higher), fluid repellent sealed well-fitting long gown, double gloves, apron, full face shield or goggles or visor, scrub hat, and disposable shoe covers or dedicated closed footwear among surgeons engaged in aerosol generating procedures of suspected or confirmed COVID-19 patients.	Strong	Very low
We recommend the use of at least a surgical face mask and face shield for protection against COVID-19 infection among healthcare workers in the outpatient setting not performing aerosol generating procedures. Additional PPEs such as medical gowns and gloves should be worn as part of standard precautions during the performance of other procedures.	Strong	Very low
We recommend the use of the following PPE: disposable hat, medical protective mask (N95 or higher standard), goggles or face shield (anti-fog), medical protective clothing, disposable gloves and disposable shoe covers or dedicated closed footwear as an effective intervention	Strong	Moderate

Recommendation	Strength of Recommendation	Certainty of Evidence
in the prevention of COVID-19 among health care workers in areas with possible direct patient care of confirmed or probable COVID-19 patients and possible performance of aerosol generating procedures.		
We recommend against the use of ionizing air purifier to reduce COVID-19 transmission in the community.	Strong	Low
We recommend against the use of footbaths for the prevention and control of COVID-19 transmission.	Strong	Very low
We recommend against the use of misting tents or disinfection chambers for preventing and controlling COVID-19 transmission.	Strong	Very low
We recommend against the use of UV lamps or other UV devices in any place outside of a controlled clinic or hospital setting to prevent and control COVID-19 transmission.	Strong	Low
We suggest the use of HEPA filter as an option to improve air quality in indoor spaces with inadequate ventilation.	Weak	Low
We recommend the use of carbon dioxide (CO2) monitors in enclosed spaces to guide actions to improve ventilation and reduce transmission of SARS-COV-2	Strong	Moderate
In situations where there is shortage of filtering facepiece respirators (FFR), we suggest the use of Hydrogen Peroxide Vapor (HPV), Ultraviolet Germicidal Irradiation (UVGI), moist heat and peracetic acid dry fogging system (PAF) as options for N95 mask decontamination as recommended by the manufacturer based on their ability to reduce SARS-COV-2 load while still maintaining N95 mask integrity. We recommend against the use of autoclave and alcohol as these methods alter filtering facepiece respirator's (N95) integrity and degrade filtration efficacy.	Weak Strong	Low Very low
We suggest against the use of protective physical barrier enclosures (ex. aerosol box) for the prevention of COVID-19 among health care providers who perform aerosol generating medical procedures*. **Proper PPEs should be used by health care providers when performing aerosol-generating procedures.*	Weak	Very low
We suggest using protective physical barriers in areas where physical distancing cannot be adhered to (e.g., offices, reception desk)**. ***Adequate ventilation, physical distancing, use of facemasks and personal hygiene should still be maintained to prevent COVID-19 infections. Regular cleaning and disinfection of physical barriers should be practiced.*	Weak	Very low
We recommend cleaning and disinfecting surfaces using the appropriate disinfecting chemical agents such as	Strong	Low

Recommendation	Strength of Recommendation	Certainty of Evidence
0.5% sodium hypochlorite solution (bleach) or 70% alcohol to prevent COVID-19 infection. For high touch surfaces and high traffic areas, such as in the workplace, disinfection should be done before shift, intermittently during shift and after the shift. For household disinfection, once daily disinfection of high touch surfaces is recommended.		

Summary of Recommendations on Vaccines and Prophylactic Interventions

Recommendation	Strength of Recommendation	Certainty of Evidence
We recommend the use of the following vaccines to prevent symptomatic SARS-CoV-2 infection among adults: a. BNT162b2 (Pfizer/BioNTech) (given as 0.3ml (30ug) intramuscular injections, in 2 doses, 21 days apart) b. mRNA-1273 (Moderna) (given as 0.5ml (100ug) intramuscular injections, in 2 doses, 28 days apart) c. ChAdOx1 (AstraZeneca) (given as 0.5 ml (5 x 106 vp) intramuscular injections, in 2 doses, at least 12 weeks apart) d. Gam-COVID-Vac (Gamaleya) (given as rAd-26 0.5ml intramuscular injection, then rAd-5S 0.5 ml intramuscular injection 21 days after) e. Ad26.COV2.S (Janssen/Johnson&Johnson) (given as 0.5ml single dose intramuscular injection)	Strong	Moderate
We recommend the use of CoronaVac (Sinovac) (given as 0.5ml (600SU) intramuscular injection, in 2 doses, at 28 days apart) to prevent symptomatic SARS-CoV-2 infection among **healthy adults**.	Strong	Low
We recommend the use of BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya) and Ad26.COV2.S (Janssen/ Johnson&Johnson) vaccines to prevent symptomatic SARS-CoV-2 infection in **older adults (>64-year-old)**.	Strong	Low
We suggest the use of CoronaVac (Sinovac) to prevent SARS-COV-2 infection in **older adults (>60 years old)**	Weak	Low
We recommend the use of BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya), CoronaVac (Sinovac) and Ad26.COV2.S (Janssen/ Johnson&Johnson) vaccines in **pregnant and lactating women** after consultation with a physician.	Strong	Very low
We recommend the use of BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya) and Ad26.COV2.S (Janssen/ Johnson&Johnson) vaccines to prevent SARS-CoV-2 infection in **adults who have stable medical comorbidities and are at risk for severe infection.**	Strong	Moderate
We suggest the use of CoronaVac (Sinovac) to prevent SARS-CoV-2 infection in **adults who have stable medical comorbidities and are at risk for severe infection**.	Weak	Very low

Recommendation	Strength of Recommendation	Certainty of Evidence
We recommend the use of BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya), CoronaVac (Sinovac) and Ad26.COV2.S (Janssen/ Johnson&Johnson) vaccines to prevent SARS-CoV-2 infection in **immunocompromised patients** (i.e., diagnosed with HIV, hepatitis B and C, those with cancer undergoing chemotherapy, transplant patients receiving immune-suppression) after medical clearance from a physician.	Strong	Low
We recommend against the use of these vaccines for those who have known allergies to the contents / excipients of the vaccine, such as polysorbate: (ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya) and Ad26.COV2.S (Janssen/ Johnson&Johnson) and polyethylene glycol or PEG200 DMG (BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna).	Strong	Moderate to high
We recommend the use of BBIBP-CorV (Sinopharm), given as 200U (WIV04) or 4ug (HBO2) in 0.5 ml in 2 doses, 21 days apart, to prevent symptomatic and asymptomatic COVID-19 infection among healthy adults (18 to 59 years old)	Strong	Moderate
We suggest the use of BBIBP-CorV to prevent severe COVID-19 infection among healthy adults (18 to 59 years old)	Weak	Low
We suggest the use of BBIBP-CorV to prevent symptomatic COVID-19 infection in the following: a. Adults with co-morbidities b. Older persons	Weak	Very Low
There is insufficient evidence to recommend for or against the use of BBIBP-CorV to prevent COVID-19 infection among the following: a. Children (3-17 years old) b. Immunocompromised population c. Pregnant and lactating women	-	Very Low
In areas where the SARS-CoV-2 variants of concern are prevalent, there is insufficient evidence to recommend for or against the use of BBIBP-CorV to prevent COVID	-	Very Low
We recommend the use of the CoronaVac (Sinovac), [given as 0.5 mL (600SU)] to prevent symptomatic SARS-CoV-2 infection in: • Healthy Adults • Pregnant women in their first trimester after consultation with a physician • Pregnant women in their 2nd and 3rd trimester and lactating women • Adults who have medical comorbidities • Immunocompromised patients after medical clearance from a physician (the immunocompromised include those diagnosed with HIV, hepatitis B and C, those with cancer	 Strong Strong Strong Strong Strong	 Low Very Low Very Low Low Low

Recommendation	Strength of Recommendation	Certainty of Evidence
undergoing chemotherapy, transplant patients receiving immunosuppression)		
We suggest the use of CoronaVac (Sinovac) to prevent SARS-CoV-2 infection in older adults (>60 years old)	Weak	Low
We suggest against the use of CoronaVac (Sinovac) to prevent SARS-CoV-2 infection in children (3 to 17 years old)	Weak	Very Low
In areas where Delta is the predominant variant of concern, we recommend the use of CoronaVac (Sinovac)	Strong	Very Low
Under the current context of low vaccine coverage and inadequate vaccine supply, we recommend against booster vaccination using CoronaVac (Sinovac) in the healthy, adult population (18 years old and above)	Strong	Low
For immunocompromised patients who received primary CoronaVac (Sinovac) vaccination, we recommend for heterologous booster vaccination	Strong	Very Low
We recommend the use of BBV152 (Covaxin/Bharat), 0.5 mL/dose, in a two-dose regimen, 28 days apart for the prevention of symptomatic COVID-19 infection in healthy adults	Strong	Moderate
We suggest the use of BBV152 (Covaxin/Bharat), 0.5 mL/dose, in a two-dose regimen, 28 days apart for the prevention of symptomatic COVID-19 infection: a. Adults who have stable medical co-morbidities and are at high risk for severe infection b. Healthy, older adults (>60 years old) c. Pregnant and lactating women, after discussing with a physician d. Immunocompromised patients, after discussing with a physician	 Weak Weak Weak Weak	 Low Low - -
We suggest against the use of BBV152 (Covaxin/Bharat) for the prevention of COVID-19 in children and adolescents	Weak	-
We recommend against the use of BBV152 (Covaxin/Bharat) in individuals who have known allergies to its contents/excipients	-	-
We suggest the use of the rAd26 (Sputnik Light), given as 10^{11}vp per 0.5ml, single dose, intramuscularly to prevent symptomatic SARS-CoV-2 infection in: a. Healthy adults b. Older adults (60 years and older) c. Adults with comorbidities	Weak	Low
We suggest against the use of rAd26 (Sputnik Light) to prevent symptomatic SARS-CoV-2 infection in: a. Children (3-17 years) b. Pregnant and lactating women c. Immunocompromised	Weak	-

Recommendation	Strength of Recommendation	Certainty of Evidence
In areas where Alpha, Beta or Delta is the predominant variant of concern, we suggest the use of rAd26 (Sputnik Light) to prevent COVID-19 infection.	Weak	Low
We suggest the following homologous booster vaccination regimen for the general adult population: a. BNT162b2 b. mRNA-1273 c. ChAdOx1 d. Ad26.Cov2. e. CoronaVac f. BBIBP-CorV	 Weak Weak Weak Weak Weak Weak	 Low Low Very Low Very Low Very Low Very Low
There is insufficient evidence to recommend the following homologous booster vaccination in the general population: a. Gam-COVID-Vac b. BBV152	-	-
We suggest the following heterologous booster vaccination regimen for the general adult population: a. BNT162b2 primary, mRNA-1273 booster b. BNT162b2 primary, Ad26.CoV2.S booster c. mRNA-1273 primary, BNT162b2 booster d. mRNA-1273 primary, Ad26.CoV2.S booster e. ChAdOx1 primary, BNT162b2 booster f. Ad26.COV2.S primary, BNT162b2 booster g. Ad26.COV2.S primary, mRNA-1273 booster h. CoronaVac primary, BNT162b2 booster i. CoronaVac primary, ChAdOx1 booster j. BBIBP-CorV primary, BNT162b2 booster	Weak	Very Low
We suggest the following homologous booster vaccination for the immunocompromised population: a. BNT162b2 b. mRNA-1273	 Weak Weak	 Very Low Low
There is insufficient evidence to recommend the following homologous booster vaccination for the immunocompromised population: a. ChAdOx1 b. Ad26.CoV2.S c. CoronaVac d. Gam-COVID-Vac e. BBV152 f. BBIBP-CorV	-	-
We suggest the following heterologous booster vaccination regimen for the immunocompromised population: a. an mRNA vaccine primary, another mRNA vaccine booster b. an mRNA vaccine primary, ChAdOx1 booster c. BNT162b2 primary, mRNA-1273 booster d. BNT162b2 primary, Ad26.CoV2.S booster e. mRNA-1273 primary, Ad26.CoV2.S booster	 Weak Weak Weak Weak Weak	 Very Low Low Very Low Very Low Very Low

Recommendation	Strength of Recommendation	Certainty of Evidence
We recommend the use of heterologous COVID-19 vaccination for those with serious adverse event to the first dose.	Strong	Very Low
We suggest the use of heterologous COVID-19 vaccination in the event of the unavailability of the second dose in the recommended schedule	Weak	Very Low
In areas where the Delta variant is the predominant circulating variant, we recommend the use of the following vaccine to prevent symptomatic and severe COVID-19: a. 2 doses of BBV152 (Covaxin/Bharat) b. 2 doses of BNT162b2 (Pfizer) c. 2 doses of mRNA-1273 (Moderna) d. 2 doses of ChAdOx1 (Astra Zeneca) 2 doses of CoronaVac (Sinovac)	 Strong Strong Strong Strong Strong	 Moderate Low Low Low Very Low
In areas where the Delta variant is the predominant circulating variant, we suggest the use of the following vaccines to prevent symptomatic and severe COVID-19: a. Ad26.CoV2 (Janssen) b. Gam-COVID-Vac (Sputnik V)	 Weak Weak	 Low Low
We recommend the use of the BNT162b2 (Pfizer/BioNTech) vaccine, [given as 0.3 mL (30 ug) intramuscular injections, in 2 doses, 21 days apart] for children 12-15 years old to prevent symptomatic SARS-CoV-2 infection.	Strong	Moderate
We suggest the use of the mRNA-1273 (Moderna) vaccine, [given as 0.5 mL (100 ug) intramuscular injections, in 2 doses, 28 days apart] for children 12-17 years old to prevent symptomatic SARS-CoV-2 infection.	Weak	Low
We suggest against the use of Coronavac (Sinovac), [given as 0.5 mL (600 SU) intramuscular injection, in 2 doses, 28 days apart] for children 3-17 years old to prevent symptomatic SARS-CoV-2 infection.	Weak	-
There is no evidence on the use of ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya), Ad26.COV2.S (Janssen/ Johnson&Johnson) among children <18 years old to prevent SARS-CoV-2 infection.	-	-

Recommendation	Strength of Recommendation	Certainty of Evidence
We suggest the use of following vaccines, after the first trimester, for the prevention of COVID-19 infection in pregnant and lactating women.		
a. BNT162b2 (Pfizer)	Weak	Low
b. mRNA-1273 (Moderna)	Weak	Low
c. ChAdOx1 (AstraZeneca)	Weak	-
d. Ad26.CoV2.S (Janssen/Johnson&Johnson)	Weak	-
e. CoronaVac (Sinovac)	Weak	-
f. BBIBP-CorV (Sinopharm)	Weak	-
g. BBV152 (Covaxin)	Weak	-
	Weak	-
We suggest <u>against</u> the use of the following vaccines for the prevention of COVID-19 infection in pregnant and lactating women:		
a. Gam-CoV-Vac (Sputnik V)	Weak	-
b. NVX-2373 (Novavax)	Weak	-
We suggest against the use of BCG vaccine for the prevention of COVID-19 infection.	Weak	Very low
We suggest the use of casirivimab-imdevimab as day 4 post-exposure prophylaxis for COVID-19 close contacts, ages 12 years and above weighing at least 40kg, who are at risk for severe disease or hospitalization	Weak	Moderate
We recommend against the use of melatonin as prevention for COVID-19 infection.	Strong	Very low
We recommend against the use of Vitamin D supplementation to prevent COVID-19 infection.	Strong	Very low
We recommend against the use of zinc supplementation to prevent COVID-19 infection.	Strong	Very low
We recommend against the use of HCQ for pre-exposure prophylaxis in adults who are at high risk of exposure to COVID-19 cases.	Strong	Moderate
We recommend against the use of HCQ for post-exposure prophylaxis in adults who are exposed to COVID-19 cases.	Strong	Low
We recommend against the use of lopinavir/ritonavir for chemoprophylaxis in individuals exposed to COVID-19 patients.	Strong	Very low
We recommend against the use of ivermectin as COVID-19 prophylaxis for the general population.	Strong	Very low
We recommend against the use of ivermectin for COVID-19 as post-exposure prophylaxis for household contacts of confirmed COVID-19 patients.	Strong	Very low
We recommend against the use of ivermectin for COVID-19 as prophylaxis for healthcare workers.	Strong	Very low

Recommendation	Strength of Recommendation	Certainty of Evidence
There is insufficient evidence to recommend the use of saline nasal irrigation (SNI) to prevent COVID-19 in healthy individuals.	-	Very low
We recommend against the use of steam inhalation in the prevention of COVID-19	Strong	Very low
There is insufficient evidence on the use of aspirin as prophylaxis against COVID-19-induced coagulopathy among patients with COVID-19.	-	Very low
There is insufficient evidence to recommend the use of antiseptic mouthwash or gargle to prevent COVID-19 in healthy individuals.	-	Very low

Summary of Recommendations on Adjunct Interventions

Recommendation	Strength of Recommendation	Certainty of Evidence
There is insufficient evidence to recommend the use of zinc as adjunct treatment for patients with COVID-19 infection.	-	Low
We suggest against the use of B vitamins as adjunct in the treatment of patients with COVID-19.	Weak	Very low
There is insufficient evidence to recommend the use of Vitamin C as adjunct treatment for patients with COVID-19 infection.	-	Low
There is insufficient evidence to recommend the use of Vitamin D supplementation as adjunct treatment for patients with COVID-19 infection.	-	Very low
There is insufficient evidence to recommend the use of melatonin as adjunct treatment for patients with COVID-19 infection.	-	Very low
There is no evidence to recommend the use of virgin coconut oil as adjunct treatment for patients with COVID-19 infection.	-	-
There is no evidence to recommend Lagundi (Vitex negundo) as adjunctive treatment for patients with COVID-19 infection	-	-
There is no evidence to recommend Tawa-tawa (Euphorbia hirta) as adjunctive treatment for patients with COVID-19 infection	-	-
There is insufficient evidence to recommend the use of fatty acid supplements as adjunctive treatment for patients with COVID-19.	-	Low
We recommend against the use of intravenous N-acetylcysteine as adjunct treatment for patients with COVID-19 infection.	Strong	Moderate
We recommend continuing maintenance RAAS blockers for hypertension among patients with COVID-19 infection.	Strong	Moderate
There is insufficient evidence to recommend statins as adjunctive treatment in patients with COVID-19	-	Very low
We suggest that ibuprofen may still be used as symptomatic treatment of patients with COVID-19 infection if clinically warranted. Concurrent use of ibuprofen is not associated with worsening of COVID-19 outcomes.	Weak	Very low
There is insufficient evidence to recommend discontinuation of aspirin as maintenance therapy for underlying medical conditions in patients with COVID-19.	-	Very low

Recommendation	Strength of Recommendation	Certainty of Evidence
We recommend against the use of any antiseptic mouthwash as an adjunctive therapy for patients with COVID-19	Strong	Very Low
We recommend against the use of any antiseptic mouthwash to prevent COVID-19 in healthy individuals	Strong	Very Low
We suggest against the use of nasal spray as an adjunct to treatment of COVID-19 infection	Weak	Low

INTRODUCTION

The coronavirus disease 2019 (COVID-19) has grown into a pandemic and global crisis infecting more than 572 million people worldwide and causing more than six million deaths [1]. As of August 27, 2022, the number of cases in the Philippines has reached more than 3.8 million with 61, 613 COVID-19 related deaths [2]. The national strategy towards the new normal is prevention, detection, isolation, treatment, and reintegration. Since the launch of the national vaccination campaign against COVID-19 in March 2021, the Philippines had 72 million fully vaccinated individuals as of August 26, 2022. Notwithstanding these strategies, none of the epidemiologic projections on COVID-19 in the Philippines point to a foreseeable end of the pandemic, especially with the rise of variants with increased transmissibility.

Given the magnitude of the impact of COVID-19 in the country, in addition to the concurrent infodemic potentially causing misinformation and disinformation among clinicians, public health officials, and policy makers, there is a need for evidence-based guidelines for the effective management and control of the spread of this disease. Existing international guidelines and living systematics reviews on COVID-19 need to be contextualized for the recommendations to be applicable to local end-users and other stakeholders.

Objectives

The Philippine COVID-19 Living CPG aimed to provide up-to-date, evidence-based recommendations on the treatment, diagnosis, infection prevention, and control of COVID-19 among adults with or at risk for COVID-19 using the GRADE methodology. Specifically, this project:

1. Identified priority questions related to COVID-19 management, infection prevention and control
2. Summarized available literature on each priority question related to COVID-19 management, infection prevention and control
3. Formulated recommendations on COVID-19 management, infection prevention, and control based on the evidence summaries presented
4. Updated selected recommendations on COVID-19 management, infection prevention and control based on predefined parameters

Target Population

This CPG was intended to apply primarily for adult Filipinos aged 18 years old and above diagnosed with, or at risk of COVID-19. The severity of COVID-19 was indicated in several recommendations if it is severity-specific. Other clinical characteristics, such as comorbidities, that would affect the recommendations were indicated clearly in the wording, as appropriate.

Intended Users

The following groups are the expected target users of this Living CPG:

1. Public health professionals, such as provincial/city/municipal health officers, program managers, public health nurses, etc., to inform their localized decisions in implementing national policies on COVID-19, such as on public health standards, management, and preventive interventions.
2. Clinicians in the hospitals, quarantine centers, and other treatment facilities handling COVID-19 patients, such as generalist physicians, internists, infectious disease specialists, pulmonologists, other specialist physicians, staff nurses, hospital administrators, etc., to inform their individual clinical decisions from diagnosis to treatment and prevention.
3. Academicians and researchers, especially those working on related COVID-19 topics, to guide their research initiatives in addressing the identified gaps during the evidence synthesis of this CPG
4. Policymakers and local government officials, such as the Department of Health, Philippine Health Insurance Corporation, Inter-agency Task Force for the Management of Emerging Infectious Diseases, Food and Drug Administration, Health Technology Assessment Council, etc., to inform their national policies on COVID-19, including standards of care in outpatient and in-patient settings

CPG DEVELOPMENT METHODOLOGY

The development process of the Philippine COVID-19 Living CPG followed the Philippine Department of Health's Manual for Clinical Practice Guideline Development [5] and the Grading of Recommendations, Assessment, Development and Evaluation or GRADE Approach [6]. The reporting of this CPG manuscript was based on the AGREE Reporting Checklist [7]. Some of the questions in the base CPG were updated following the living CPG methodology [8].

Overview of Philippine COVID-19 Living CPG Development Process

The following development process was undertaken by the Philippine COVID-19 Living CPG. Further details were presented in succeeding sections.

1. **Guideline Preparation** – The Steering Committee (SC) identified and convened members of the Living CPG task force: Evidence Review Experts (ERE) or Technical Working Group (TWG) and the Consensus Panel. A total of 24 specialty societies and stakeholders were represented in the second phase of the Philippine COVID-19 Living CPG. The SC reviewed and determined the scope of the guideline and also identified new and existing interventions that needed to be updated. Key questions were judged according to the criteria enumerated in the DOH Manual for CPG development

   Several orientation sessions were conducted for the technical reviewers and consensus panel members on the COVID CPG development process. Technical reviewers were re-trained on evidence synthesis and the GRADE methodology. Consensus panel members were oriented on how to interpret the evidence summaries and apply the GRADE evidence-to-decision framework.

2. **Evidence Synthesis** - Evidence Review Experts (ERE) reviewed and appraised existing CPGs, systematic reviews, preprints and published literature, prepared evidence summaries, and drafted evidence-based recommendations. During the second phase of the CPG, five technical coordinators with expertise in CPG Development and Evidence-Based Medicine oversaw the retrieval and appraisal of evidence and the creation of the draft recommendations. Technical assistants were also assigned to each task force as search specialists to perform continuous surveillance for new evidence on existing guideline questions. Four technical writers ensured that the evidence summaries are uniform, concise, and clear. The Steering Committee organized several practice sessions for the ERE to finalize their presentations, and discuss them with other EREs, Steering Committee, and technical experts. Evidence summaries were collated, formatted, and prepared for presentation to the consensus panel.

3. **Evidence to Decision** – Upon completion of the evidence summaries by the ERE, several *en banc* meetings with the multidisciplinary Consensus Panel were conducted to present and discuss the evidence summaries and draft recommendations. The consensus panel voted on the strength and direction of the recommendations.

4. **Living CPG Process** – From the base CPG created in the above standard guideline development process, some of the questions were prioritized to a *living* status and updated depending on the following: (1) current priority for decision making, or (2) new evidence available likely to change existing recommendation [8]. The EREs working on living recommendations performed continued surveillance of literature to update the living systematic review with new evidence and updated the Evidence Summary tables and draft recommendations for the panel discussion. The Steering Committee reviewed the updated evidence summary document and revised draft recommendation. As needed, the Consensus Panel concerned was convened again in an online meeting to discuss the new evidence and any changes in the living recommendation.

The Living CPG Development Process is summarized in Figure 1 below:

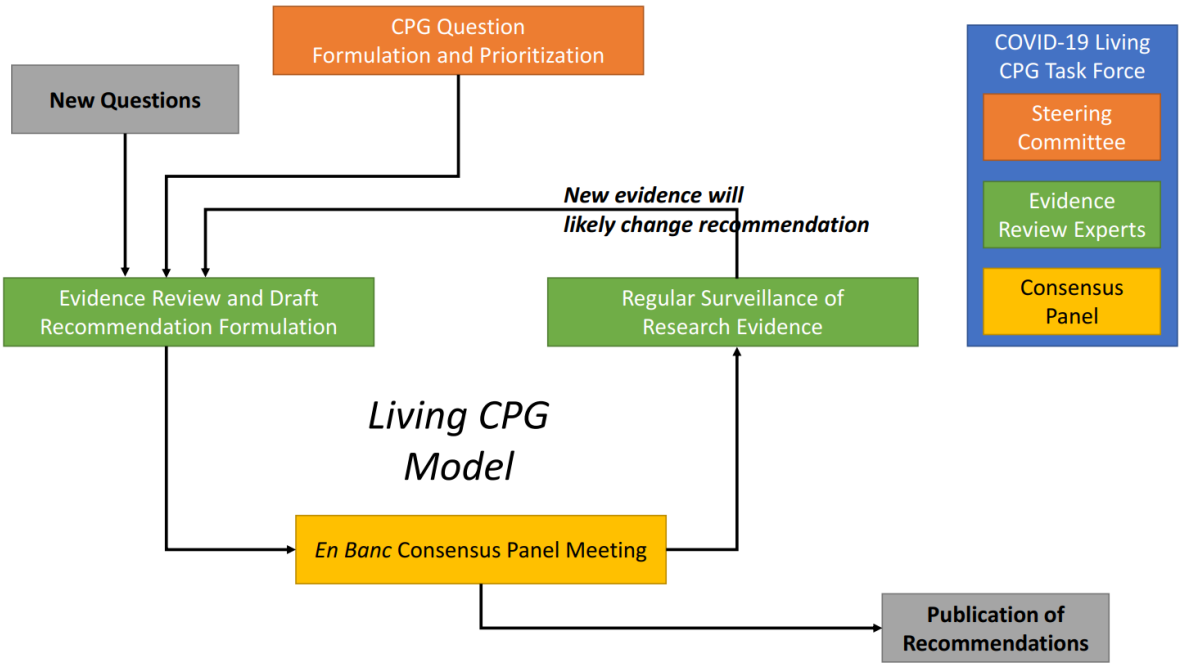


Figure 1. Philippine COVID-19 Living CPG Development Process.

Guideline Preparation

COMPOSITION OF THE GUIDELINE TASK FORCE

The Steering Committee were composed of members representing one or more of the following expertise: CPG methodology, clinical epidemiology, family medicine, internal medicine, infectious diseases, pulmonology and critical care, infection control, and public health. Aside from clinicians, there was also a representative from the DOH. All members have technical knowledge and expertise on clinical management and policy development related to COVID-19.

The Evidence Review Experts (ERE) were composed of members with one or more of the following expertise: methodologists, clinical epidemiologists, evidence-based medical practitioners. They preferably had previous training and experience in CPG development and evidence synthesis.

The Consensus Panel was composed of multi-sectoral representatives such as health practitioners, both specialists and non-specialists, and patient advocates. Aside from clinicians, there were also representatives from the DOH. All panel members were the designated representatives of the relevant professional groups and stakeholder organizations and were selected based on their content expertise and experience, and potential conflicts of interest. The panelists, being involved directly in COVID-19 patient care and some having been infected themselves, acted also as patient advocates to reflect patients' and public's views and preferences.

Refer to Appendix A for the full composition of the Philippine COVID-19 Living CPG Task Force, including their professional and institutional affiliations. Their declarations of conflicts of interest are presented in Appendix B.

KEY CLINICAL ISSUES AND QUESTIONS

The Philippine COVID-19 Living CPG tackled six central themes in COVID-19, and each theme was represented by a task force headed by a technical coordinator:

- Screening and diagnosis
- Treatment
- Critical care and respiratory management
- Non-pharmacologic interventions
- Vaccines and prophylactic interventions
- Adjunct interventions

Table 1 below summarizes the topics covered per panel. The Steering Committee, together with the TWG and other key stakeholders, finalized the health questions to be addressed in the CPG. The detailed population, interventions/ tests, and outcomes were presented in the appropriate sections for each theme.

Table 1. Topics covered in the Philippine COVID-19 Living CPG.

Screening and Diagnosis	Treatment
• 14-day COVID-19 symptom-based test • Pulse oximeter monitoring • Choice of sample for RT-PCR (including saliva testing) • Rapid antigen tests • Self administered rapid antigen tests • Breath test • Pooled sample testing using RT-PCR • Repeat testing using RT-PCR • Antibody testing for reinfection • Antibody tests (LFIA, ECLIA, and ELISA) for seroprevalence • Clinical risk assessment and RT-PCR testing for patients undergoing surgery • Return to work after COVID-19 (non HCW and HCWs) • Thoracic Imaging in the diagnosis of COVID-19 (Chest X-ray, Chest CT Scan and Lung Ultrasound) • Prognostic factors of severe disease and mortality • LDH, CRP, and Ferritin for immunotherapy • D-dimer for anticoagulation • Heparin Induced Thrombocytopenia (HIT) Test kits • Risk Factors for Long COVID • Serum Tryptase	• Hydroxychloroquine (HCQ) or Chloroquine (CQ) with or without Azithromycin • Azithromycin • Favipiravir • Remdesivir • Molnupiravir • Baloxavir • Oseltamivir • Lopinavir/ritonavir • Tocilizumab • Baricitinib • Imatinib • Tofacitinib • Leronlimab • Infliximab • Bevacizumab • Ivermectin • Artesunate • Colchicine • Interferon • Fluvoxamine • Bamlanivimab-etesevimab • Casirivimab-imdevimab • Regdanvimab • Convalescent Plasma • Intravenous immunoglobulin • Mesenchymal stem cell therapy • Inhalational steroids • Steam inhalation • Virgin coconut oil • Traditional Chinese Medicine (Lianhua capsules) • Famotidine • Ibuprofen
Critical Care and Respiratory Management	**Non-Pharmacologic Interventions**
• Systemic corticosteroids • Anticoagulation • Empiric antimicrobials • Hemoperfusion • Fluid management • Proning and side-lying in non-intubated COVID-19 patients • High-Flow Nasal Cannula (versus Non-invasive ventilation or Conventional oxygen therapy) for acute hypoxemic respiratory failure • Non-invasive ventilation	• Cloth masks • Face masks and protective eyewear (face shield or goggles) • Copper mask • Ionizing air filters • Foot bath • Misting tents • UV lamps • HEPA filter • Carbon dioxide monitors • Methods of decontaminating N95 mask for reuse

- Lung protective ventilation, PEEP, and driving pressure for ARDS patients
- Rapid sequence intubation versus delayed intubation
- ECMO
- Hyperbaric Oxygen Therapy
- Sedation, neuromuscular blockade and paralysis
- Inhaled Nitric Oxide
- Etoposide for cytokine storm
- Pulmonary rehabilitation for patients with long COVID-19
- Pirfenidone vs. Nintedanib for Long COVID

- Minimum PPE during surgeries
- PPEs for HCWs in OPDs in areas with sustained community transmission
- PPEs for HCWs in the hospital setting (wards, ICUs, and emergency rooms)
- Acrylic physical barriers
- Methods of surface disinfection

Vaccines and Prophylactic Interventions	Adjunct Interventions
• COVID-19 Vaccines • Vaccination for children • Vaccination for Pregnant and Lactating Women • Booster Dosing • Heterologous vaccination • Vaccines against the Delta variant • Hydroxychloroquine (HCQ) or Chloroquine (CQ) • Lopinavir/ Ritonavir • Melatonin • Nasal saline irrigation • Antiseptic mouthwash/ gargle • Steam inhalation • Vitamin D • Zinc supplements • BCG vaccine • Ivermectin • Aspirin as prophylaxis against COVID-19 induced coagulopathy • Casirivimab-imdevimab	• Zinc • Vitamin B • Vitamin C • Vitamin D • Melatonin • Virgin Coconut Oil • Lagundi • Tawa-tawa • Oral fatty acid supplements • N-Acetylcysteine • RAAS antagonists as maintenance therapy • Statins • Ibuprofen and worse COVID-19 symptoms • Aspirin as maintenance therapy • Antiseptic mouthwash or gargle • Nasal sprays

Evidence Synthesis

The general approach for the evidence reviews for this CPG was the identification of existing systematic reviews and CPGs on COVID-19. Reference lists were checked vis-a-vis the search yield of the evidence reviewers. If there were none found, or the systematic reviews and CPGs were not high-quality nor updated, a *de novo* systematic review was done. Otherwise, high-quality and up-to-date review CPG evidence summaries were used for generating recommendations.

Each clinical question was reviewed by at least two reviewers, with the oversight of an expert technical coordinator. This was done to ensure reproducibility of the following study assessments: Inclusion/ exclusion of studies, study quality appraisal, and data extraction.

SEARCH METHODS

Primary studies and systematic reviews were searched from December 2020 to December 2021, using the following sources:

- Electronic databases: MEDLINE through PubMed and Cochrane CENTRAL Database
- Pre-print databases: ChinaXiv.org, MedRxiv.org, and BioRxiv.org
- Trial registries: USA ClinicalTrials.gov, China ChiCtr.org, and WHO ICTRP
- Living COVID-19 databases: COVID-19 Open Living Evidence Synthesis (https://covid-nma.com/), COAP Living Evidence on COVID-19 (https://zika.ispm.unibe.ch/assets/data/pub/search_beta/), and L-OVE Database (https://iloveevidence.com)
- COVID-19 Living CPGs: Australia (https://covid19evidence.net.au/), US NIH (https://www.covid19treatmentguidelines.nih.gov/), and WHO (https://www.who.int/publications/i/item/therapeutics-and-covid-19-living-guideline)

A final check of the comprehensiveness and completeness of the search was done by checking references used in relevant articles on the UpToDate Clinical Decision Support System (http://uptodate.com/).

Detailed search strategies for each clinical question were presented in the respective full-text evidence summaries. Refer to Appendix C for the search terms used for COVID-19 and the study design filters.

INCLUSION AND EXCLUSION CRITERIA

As a rule, questions on clinical efficacy and safety of interventions were answered using randomized controlled trials. If there were limited or no RCTs available, observational studies were included. For questions on diagnostic tests, appropriately designed diagnostic accuracy studies were sought.

The target population depended on the clinical question, whether it was on patients with COVID-19, individuals at high risk of COVID-19, or the general population. Due to the limited resources available, only those articles in the English language were

included. Specific details on inclusion and exclusion criteria were presented in the respective full-text evidence summaries.

STUDY QUALITY ASSESSMENT

Quality appraisal of primary studies and systematic reviews was done by at least two independent reviewers. The Painless EBM questions on validity [8] were prescribed to be used for quality appraisal of therapy, diagnosis, harm, and systematic review questions. Risk of bias assessments were summarized in evidence tables within the respective full-text evidence summaries.

Certainty of evidence for each outcome was determined using the GRADE approach [5]. The overall certainty of evidence was determined by the ERE by considering the lowest certainty across all critical and important outcomes. There were different factors considered by the reviewers in determining the certainty of evidence, as summarized in Table 2.

DATA SYNTHESIS

Meta-analysis was done to pool the treatment effects or the diagnostic performance indices, as appropriate to the clinical question. When studies and results cannot be combined, a narrative synthesis was done, and relevant information was summarized in a table.

Table 2. Factors influencing certainty of evidence [6].

Certainty of Evidence	Study Design – Intervention Questions	Study Design – Diagnosis Questions	Factors that Decrease COE (by 1 to 2 levels)	Factors that Increase COE (by 1 to 2 levels)
High	Randomized controlled trial	Appropriate cross-sectional or cohort studies in patients with diagnostic uncertainty	• Risk of Bias • Inconsistency • Indirectness • Imprecision • Publication Bias	• Large magnitude of effect • Plausible confounding • Dose-response gradient
Moderate				
Low	Observational study			
Very Low				

Evidence to Decision: Formulating Recommendations

The Consensus Panel evaluated the direction and strength of recommendation using the GRADE approach and the Evidence to Decision Framework, based on the (1) overall quality of evidence for each question, (2) balance between benefits and harms, (3) values, preferences, and burden on patients, (4) cost and resource use, and (5) other considerations such as feasibility, equity and acceptability.

CERTAINTY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

The certainty of evidence was one of the bases of the Consensus Panel in making the final recommendation. Table 3 shows the definition and implication of each:

Table 3. Definitions and Implications of each GRADE Certainty of Evidence [6].

GRADE Certainty of Evidence	Definition	Implication
High	We are very confident that the true effect lies close to that of the estimate of the effect.	Further research is **very unlikely to change confidence** in the estimate of effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is **likely to have an important impact on confidence** in the estimate of effect and may change the estimate
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.	Further research is **very likely to have an important impact on confidence** in the estimate of effect and is likely to change the estimate
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	Any estimate of effect is **very uncertain**

The strength of recommendation could either be strong or weak. However, there were three reasons where the consensus panels were unable to make a recommendation [6]:

1. Confidence in effect estimates is so low that the panels feel a recommendation is too speculative.
2. Trade-offs are so closely balanced, and the values and preferences, and resource implications are not known or too variable.
3. Management options have very different undesirable consequences, and individual patients' reactions to these consequences are likely to be variable

A strong recommendation was stated as "We recommend/ We recommend against…", while a weak recommendation was worded "We suggest/ We suggest against…".

Finally, when no recommendation can be made, the sentence starts with “There is no/ insufficient evidence to recommend…”
The implications of strong and conditional recommendations are enumerated in Table 4 [5].

PATIENT VIEWS AND PREFERENCES

Patient views and preferences were represented by the nurses who had direct patient care encounters and consensus panel members who were directly involved in various aspects of COVID-19 care: clinician, administrator, researcher. Some of the panelists were COVID-19 patients themselves or had relatives and friends afflicted with COVID-19. This strategy ensured that patient views and preferences are still considered in the formulation of recommendations.

Table 4. Implications of the Strength of Recommendation to Patients, Clinicians, and Policymakers [6].

	Strong Recommendation	Weak Recommendation
Patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for different patients. Clinicians must help each patient arrive at a management decision consistent with her or his values and preferences.
Policy makers	The recommendation can be adopted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and the involvement of many stakeholders. Policies are also more likely to vary between regions.

RESOURCE IMPLICATIONS

Since COVID-19 is a relatively new disease that is being studied internationally, and most COVID-19 diagnostics and interventions are still investigational, there were limited economic evaluations available. In the absence of this information, consensus panelists considered the cost and other local resources needed for the recommendations. This discussion could be found in the *Consensus issues* subsection of each evidence summary, when appropriate.

RATING OF OUTCOMES

The Consensus Panel rated outcomes for each set of clinical questions according to whether they were critical, important but not critical, or of low importance for decision making. Critical outcomes were primary factors that should influence a recommendation, while those with lower importance did not bear on these recommendations. On a scale of 1-9, those rated 7-9 were critical outcomes, 4-6 were important but not critical outcomes, and 1-3 were outcomes of limited importance. Table 5 below shows the result of the ranking of outcomes per CPG panel:

Table 5. Outcome ratings for each CPG panel.

CPG Panel	Critical Outcomes	Important but not critical outcomes
Screening and Diagnosis	• Sensitivity and specificity • Positive and negative predictive values • Development of COVID-19 • Mortality • Positive and negative likelihood ratios • False positive and false negative rates • Resource savings • Number of RT-PCR positive samples	• Psychological effects of testing • Physical harm of testing
Treatment – Outpatients and Mild to Moderate COVID Patients	• All-cause mortality • Clinical improvement/ Time to clinical cure • Respiratory distress/ Need for mechanical ventilation or oxygen support therapy • Progression to severe COVID-19 • Need for hospitalization or ICU admission (including duration) • Adverse events • Serious adverse events	• Duration of mechanical ventilation • Improvement in Chest x-ray or CT scan • Viral negative conversion/ viral clearance • Time to negative conversion (PCR)
Treatment – Severe to Critical COVID Patients	• All-cause mortality • Clinical improvement/ Time to clinical cure • Respiratory distress/ Need for mechanical ventilation • Hospitalization • ICU admission • Need for supportive oxygen therapy • Adverse events • Serious adverse events	• Duration of mechanical ventilation • Duration of hospitalization • Viral negative conversion/ Viral clearance • Improvement in Chest X-ray/ CT Scan • Time to negative conversion (PCR)
Critical Care and Respiratory Management	• COVID-19 related deaths • Need for mechanical ventilation • Clinical improvement • Length of hospital and ICU stay • Thromboembolic events • Bleeding • Serious adverse events	• Duration of Mechanical ventilation • Adverse events • Improvement in oxygenation • Length of hospital and ICU stay
Non-Pharmacologic Interventions	• Incidence of COVID-19 infection (any severity) • Filtration efficacy • Prevention of influenza-like illness • Safety of use	
Vaccines and Prophylactic Interventions	• COVID-19-related deaths • Incidence of COVID-19 • Incidence of hospitalization or ER visit • Incidence of mechanical ventilation • Adverse events • Serious adverse events	

Vaccines and Prophylactic Interventions - Pregnant and Lactating Women	• Newborn antibody levels
	• Pregnancy outcomes:
	  ○ Gestational Hypertension
	  ○ Gestational Diabetes
	  ○ Premature Rupture of membranes
	  ○ IUGR
	• Delivery Outcomes
	  ○ Spontaneous Abortion
	  ○ Fetal death in utero or still birth
	  ○ Preterm delivery
	  ○ APGAR Score <7
	• Neonatal outcomes
	  ○ NICU Admission
	  ○ Presence of congenital anomalies
	• Breastmilk antibodies
	• Changes in breastmilk
		• Fetal, placental or cord blood antibody levels

Adjunct Interventions	• Clinical recovery/improvement • All-cause mortality • Need for/ Duration of mechanical ventilation • Need for hospitalization • Adverse events • Serious adverse events • Clinical deterioration/ progression of respiratory distress/progression to severe COVID-19 • Need for ICU admission • Need for supportive oxygen therapy/mechanical ventilation	• Time to negative conversion • Duration of hospital stay • Improvement in Chest x-ray/CT Scan • Duration of mechanical ventilation

CONSENSUS PROCESS

A skilled facilitator moderated the discussions during the consensus meetings. Each member voted on the draft recommendation as follows: yes, no, or abstain. The consensus was defined as at least 75% agreement among the members for both the direction and strength of recommendation. If consensus was not reached, members discussed the reasons in support of their votes for or against the recommendation. The voting was repeated, up to three rounds, until a consensus was reached. Any issues left unsettled after the *en banc* meeting were finalized through a modified Delphi activity.

There were two recommendations that did not reach a consensus after voting for three rounds and a repeat meeting after a modified Delphi activity. These were on the recommendations for heterologous booster vaccination (October 2021) and the use of nasal sprays as adjunctive therapy (December 2021). The recommendation on heterologous vaccination has been resolved as of December 27, 2021 following an update on the evidence available.

Guideline Dissemination

Three methods were used in the dissemination of the Philippine COVID-19 Living CPG: (1) online webpage, (2) Living Recommendations document, and (3) full-text CPG manuscript.

The online webpage of the Philippine COVID-19 Living CPG (Figures 2 and 3) was hosted on the PSMID website. This was launched on March 21, 2021, and has undergone improvements from the feedback of CPG users and members of the Living CPG task force.

The short *Living Recommendations document* (Figure 4) contained the content in the PSMID website, including the introduction, CPG methodology, members of the living CPG task force, and the actual recommendation statements. The evidence summaries were not included in this document. This shorter format allowed for an easily accessible document for use by practitioners and selected laypersons.

This full-text CPG manuscript, as well as the complete evidence base, will be submitted to the DOH National Clearinghouse for national promotion regarding use and uptake of the recommendations, including activities such as releasing a department memorandum to notify stakeholders, publicizing the CPG through the DOH newsletter and to other appropriate agencies, and issuing press releases, news articles, and social media posts. The final manuscript will be made available as electronic copies through the websites of DOH and PSMID.

Furthermore, several dissemination fora have already been conducted during relevant meetings of professional societies, where several members of the Steering Committee and Consensus Panels presented. More avenues for dissemination will be undertaken to promote the use and value of this CPG's recommendations.

Real-time updates of living recommendations were published on the CPG webpage and disseminated to various stakeholders. Further updates will be announced during the DOH daily updates on COVID-19, promoted on various social media platforms, and published on the PSMID website

Figure 2. Initial PSMID Webpage for the Philippine COVID-19 LCPG in March 2021.

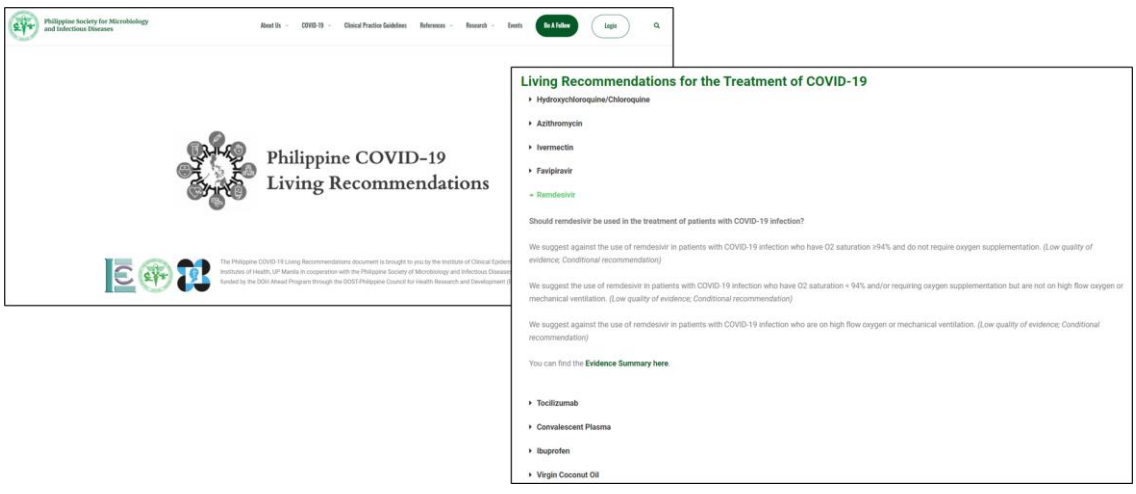


Figure 3. Latest PSMID Webpage for the Philippine COVID-19 LCPG.

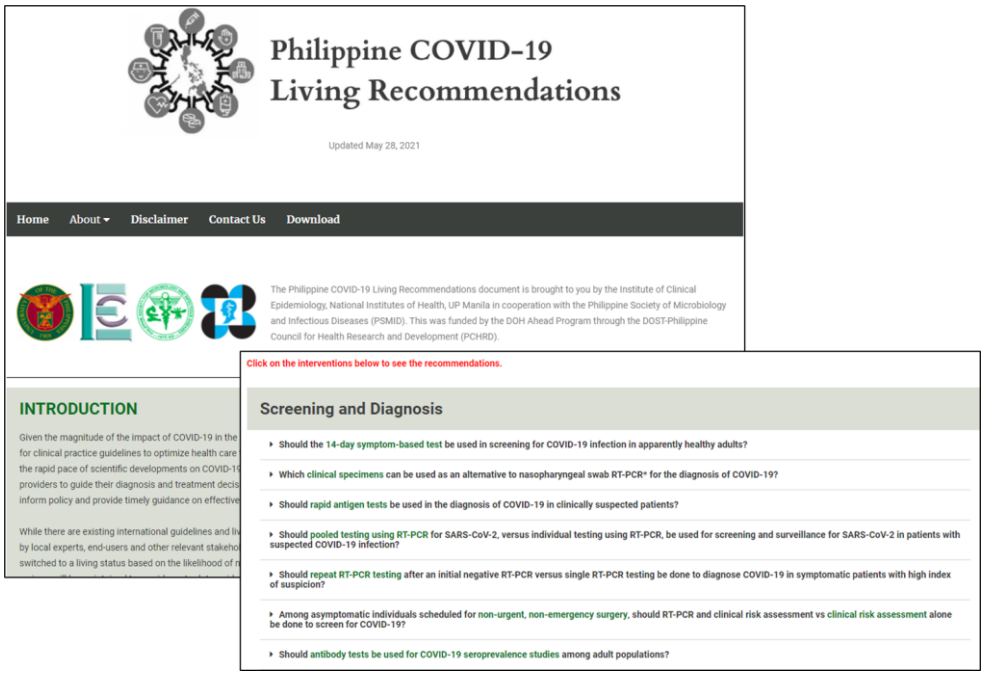
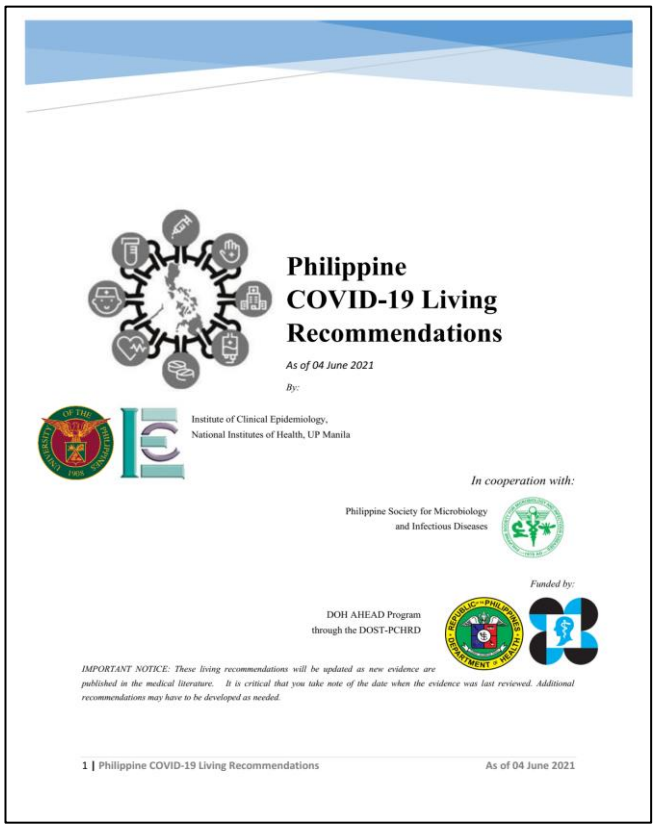


Figure 4. Living Recommendations Document for the Philippine COVID-19 Living CPG.



Guideline Monitoring and Evaluation

Guideline implementation would be assessed through process and impact evaluation. Only a process evaluation was feasible during the project implementation using webpage analytics. Refer to the subsection on *Process Evaluation* in the *Discussion* section of this manuscript.

Impact evaluation for the Philippine COVID-19 Living CPG would include bi-annual surveys of the following (1) clinicians managing COVID-19 patients, (2) public health practitioners coordinating local PDITR+ strategies in the community, and (3) the public regarding their compliance to non-pharmacologic interventions and any preventive measures.

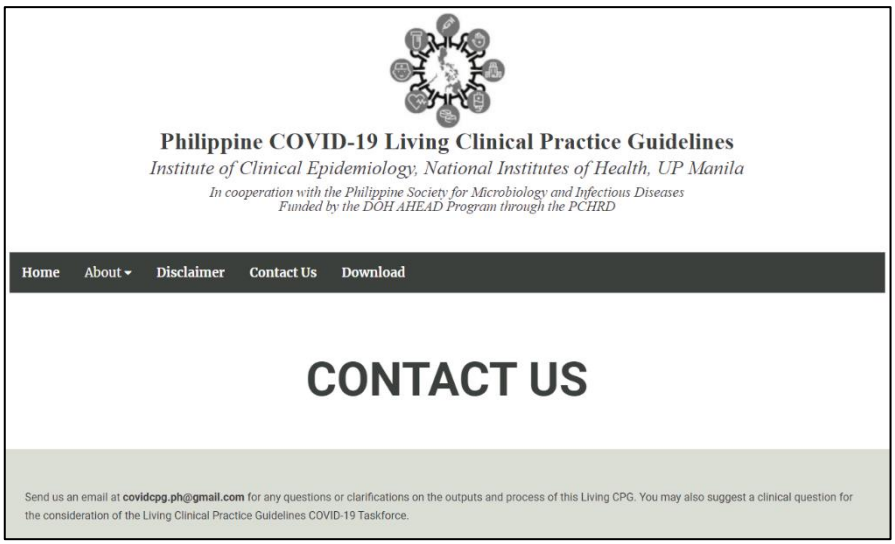
The quality of care rendered to COVID-19 patients can be assessed by measuring adherence of healthcare providers and institutions to the recommendations of the Philippine COVID-19 Living CPG. Strong recommendations would be included in a quality-of-care checklist on COVID-19 care, while weak recommendations would be relevant if the identified conditions are satisfied.

Finally, a scheduled bi-annual review would be conducted to evaluate the process efficiency and scientific quality of the Philippine COVID-19 Living CPG.

External Review

The CPG webpage served the dual purpose of a dissemination method and a way to collect the external reviews of the CPG processes, evidence summaries, and recommendations. This website (Figure 5) also allowed health professionals and key stakeholders to suggest additional clinical questions that could be included in the scope of this CPG.

Figure 5. Contact details in the Webpage for the Philippine COVID-19 Living CPG.



Over the weeks and months, we have gathered feedback from users and members of the Living CPG Taskforce to improve the readability of the webpage, such as toggling of topics, recommendations, and evidence summaries, changing from topics to questions in the listing, rearranging various sections into headers (such as CPG methodology, task force members, contact details, etc.), and other formatting changes. As an illustration, one feedback received on Lianhua led to the update of that evidence summary, and the inclusion of the health professional who gave the feedback in the evidence review team on Lianhua.
Furthermore, the *en banc* project review meeting with the Philippine Council for Health Research and Development and the screening appraisal of the Department of Health-Disease Prevention and Control Bureau will provide important inputs on the improvement of the living CPG development.

Updating of Guidelines

Due to the rapidly evolving science of COVID-19 treatment and diagnosis, the Philippine COVID-19 Living CPG was updated continuously. See the *Living CPG Process* under the *Overview of Philippine COVID-19 Living CPG Development Process* section for specific details on the process of updating this Living CPG.
After the initial DOH-PCHRD funding for six months, the DOH Disease Prevention and Control Bureau has provided funding support for another two and a half months to continue the surveillance search for the “living recommendations”. Further funding will be sought from professional societies and other government agencies to ensure the sustainability of the living CPG throughout the COVID-19 pandemic.

Editorial Independence

FUNDING SOURCE

This CPG project was funded by the Department of Health AHEAD Program through the Philippine Council for Health Research and Development for the first 6 months and subsequently funded by the DOH Disease Prevention and Control Bureau during the last quarter of 2021. Though the DOH was part of the Steering Committee and the Consensus Panels, their influence on the guideline content was limited to the identification of key clinical questions and the discussion of the recommendations. The funding agency did not have any undue influence on the evidence review conducted, as well as on the interpretation of the research data available.

MANAGEMENT OF CONFLICTS OF INTEREST

All members involved in the creation of this Clinical Practice Guideline, including the Steering Committee, Technical Working Group, and Consensus Panel, declared any potential conflicts of interest within the last 4 years, using a uniform Declaration of Conflict of Interest (DCOI) form as recommended in the DOH Manual [5]. These were reviewed by an independent Oversight Committee (OC) and the Steering Committee, to screen and manage the COIs declared. The Oversight Committee is responsible for recommending the extent of participation that can be allowed. The decisions of the

Oversight Committee will be reported and published in the final manuscript of the Living CPG.

The Oversight Committee has come up with the following guide as bases for their decisions:

a. **Manageable A** - if there are intellectual conflicts of interest only. They can vote but they need to declare their intellectual conflicts (e.g., affiliation with institutions, positions in an organization, authorship in paper or CPG)
b. **Manageable B** - if there are some intellectual and financial conflicts of interest. They cannot vote but they can share their expertise with the group. Examples include panelists from government agencies directly involved in the implementation of the program and panelists from the agency funding the guidelines. The specific terms of management shall be set forth by the OC and shall relate to specific clinical questions.
c. **Disqualifying** - the scope or nature of some relationships negates management and will sometimes outweigh the content expertise an individual may bring by serving as a full panelist, resulting in disqualification.

Evidence and Recommendations for the Screening and Diagnosis of COVID-19

Should the 14-day symptom-based test be used in screening for COVID-19 infection in apparently healthy adults and children?

As of 29 November 2021

RECOMMENDATION

We suggest doing an initial screening for ANY influenza-like illness, typical and atypical COVID-19 symptoms* within the past 14 days in apparently healthy adults and children, especially for individuals with known exposure to a laboratory-confirmed case of COVID-19. *(Very low certainty of evidence; Weak recommendation)*

**Symptoms include but not limited to: fever/chills, cough, shortness of breath/dyspnea, sore throat, runny nose, myalgia, headache, fatigue/malaise, diarrhea, nausea/vomiting, abdominal pain, anosmia, ageusia, wheezing, chest pain, altered mental status, seizures, rash, pink eye*

KEY FINDINGS

- Evidence on the accuracy of 14-day symptom-based testing was found from three observational studies (n=8,475).[1-3] This symptom-based test had a wide range of sensitivity (2.2-100%) and specificity (29-99%) in detecting COVID-19 among adults and children. Variability in accuracy appeared to be associated with heterogeneity in the populations tested and the characteristics of the index test.
- The diagnostic accuracy of individual symptoms differed depending on the exposure history of the populations where the test was applied. For those with unclear exposure, individuals had excellent specificity (>90%) but poor sensitivity (<50%). For close contacts of confirmed COVID-19 cases, nasal congestion/rhinorrhea, headache, cough, sore throat, were the individual symptoms that had at least 70% sensitivity. For children, accuracy was highest for headache, nasal congestion or rhinorrhea, fever or chills, and sore throat.
- Combining individual symptoms can increase the specificity to as high as 99.9% but with no substantial improvements in sensitivity. The Centers for Disease Control (CDC) symptom list showed the highest sensitivity (100%) but lowest specificity (21-45%) in both adults and children population while influenza-like illness showed the highest specificity (86-96%) but lowest sensitivity (43-54%).

CONSENSUS ISSUES

A weak recommendation was made based on evidence including studies that were conducted prior to the new variant of concern, Omicron, which was noted to present with symptoms not typical of previous variants. Additionally, majority of the studies were on adults while one study was on the pediatric population. The panelists emphasized that the list of symptoms is not exhaustive and that presence of any of the symptoms would warrant further investigation through a follow-up confirmatory diagnostic test.

Should pulse oximetry be used for at-home monitoring of COVID-19 patients?

As of 22 November 2021

RECOMMENDATION

We suggest pulse oximetry with close clinical monitoring by qualified medical personnel in suspected and confirmed COVID-19 patients especially those who are at high risk for deterioration. *(Very low certainty of evidence; Weak recommendation)*

KEY FINDINGS

- A total of 20 observational studies [4-23] on pulse oximetry monitoring for suspected and confirmed COVID-19 patients were included in this review.
- Effect estimates could not be pooled due to serious heterogeneity across studies. Lowered percentages of admissions, readmissions, and mortalities with pulse oximetry monitoring compared to no monitoring suggest feasibility and safety of remote monitoring using pulse oximetry but the certainty of evidence was very low.
- A single study [22] on device accuracy showed that medical and consumer-grade pulse oximeters, particularly Oxywatch (Sn 92.2%, 95% CI 87.3-97.1; Sp 60%, 95% CI 49.59-70.41), SM (Sn 90.7%, 95% CI 85.7-95.7; Sp 67.6%, 95% CI 56.7-78.5), and Onyx (Sn 92.1%, 95% CI 87.3-96.8; Sp 67.6%, 95% CI 56.9-78.2), were comparable to standard emergency department (ED) monitor units.
- Another study [23] reported that certain levels of oxygen saturation (SpO_2) have high sensitivity and specificity for risk of mortality and intensive care unit (ICU) admission. However, the overall certainty of evidence for this outcome was very low because of non-blinding, imprecision, and significant heterogeneity.

CONSENSUS ISSUES

A weak recommendation was made due to the limitations and risk of inaccuracy of pulse oximeters. The panel emphasized (1) ensuring the quality of the device by purchasing from reliable sources and (2) taking measures to get the best reading (e.g., following manufacturer instructions and ensuring adequate battery supply).

Considering the risk of inaccurate measurements that may result in unrecognized low oxygen saturation levels, the role of qualified medical personnel in pulse oximetry monitoring was highlighted by the panelists. Medical personnel should be available to provide instructions, to respond to caregiver and/or patient concerns, and to monitor signs and symptoms of deterioration

Which clinical specimens can be used as an alternative to nasopharyngeal swab RT-PCR* for the diagnosis of COVID-19?

As of 20 February 2021

RECOMMENDATION

We recommend the use of the following specimens as alternative specimens to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 among symptomatic and asymptomatic patients suspected of COVID-19 in hospital and outpatient settings:

- Oropharyngeal swab *(Moderate certainty of evidence; Strong recommendation)*
- Saliva drool/spit and oral saliva *(Moderate certainty of evidence; Strong recommendation)*
- Nasal swab/wash *(Moderate certainty of evidence; Strong recommendation)*
- Throat swab *(Low certainty of evidence; Strong recommendation)*

We suggest the use of saliva swab and posterior oropharyngeal saliva specimens as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 among symptomatic and asymptomatic patients with suspected COVID-19 in hospital and community/outpatient settings. *(Low certainty of evidence; Weak recommendation)*

RECOMMENDATION

We recommend against the use of sputum as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19. *(Very low certainty of evidence; Strong recommendation)*

RECOMMENDATION

There is no evidence to recommend the use of bronchoalveolar lavage as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19.

*SARS COV-2 RT-PCR of nasopharyngeal swabs remains the diagnostic test of choice to confirm the diagnosis of COVID-19 among suspected individuals.

KEY FINDINGS

- One cross-sectional study [24] on the use of oropharyngeal swab RT-PCR as an alternative clinical specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 showed that oropharyngeal swab had comparable sensitivity and specificity to nasopharyngeal swab RT-PCR.
- A meta-analysis [25] of 19 observational studies on the use of saliva as an alternative clinical specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 concluded that saliva had comparable sensitivity and specificity to nasopharyngeal swab RT-PCR.
- Two cross-sectional studies [24,26] on the use of nasal swab/wash RT-PCR as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 showed that nasal swab/wash had comparable sensitivity and specificity to nasopharyngeal swab RT-PCR.

- A cross-sectional study [26] on the use of throat swab RT-PCR as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 also showed that throat swab had comparable sensitivity and specificity to nasopharyngeal swab RT-PCR.
- A cross-sectional study from a meta-analysis [25] on the use of sputum RT-PCR as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 showed that sputum had lower sensitivity and specificity compared to nasopharyngeal swab RT-PCR.
- All the above studies were assessed to have low risk of bias.
- No studies compared the sensitivity and specificity of bronchoalveolar lavage RT-PCR to nasopharyngeal swab RT-PCR. Hence, no conclusion and recommendation can be made for this clinical specimen.

CONSENSUS ISSUES

Currently, oropharyngeal, and nasopharyngeal specimens are collected simultaneously; however, in resource-limited settings, the panel recognized the need for alternative clinical specimens to nasopharyngeal swab RT-PCR, along with the positive implication of single specimens on resource use. As a result, the use of oropharyngeal swab, oral saliva specimens, nasal swab/wash and throat swab were recommended as alternative clinical specimens to nasopharyngeal swab RT-PCR.

The differences between oropharyngeal swab and throat swab samples were clarified. Although the two specimens are collected in the same area, they were considered by the panel as dissimilar specimens due to the differences in sample collection technique. The panel made a strong recommendation for using throat swab samples due to its relatively high sensitivity.

The panel opted to strongly recommend against the use of sputum specimens as an alternative to nasopharyngeal swab samples. This was primarily due to the risk of viral transmission when obtaining sputum samples, coupled with the very low certainty of the evidence for its use.

Among patients suspected to have COVID-19, how accurate are rapid antigen tests compared to RT-PCR for the diagnosis of COVID-19?

As of 22 November 2021

RECOMMENDATION

We suggest the use of rapid antigen test for the diagnosis of symptomatic individuals suspected of COVID-19 as an alternative to RT-PCR if all the following conditions are met: *(Low certainty of evidence; Weak recommendation)*

a. Individuals are in the early phase of illness (less than or equal to 7 days from onset of symptoms); AND
b. Testing kits demonstrated sensitivity of more than or equal to 80% AND have very high specificity of more than or equal to 97%.

We suggest the use of rapid antigen tests for the diagnosis of individuals suspected of COVID-19 during the setting of an outbreak provided that all the following conditions are met: *(Very low certainty of evidence; Weak recommendation)*

a. Individuals are in the early phase of illness (less than or equal to 7 days from onset of symptoms); AND
b. Testing kits demonstrated sensitivity of more than or equal to 80% AND have very high specificity of more than or equal to 97%.

RECOMMENDATION

We suggest against the use of rapid antigen test for screening purposes. *(Low certainty of evidence; Weak recommendation)*

We suggest against the use of saliva as specimen for rapid antigen test in patients suspected of COVID-19 infection. *(Low certainty of evidence; Weak recommendation)*

We suggest against the use of rapid antigen tests alone in asymptomatic patients suspected of COVID-19 infection. *(Low certainty of evidence; Weak recommendation)*

RECOMMENDATION

There is insufficient evidence to recommend for or against the use of repeat antigen testing for screening or diagnosis of COVID-19. *(Very low certainty of evidence)*

A negative rapid antigen test should be confirmed with an RT-PCR in settings or situations wherein COVID-19 is highly suspected (e.g., symptomatic or asymptomatic close contacts of probable or confirmed COVID-19 individuals).

KEY FINDINGS

- A total of 164 observational studies [27-190] assessed the diagnostic accuracy of rapid antigen tests (RAgTs) against reverse transcriptase-polymerase chain reaction (RT-PCR) as the reference standard. Studies included different test brands, specimen types and timing of collection, symptom status, cycle threshold

(CT) values, and populations, namely impatiens, children, and healthcare workers among others.

- The overall sensitivity of RAgTs was moderate at 0.71 (95% CI 0.68-0.73) while specificity was excellent at 0.995 (95% CI 0.993-0.996). This was comparable to the data of the previous evidence summary with a pooled sensitivity of 0.72 (95% CI 0.64-0.78) and specificity of 0.99 (95% CI 0.99-1.0).
- On subgroup analysis, RAgT showed higher sensitivity when used in symptomatic individuals (Sn 0.74, 95% CI 0.71-0.78), when conducted during the early phase or first week of illness (Sn 0.79, 95% CI 0.75-0.82), in positive specimens with Ct value <25 (Sn 0.94, 95% CI 0.92-0.96), and in other Ct thresholds considered as “high” viral load (Sn 0.89, 95% CI 0.0.85-0.92). Pooled sensitivity of commonly used specimen types falls between 65% to 79%. FDA-approved RAgT brands have pooled sensitivities ranging from 0-90% with improved performance of commonly used RAgT brands when used in symptomatic individuals.
- In outbreak settings, RAgT use remained to have excellent specificity (Sp 0.966, 95% CI 0.997-0.999) with similar sensitivity (Sn 0.68, 95% CI 0.45-0.84) but with less precise estimates.
- The overall certainty of evidence was low because of serious risk of bias in all domains (high and unclear risk in patient selection, conduct of index test and reference standard, and flow and timing) and serious inconsistency. Despite performing pre-specified subgroup analyses, significant heterogeneity was still observed. In certain subgroup analyses such as the use of RAgT in outbreak settings and saliva specimens, certainty of evidence was further downgraded to very low due to imprecision attributed to wide interval estimates.

CONSENSUS ISSUES

The panel was unanimous against (1) the use of rapid antigen test for screening purposes, (2) the use of saliva as specimen for rapid antigen tests, and (3) the use of rapid antigen test alone in asymptomatic patients suspected of COVID-19 infection due to the observed lower sensitivity of these tests under such conditions. A unanimous decision on the insufficiency of evidence to recommend for or against the use of repeat antigen testing was also made.

Majority of the panelists agreed that the following conditions should be met when using rapid antigen tests:

a. Individuals are in the early phase of illness, because antigen tests perform best during this period; and
b. Testing kits have a sensitivity of more than or equal to 80% and specificity of more than or equal to 97%, because the quality of the test kit should be ensured.

One of eleven panelists raised a concern on the specified sensitivity and specificity of the testing kits, as these are based on the Health Technology Assessment Council (HTAC) of the local Department of Health (DOH).

A weak recommendation on the use of rapid antigen tests for diagnosing COVID-19 suspects during outbreaks was made based on nine observational studies with unclear patient selection, conduct of reference standard, and patient flow and timing. The risk of exposure was an important consideration for the panel, citing that it is not cost-effective to test everyone during an outbreak. However, the risk stratification of participants was not specified in any of the studies.

Among patients suspected to have COVID-19, how accurate are self-administered rapid antigen tests alone compared to RT-PCR for the diagnosis of COVID-19?

As of 11 November 2021

RECOMMENDATION

We suggest the use of self-administered rapid antigen test for the diagnosis of COVID-19 in symptomatic individuals, provided that ALL OF THE FOLLOWING conditions are met: *(Low certainty of evidence; Weak recommendation)*

1. Ease of collecting samples is ensured;
2. Ease of interpretation is ensured;
3. Test kits have passed flex studies; AND
4. Individuals present with symptoms for less than 7 days.

RECOMMENDATION

We suggest against the use of self-administered rapid antigen test for routine screening of COVID-19. *(Low certainty of evidence; Weak recommendation)*

KEY FINDINGS

- Seven observational studies [191-197] assessed the diagnostic accuracy of self-administered rapid antigen tests against RT-PCR as the reference standard. The studies included varied test brands (n=6), specimen types, and symptom status.
- The pooled sensitivity of self-administered rapid antigen test was moderate at 0.77 (95% CI 0.62-0.87) while the pooled specificity was high at 0.996 (95% CI 0.99-1.00). Pooled sensitivity estimates must be interpreted with caution due to the substantial heterogeneity (I^2=94%) across studies.
- On subgroup analysis, self-administered rapid antigen test showed higher sensitivity when used in the following conditions:
  - Symptomatic individuals (Sn 0.81, 95% CI 0.69-0.89);
  - Specimens taken from exhaled breath (Sn 0.92, 95% CI 0.64-1.0) or nasal mid-turbinate (Sn 0.81, 95% CI 0.73-0.87);
  - Specimens with high viral loads at RT-PCR cycle threshold <25 (Sn 0.87, 95% CI 0.68-0.88);
  - Specific brands of rapid antigen test, namely Inflammacheck device (Sn 0.92, 95% CI 0.64-1.0), Drager antigen test (Sn 0.89, 95% CI 0.79-0.95), and Abbott Panbio (Sn 0.84, 95% CI 0.71-0.94); and
  - Studies with high methodological quality or low risk of bias (Sn 0.79, 95% CI 0.68-0.86).
- The overall certainty of evidence for test sensitivity was low because of serious inconsistency (high heterogeneity) and risk of bias issues (patient selection, conduct of index test, and reference standard).

CONSENSUS ISSUES

The Panel unanimously agreed that all the following four conditions should be met when using self-administered antigen tests for the diagnosis of COVID-19:

1. Ease of sample collection, because incorrect performance of self-administered tests largely affects diagnostic accuracy;

2. Ease of interpretation, because proper interpretation is important for the accurate clinical management of patients;
3. The test kits should have passed the flex studies, because the quality of the self-administered test kit should be ensured; and
4. Individuals present with symptoms for less than 7 days, because antigen tests perform best during this period; and beyond this, the use of the test is not cost-effective, thereby incurring costs without added benefit.

The panel decided on a weak recommendation based on evidence including seven observational studies where performance of self-testing by participants was supervised by trained personnel either onsite or via telehealth. None were conducted in a home setting. Additionally, the studies did not specify if the participants were close contacts of COVID-19 patients or if they have a high- or low-risk of contracting COVID-19.

Other issues raised include (1) the lack of locally FDA-approved self-administered antigen test kits, (2) differentiating antigen tests manufactured for self-administration versus those that are not (i.e., for trained personnel), (3) the method of reporting the test results, and (4) the subsequent management and/or protocols after a positive test result (e.g., contact tracing).

Should breath tests be used to diagnose COVID-19 infection?

As of 29 November 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of breath test in detecting COVID-19 infection. *(Low certainty of evidence)*

KEY FINDINGS

This review included three cross-sectional [198-200] and three prospective studies [201-203] on the use of breath tests in the diagnosis of COVID-19 infection. The overall accuracy of breath tests was high, with sensitivity of 97% (95% CI 0.90-0.99) and specificity of 85% (95% CI 0.72-0.92). However, the overall certainty of evidence was low due to significant heterogeneity. This heterogeneity may be attributed to the different mechanisms of the devices despite using the same idea of breath testing.

CONSENSUS ISSUES

Despite the addition of five new studies since the previous recommendation, insufficient evidence remains to recommend for or against breath tests. The diagnostic accuracy of breath tests cannot be ascertained due to the heterogeneity across studies. The panel also raised concerns on the availability and accessibility of the test, its cost, and ease of use.

Should pooled testing using RT-PCR for SARS-CoV-2, versus individual testing using RT-PCR, be used for screening and surveillance for SARS-CoV-2 in patients with suspected COVID-19 infection?

As of 6 March 2021

RECOMMENDATION

We suggest the use of pooled RT-PCR testing in targeted* low-risk and low-prevalence populations using a pool size of 5 in individuals suspected of COVID-19 infection. *(Moderate certainty of evidence; Weak recommendation)*

**For targeted populations refer to the list of Philippine Society of Pathologists and Department of Health*

KEY FINDINGS

- Twenty-one cross-sectional studies [204-224] (N=220,253) were found that used pooled RT-PCR testing for SARS-CoV2. Six were diagnostic accuracy studies that compared pooled testing with individual testing, and 15 were pragmatic clinical validation studies of pooled testing that did individual testing of positive pools. Studies had varying study populations, use case, index test kits, and pool sizes (5 to 16).
- Among the six diagnostic accuracy studies with a total of 5,987 participants, there was moderately high pooled sensitivity (Sn 81%, 95% CI 72-88%; I^2=73.6%; moderate certainty of evidence) and high pooled specificity (Sp 99%, 95% CI 98-100%; I^2=1.84%; high certainty of evidence), given the positivity rate of 2.7 to 15% within the study populations.
- The positive predictive value based on 21 studies ranged from 67 to 100%.
- Resource savings in the number of test kits used ranged from 49 to 89%.
- Identified harms of pooled testing were delayed turnaround time for positive samples and laboratory errors.
- The overall risk of bias was low in seven studies, among which were six diagnostic accuracy studies that contributed to pooled sensitivity and specificity, and low in 14 studies, mainly due to the lack of independent assessment between the index and reference tests.

CONSENSUS ISSUES

The set recommendation included positivity rate and pool size; however, there were no studies that investigated the specificity and sensitivity of pooled testing for different pool sizes across different prevalence settings. Since the data presented did not clearly define the risk or the prevalence settings, pooled testing was suggested to be used only at a specific target population despite the moderate quality of evidence.

Should repeat RT-PCR testing after an initial negative RT-PCR (versus single RT-PCR testing) be done to diagnose COVID-19 in symptomatic patients?

As of 6 March 2021

RECOMMENDATION

We suggest repeating RT-PCR testing when the initial RT-PCR test is negative in symptomatic patients with high index of suspicion for COVID-19 infection. *(Low certainty of evidence; Weak recommendation)*

KEY FINDINGS

- Two cohort studies [225-226] involving 368 patients were found on the accuracy of repeat RT-PCR testing after an initial negative test to diagnose COVID-19 in symptomatic patients with a high index of suspicion. The evidence was assigned a low-quality rating due to the serious risk of bias and serious imprecision.
- The sensitivity of repeat RT-PCR testing ranged from 0.83 (95% CI 0.75-0.90) to 0.85 (95% CI 0.62-0.97), approximately 15% higher compared to the sensitivity of a single RT-PCR test, which ranged from 0.68 (95% CI 0.58-0.76) to 0.70 (95% CI 0.46-0.88).
- The specificity of repeat testing was consistently very high (Sp 1.00, 95% CI 0.89-1.00).

CONSENSUS ISSUES

The recommendation applies only to symptomatic patients with high index of suspicion for COVID-19. Since the disease severity and the level of suspicion were not clearly defined in the studies, the level of suspicion may vary. Moreover, no specific recommendation was made regarding the specific time interval between the initial and the repeat test as well as the frequency of repeat PCR tests.

Among COVID-19 confirmed patients, should certain RT-PCR cycle threshold values be used to determine infectivity?

As of 15 December 2021

RECOMMENDATION

There is insufficient evidence to recommend an RT-PCR cycle threshold cut-off value to determine infectivity among COVID-19 confirmed patients. Interpretation of RT-PCR cycle threshold values may vary and is dependent on the PCR assay used, gene target, sample type, and timing of sample collection. *(Very low certainty of evidence)*

KEY FINDINGS

- Twelve observational studies [227-238] were included in this review on the use of cycle threshold (Ct) as a surrogate marker of infectivity as evidenced by viral isolation in culture. One systematic review and meta-analysis [239] was included on the association of Ct value with patient clinical outcomes.

- Very low certainty evidence showed that among COVID-19 cases, Ct values of 24 to 35.6 were associated with isolation of SARS-CoV-2 virus in culture. Lower Ct values (Ct <25-30) were associated with increased disease severity and mortality.
- Among convalescent and clinically recovered patients with persistent positive RT-PCR test, Ct values ranged from 30 to 41.7. Samples from these cases had a low yield of virus isolation in culture and had degraded viral fragments on genome sequencing.
- Interpretation of Ct values must be done with caution due to variations in PCR assay methods, target gene, sample type, and timing of sample collection.

CONSENSUS ISSUES

RT-PCR cycle threshold values may have utility specifically for patients with previously documented COVID-19 infection. However, evidence remains insufficient on the cut-off cycle threshold value that differentiates infectious virus from viral remnants.

Should antibody tests be used for COVID-19 seroprevalence studies and monitoring vaccine response among adults?

As of 22 November 2021

RECOMMENDATION

We suggest using antibody tests that accurately measure IgG or total antibodies to determine COVID-19 seroprevalence among adults when needed for public health purposes. *(Very low certainty of evidence; Weak recommendation)*

RECOMMENDATION

We suggest against using antibody tests detecting IgM to determine COVID-19 seroprevalence among adults. *(Very low certainty of evidence; Weak recommendation)*

We suggest against using lateral flow immunoassay (LFIA) tests to determine COVID-19 seroprevalence among adults. *(Very low certainty of evidence; Weak recommendation)*

We recommend against routine measurement of SARS-CoV-2 antibody titers after vaccination. *(No evidence; Strong recommendation)*

KEY FINDINGS

- This review included 19 observational studies [243-261] with a total of 28,566 samples that evaluated the diagnostic accuracy of antibody tests compared with reverse transcription polymerase chain reaction (RT-PCR) in seroprevalence studies.
- The studies were of moderate to high methodologic quality. The overall certainty of evidence was rated very low due to serious risk of bias (recall bias) and inconsistency.
- Heterogeneity across studies was substantial (I^2>90%). The sensitivity of antibody tests ranged from 14.4 to 100% while specificity ranged from 54.9 to 99.6%.
- No studies evaluating the accuracy of antibody tests in determining vaccine response compared to RT-PCR-diagnosed breakthrough infections were found.

CONSENSUS ISSUES

Recommendations on antibody testing were made in the context of public health purposes (i.e., to identify the percentage of people in a population who may have been previously infected). The panel was unanimous against the use of antibody tests detecting IgM and LFIA tests while the majority voted for the use of antibody tests detecting IgG or total antibodies with a weak recommendation. Concern was raised on the cross-reactivity of the tests with other coronaviruses. Thus, emphasis was made on ensuring the accuracy of the antibody test kits used.

The panel was initially divided about antibody testing post-vaccination. Six of eleven panelists voted that there is insufficient evidence to recommend for or against it, citing that the public should be given the choice given the lack of evidence. On the other hand, five panelists voted against routine antibody testing post-vaccination despite the lack of evidence due to: (1) the unavailability of a real neutralizing antibody test in the market and (2) the unclear cutoff of antibody level that is predictive of COVID-19 protection. The panelists eventually reached consensus in the second round of voting, with the majority choosing for a strong recommendation because antibody tests post-vaccination lack clinical utility at this point.

Among symptomatic individuals previously diagnosed with COVID-19, should antibody testing be done to diagnose presumptive COVID-19 reinfection?

As of 09 April 2021

RECOMMENDATION

We recommend against the use of SARS-CoV-2 Ab testing to diagnose presumptive COVID-19 reinfection among symptomatic patients previously diagnosed with COVID-19* *(Very low certainty of evidence; Strong recommendation).*

**NAAT (RT-PCR) and Genomic sequencing are the recommended diagnostic tests to confirm COVID-19 reinfection.*

KEY FINDINGS

- No studies directly assessed the accuracy of SARS-CoV-2 Ab testing in diagnosing presumptive COVID-19 reinfection compared to RT-PCR as the reference standard. Only three retrospective observational studies [262-264] reported on the accuracy of SARS-CoV-2 IgG/IgM Ab in diagnosing COVID-19. There is very low certainty regarding these estimates due to very serious risk of bias concerns, imprecision, indirectness, and inconsistency.
- The sensitivity of SARS-CoV-2 IgG/IgM ranged from 0.19 (95% CI 0.4-0.46) to 0.89 (95% CI 0.71-0.98) and specificity of 0.50 (95% CI 0.01-0.99) to 1.00 (95% CI 0.89-1.00).
- Subgroup analysis suggested that the sensitivity of Ab testing was low under the following conditions: (a) when used within 0-15 days from symptom onset, (b) Ab tests that assess IgM, (c) using lateral flow qualitative immunoassay (LFIA) technique.
- Specificity was consistently high (>89%) regardless of the type of antibody detected or if either LFIA or chemiluminescence immunoassay (CLIA) techniques were done. However, specificity was high only if the test was performed more than 16 days from symptom onset.

CONSENSUS ISSUES

The studies reviewed did not perform subgroup analysis according to 4-fold titer rise at a given interval. Due to the very low quality of evidence, the use of SARS-CoV-2 Ab testing to diagnose presumptive COVID-19 reinfection was not recommended.

Among asymptomatic individuals scheduled for non-urgent, non-emergency surgery, should RT-PCR and clinical risk assessment vs clinical risk assessment alone be done to screen for COVID-19?

As of 09 April 2021

RECOMMENDATION

We recommend using both clinical risk assessment and RT-PCR* to screen for COVID-19 among asymptomatic individuals scheduled for non-emergency surgery. *(Very low certainty of evidence; Strong recommendation)*

We recommend the use of both clinical risk assessment and Antigen-Rapid Diagnostic Test (Ag-RDT)** to screen for COVID-19 among asymptomatic individuals scheduled for non-emergency surgery when RT-PCR testing is not available or turnaround time of results is prolonged. *(Very low certainty of evidence; Strong recommendation)*

**Always use high-risk PPE regardless of RT-PCR or Ag-RDT test results in areas with prevalence of 1% or higher*
***Ag-RDT should have a Sn of 80% and Sp of 97%*

KEY FINDINGS

- Based on one cohort study [240] with very low quality, the diagnostic accuracy of clinical risk assessment alone in detecting COVID-19 compared to RT-PCR was found to be poor, with a sensitivity of 0.42 (95% CI 0.15-0.72) and a specificity of 0.85 (95% CI 0.76-0.92). Clinical risk assessment also resulted in more false negative and false positive results.
- Very low certainty evidence from one economic modeling study [241] suggested that universal pre-endoscopy virus testing using Ag-RDT, standard RT-PCR, or rapid PCR combined with high-risk PPE use in all patients irrespective of test results was more cost-effective compared to no pre-endoscopy testing and no high risk PPE use, at an assumed prevalence rate of 1% or higher among asymptomatic individuals.
- Patients for elective surgery who tested positive on any pre-operative COVID-19 tests or clinical assessment were at least three times more at risk of experiencing pulmonary complications or death compared to those who tested negative based on one cohort study [242] with very low quality. Delaying surgery to at least seven weeks from a COVID-19 diagnosis also showed benefit. Given this data on the risks and benefits associated with a COVID-19 diagnosis as well as the high false negative rates of clinical risk assessment alone, clinical risk assessment would appear to cause more harm compared to more objective tests.

CONSENSUS ISSUES

Despite the very low quality of evidence, the majority voted to strongly recommend the use of both RT-PCR testing and clinical risk assessment to screen for COVID-19 among asymptomatic individuals scheduled for non-emergency surgery primarily due to the potential impact of a false negative result on the safety of the patient and health care staff involved as well as on the infection control processes of hospitals. RT-PCR

was also recommended as it is now readily available in most hospitals. However, a panelist suggested that RT-PCR and PPE should only be conditionally recommended in areas with prevalence rates of 1% or higher.

The specification of the sensitivity and specificity for the Ag-RDT was the reason for the strong recommendation on the use of clinical risk assessment and Ag-RDT to screen for COVID-19 among asymptomatic individuals scheduled for non-emergency surgery when RT-PCR testing is not available. However, other panelists were concerned about the availability of antigen tests that would meet the set specification in terms of sensitivity and specificity.

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

As of 17 December 2021

RECOMMENDATION

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

KEY FINDINGS

- This review included six observational studies [265-270] 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 [268] 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 [267] 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, [265,266,269] 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% CI 0.60-0.88), 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.

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.

Among individuals suspected of COVID-19, how accurate are thoracic imaging modalities compared to RT-PCR alone in diagnosing COVID-19?

As of 13 December 2021

RECOMMENDATION

We suggest against the use of chest x-ray to diagnose COVID-19 infection among asymptomatic individuals. *(Very low certainty of evidence; Weak recommendation)*

We suggest against the use of lung ultrasound alone in diagnosing patients with suspected COVID-19 infection. *(Very low certainty of evidence; Weak recommendation)*

We suggest against the routine use of CT scan for diagnosing COVID-19 among suspected patients with COVID-19 presenting at the emergency department if RT-PCR testing is readily available with timely results. *(Very low certainty of evidence; Weak recommendation)*

RECOMMENDATION

We suggest chest x-ray to facilitate rapid triage, infection control, and clinical management among any of the following: *(Very low certainty of evidence; Weak recommendation)*

a. Patients with mild features of COVID-19 at risk for progression
b. Patients with moderate to severe features of COVID 19
c. Patients with symptoms of at least 5 days duration

If RT-PCR is not available, we suggest using non-contrast chest CT scan for symptomatic patients suspected of having COVID-19 to guide early triage and management under the following conditions: *(Very low certainty of evidence; Weak recommendation)*

a. Mild COVID-19 patients who are at risk for progression
b. Moderate to severe COVID-19 patients

KEY FINDINGS

- A total of 81 observational studies [271-351] were assessed for the diagnostic accuracy of chest x-ray, lung ultrasound, and chest CT scan against reverse transcriptase-polymerase chain reaction (RT-PCR) on individuals suspected of COVID-19.
- **Chest x-ray:** Overall sensitivity was 72% (62-81%) and overall specificity was 76% (67-86%). Results were comparable to the findings of the previous review that showed a sensitivity of 74% and specificity of 76%. Considerable heterogeneity is still seen (I^2=95%). Sensitivity was higher for studies that involved experienced readers, used standardized chest x-ray scoring systems, and when testing was done late in the disease course. Studies with high risk of bias tended to produce similar but less precise estimates. Overall certainty of evidence remained very low due to very serious risk of bias and inconsistency, and serious imprecision.
- **Lung ultrasound:** Overall sensitivity was 93% (86-97%) and specificity was 52% (33-71%). The previous review showed a lower sensitivity of 88% but a higher

specificity of 63%. Sensitivity appeared higher when the test is used for symptomatic patients and when reader impression is used instead of a scoring system. The highest accuracy estimates were produced when only high quality studies were included in the analysis (Sn 97%, 95% CI 89, 100%; Sp 73%, 95% CI 45, 92%). Overall certainty of evidence was downgraded from low to very low due to very serious inconsistency, and seriousness on risk of bias and imprecision.

- **Chest CT scan:** Overall sensitivity was 85% (81-88%) and overall specificity was 78% (71-84%). Heterogeneity was very high at I^2=100%. Findings were almost similar to the estimates (Sn 88% and Sp 80%) of the previous review. Accuracy estimates were higher under the following situations: (1) test is used among symptomatic patients, (2) contrast-enhanced CT scan machines, (3) results are interpreted by experienced readers, (4) standardized scoring systems are used, (5) when only high-quality studies were considered. Overall certainty of evidence remained very low due to the seriousness of risk of bias and impression, and the very serious issues on inconsistency.

CONSENSUS ISSUES

The panel was unanimous against the use of chest x-ray and lung ultrasound in diagnosing COVID-19 due to the widespread availability of alternatives, such as antigen testing, even in the absence of RT-PCR. Additionally, the evidence base showed that detecting COVID-19 through these imaging modalities are dependent on the experience of the reader. However, a weak recommendation was decided since the evidence did not compare these imaging modalities with rapid antigen tests.

The panel was also unanimous in recommending chest x-ray to facilitate triage, infection control, and clinical management, especially in the absence of RT-PCR and rapid antigen tests, due to the widespread availability and rapid results of chest x-ray. A weak recommendation was made, however, since the accuracy of this modality varies depending on the experience of the reader.

Similarly, the panel was for the use of non-contrast chest CT scan in guiding early triage and clinical management if RT-PCR is not available. A weak recommendation for this was made due to concerns on its risk of radiation and cost, and the evidence base including studies conducted abroad.

Among adult patients diagnosed with COVID-19, should prognostic models be used to predict the likelihood of severe disease and mortality?

As of 17 December 2021

RECOMMENDATION

To guide the decision to admit adult patients with COVID-19 to the hospital:
We suggest the use of age, BUN, number of comorbidities, CRP, SpO2/FiO2 ratio, platelet count, Heart rate (ABC2-SPH) risk score, Confusion Urea Respiration Blood Pressure (CURB-65) severity score, Risk Stratification in the Emergency Department in Acutely Ill Older Patients (RISE-UP) score, and Rapid Emergency Medicine Score (REMS). *(Low certainty of evidence; Weak recommendation)*

To guide in the expectant monitoring of hospitalized adult patients, we suggest the use of the 4C Deterioration model. *(Low certainty of evidence; Weak recommendation)*

RECOMMENDATION

To guide the decision to admit adult patients with COVID-19 to the hospital, there is insufficient evidence to recommend the use of 4C Mortality Score, COVID Outcome Prediction in the Emergency Department (COPE) model, and Quick Sepsis-related Organ Failure Assessment (qSOFA) score. *(Very low certainty of evidence)*

To guide in the expectant monitoring of hospitalized adult patients, there is insufficient evidence to recommend the use of Modified Early Warning Score (MEWS) and National Early Warning Score 2 (NEWS2), Clinical Frailty Scale (CFS), and the COVID-GRAM model. *(Very low certainty of evidence)*

KEY FINDINGS

- In this version, two new prognostic models were reviewed and 13 new studies [352-364] were added. One study is a binational prospective cohort which validated 4C mortality score and COVID-GRAM on a larger population in South America and Europe [352]. Three more studies [353-355] validated COVID-GRAM but have an overall unclear risk of bias and low quality of evidence. Nine studies [356-364] validated the use of Clinical Frailty Scale in prognosticating elderly COVID-19 patients, but the overall assessment for risk of bias was rated high and the level of evidence was rated very low.
- In total, 46 cohort studies [352-397] on prognostic models for clinical deterioration and mortality of individuals with COVID-19 were found. Most of the studies (n=36) were assessed to have high risk of bias due to issues in participant selection and analysis. There were eight studies [352, 357-358, 360, 364-367] with unclear, and two studies [368-369] with low risk of bias.
- For predicting mortality, the following models demonstrated fair-to-good predictive ability: 4C mortality score, ABC2-SPH, CURB-65, REMS, RISE UP and COVID-GRAM models. Poor to fair prediction was noted for the qSOFA model, with one new study yielding lower AUC estimates compared to the previously included studies. Only one model, the QCOVID model for mortality validated for the UK setting, demonstrated high predictive ability.

- For predicting clinical deterioration, available prognostic models showed varied performance. The 4C deterioration which has been investigated in only one study with low risk of bias, showed fair predictive ability. The MEWS model has poor prediction of clinical deterioration while NEWS2 has inconsistent prediction (poor to good). The Clinical Frailty Scale (CFS), increases the risk of mortality among elderly COVID-19 patients.
- None of these models have been validated in the Philippine population. Thus, validation studies are needed before these models can be used to inform practice.

CONSENSUS ISSUES

The recommendations on prognostic models are limited to adult patients since the evidence base included studies only on the adult population. No studies were conducted among pediatric patients. The panelists were unanimous in all recommendations on prognostic models.

Should LDH, CRP, and Ferritin be used to guide immunotherapy in patients with COVID-19?

As of 13 December 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of specific cut-off values of CRP, LDH and Ferritin to guide the initiation of immunotherapy in patients with COVID-19 *(Very low certainty of evidence)*

KEY FINDINGS

- Moderate quality of evidence showed significant correlation of CRP >10 mg/L with mortality (four studies [398]) and poor outcome (ten studies [399]).
- High quality of evidence from seven studies [398] showed significant correlation between elevated LDH and progression to severe disease.
- Moderate quality of evidence from 18 studies [399] showed significant correlation between LDH >250 U/L and poor outcome.
- Low quality of evidence from four studies [398,400-402] did not find significant correlation between elevated LDH and mortality.
- Very low quality of evidence showed significant correlation between elevated CRP and progression to severe disease (one study [403]) and ICU admission (one study [403]) in pediatric patients.

CONSENSUS ISSUES

The evidence base included studies that investigated the levels of LDH, CRP, and ferritin that are correlated with progression to severe disease, poor outcomes, or mortality, rather than improved survival with immunotherapy. Thus, the panel unanimously decided that insufficient evidence remains to use specific cut-off values of these markers to guide immunotherapy. Additionally, the panel cited the availability of other parameters that may be used to guide initiation of immunotherapy besides these markers.

Should D-dimer be used to guide anticoagulation among adult patients with COVID-19?

As of 26 May 2021

RECOMMENDATION

We suggest the use of D-dimer to guide anticoagulation of adult patients with COVID-19, because of its significant association with mortality, thromboembolism, and worsening of disease *(Low certainty of evidence; Weak recommendation)*

KEY FINDINGS

- We found a total of 25 observational studies [404-428] on the association between D-dimer and the outcomes of mortality, worsening severity, or thromboembolism. In general, the included studies showed increased odds of in-hospital mortality (OR 5.57, 95% CI 2.74-11.31), worsening severity (critical illness OR 1.91-2.58); disease progression (HR 2.84, 95% CI 2.10-3.85), or need for mechanical ventilation (HR 3.28, 95% CI 1.071-0.10), and thromboembolism (OR 5.61, 95% CI 3.97-7.94), with higher D-dimer levels across different COVID-19 severities.
- Most studies yielded imprecise effect measures, due to the small number of event outcomes. Most of the studies were found to have serious risk of bias, with issues on data censoring, incomplete laboratory data, and unclear adequacy of follow-up rates. Differences in D-dimer cut-offs, definitions of critical illness and disease progression, and severities of COVID-19 in the study population contributed to the heterogeneity across studies.
- While the predictive ability of D-dimer for mortality appeared to be fair to good, prediction of worsening severity or progression of disease is inconsistent.

CONSENSUS ISSUES

Due to the varied cut-off values used in the included studies for this review, the recommendation did not include a specific cut-off value of D-dimer to predict mortality, thromboembolism, and worsening severity of disease. Further, the laboratories in the Philippines also make use of varying cut-offs due to the different assays and machines used, hence, it is difficult to define a specific cut-off value.

Should procalcitonin be used to guide the initiation of antibiotic therapy in patients diagnosed with COVID-19?

As of 13 December 2021

RECOMMENDATION

For initiating antibiotic therapy, we suggest against the use of procalcitonin alone as a basis for initiating antibiotic therapy among COVID-19 confirmed patients. *(Very low certainty of evidence; Weak recommendation)*

RECOMMENDATION

For discontinuing antibiotic therapy:
If available, we recommend using a procalcitonin level of less than or equal to 0.25 ng/mL for discontinuing antibiotic therapy among COVID-19 confirmed patients. *(Very low certainty of evidence; Strong recommendation)*

KEY FINDINGS

- Four retrospective cohort studies [429-432] were included in this review. Three [429-431] provided data for calculation of diagnostic accuracy estimates, while one [432] reported on the benefits and safety of using an antimicrobial therapy discontinuation protocol based on procalcitonin measurements. Studies used varying cut-off levels for procalcitonin and used it for guiding discontinuation of antibiotics.
- Sensitivity ranged from 0.40 to 0.87, while specificity ranged from 0.43 to 0.88. Across the three studies, a total of 42/816 (5.1%) had positive results on microbiological testing. No stratification as to whether patients with higher procalcitonin levels were associated with more severe or less severe COVID-19 cases.
- Using procalcitonin-based algorithms was found to be associated with lower antimicrobial exposure (mean 5.4 vs. 4.4 days) and consumption (mean DDD 8.4 vs. 6.8). This translates to a 30% lower risk for both mean duration of antibiotic therapy (adjusted ratios of means [ROM] 0.70; 95% CI 0.6, 0.9) as well as mean DDD (ROM 0.70, 95% CI 0.6, 0.8). A trend towards lower 30-day mortality rates was noted for participants with procalcitonin measurements (adjusted prevalence ratio [PR] 0.6, 95% CI 0.4, 1.1). Mean patient antimicrobial consumption also showed a decreasing trend over time in the procalcitonin group (βslope −0.07, 95% CI −0.11, −0.03) compared to those without procalcitonin measurements.
- Overall certainty of evidence was rated very low due to serious risk of bias, imprecision, and inconsistency.

CONSENSUS ISSUES

Antibiotic misuse and abuse among COVID-19 patients is a common practice that needs to be addressed. Thus, the panel recognized that procalcitonin may have utility in guiding antibiotic use among COVID-19 patients. However, the panel was against the use of procalcitonin alone in initiating antibiotic therapy, citing that clinical evaluation and other laboratory parameters should be considered as well since procalcitonin levels can be elevated in certain conditions even in the absence of bacterial infection. Additionally, the evidence base included studies that investigated

absolute cut-offs of procalcitonin rather than the comparative decrease or increase in its levels.

In contrast, the panel was unanimous in recommending the use of procalcitonin levels to discontinue antibiotic therapy among COVID-19 patients. This was to provide guidance to practitioners due to the common practice of continuing antibiotics indefinitely among critically ill patients.

Cited reasons for a weak recommendation on the use of procalcitonin for discontinuing antibiotic therapy include:

1. concerns on the cost and availability of procalcitonin;
2. very low certainty of evidence; and
3. use of indirect evidence to identify the cut-off level for discontinuation (i.e., the evidence base aimed to identify procalcitonin levels that differentiate the presence or absence of co-infection rather than the continuation or discontinuation of antibiotic therapy).

Cited reasons for a strong recommendation on the use of procalcitonin for discontinuing antibiotic therapy include:

1. the need to prevent antibiotic resistance, considering that multidrug resistance is a common cause of death among critically ill or severe COVID-19 patients; and
2. to prevent the higher costs associated with unnecessary antibiotic use (i.e., While procalcitonin is expensive, even an extra day of unnecessary antibiotic therapy would equate to higher costs for the patient).

Should certain risk factors be used to predict the development of long COVID?

As of 29 November 2021

RECOMMENDATION

There is insufficient evidence in using symptoms*, biologic factors or severity of acute COVID-19 in predicting the development of long covid symptoms. *(Very low certainty of evidence)*

**The most common symptoms of long COVID identified were fatigue, dyspnea, sleep disturbance, anxiety or depression, and memory impairment.*

KEY FINDINGS

- Evidence for this review was obtained from 37 observational studies included in two systematic reviews [433-434] as well as three additional observational studies [435-437] describing possible risk factors for the development of long COVID.
- Majority of hospitalized patients diagnosed as having long COVID presented with the following symptoms: weakness, fatigue, dyspnea, cognitive/memory impairment, sleep disorder, and anxiety/psychosocial symptoms.
- For patients in the community setting, dyspnea, reduced quality of life, weakness, chest pain, palpitations, arthralgia, and myalgia were highly common. Older age, female sex, presence of comorbidities, and more severe status during the initial infection were likely to be associated with the development of long COVID during follow-up, although studies showed inconsistent results.
- Very low certainty evidence showed that some of these risk factors were associated with individual symptoms characteristic of long COVID. Our analysis was limited by the significant heterogeneity among the studies included, the different time frames of follow-up, and the studies' inclusion criteria.

CONSENSUS ISSUES

Predicting the development of long COVID-19 using risk factors can help identify which patients should be followed up more closely. However, there is insufficient evidence on the predictive risk factors, precluding any recommendation to be made.

Should heparin induced thrombocytopenia (HIT) test kits be used for COVID-19 vaccine induced thrombosis with thrombocytopenia (VITT)?

As of 29 November 2021

RECOMMENDATION

We suggest against the use of PF4 antibody ELISA Heparin Induced Thrombocytopenia (HIT) test kits and non-ELISA rapid HIT test kits for COVID-19 Vaccine Induced Thrombosis and Thrombocytopenia (VITT). *(Very low certainty of evidence; Weak recommendation)*

KEY FINDINGS

- One cross-sectional observational study [438] was included on the use of anti-platelet factor 4 (anti-PF4) assay test kits for the diagnosis of COVID-19 vaccine-induced thrombosis and thrombocytopenia (VITT).
- The overall certainty of evidence was very low because of serious concerns of risk of bias, inconsistency, and imprecision.
- The study analyzed samples from 43 patients with suspected VITT using six brands of anti-PF4 ELISA test kits and four brands of anti-PF4 non-ELISA test kits. Sensitivity ranged from 0.71-0.97 and specificity ranged from 0.56-1.00 for the ELISA test kits, while sensitivity ranged from 0.00-0.45 and specificity ranged from 0.67-1.00 for the non-ELISA test kits.

CONSENSUS ISSUES

The panel unanimously decided against the use of HIT test kits for COVID-19 VITT, citing that the test has a slow turnaround time and immediate clinical management remains the same regardless of the test result. Concerns were also raised on its cost-effectiveness as well as availability in the local setting. Test kits employing ELISA demonstrate relatively high sensitivity and specificity but have limited availability locally.

Should serum tryptase be used to test individuals who had anaphylaxis after receiving COVID-19 vaccine?

As of 29 November 2021

RECOMMENDATION

We suggest against using serum tryptase for patients who had anaphylaxis after receiving COVID-19 vaccine. *(Very low certainty of evidence; Weak recommendation)*

KEY FINDINGS

- Eleven observational studies (five case reports [439-443], two case series [444-445], three retrospective chart reviews [446-448] and one prospective survey [449]) with 33 total patients showed conflicting results and uncertainty with regards to the use of serum tryptase in the diagnosis of COVID-19 vaccine induced anaphylaxis.
- Nine patients presented with a history of allergy but none of them showed elevated tryptase levels.
- Four patients presented with elevated serum tryptase levels but have no allergic history elicited/provided.
- There is uncertainty with regards to the accuracy of serum tryptase in the diagnosis of COVID-19 vaccine-induced anaphylaxis due to the lack of study samples.
- The overall certainty of evidence was very low because of heterogeneity in duration of tryptase determination, definition of elevated values, variable clinical classification criteria, and lack of an objective reference standard for diagnosis of anaphylaxis.

CONSENSUS ISSUES

The panel unanimously decided against the use of serum tryptase to diagnose COVID-19 vaccine-induced anaphylaxis, citing that the test is not cost-effective, and anaphylaxis remains to be a clinical diagnosis. While serum tryptase may have a role in patients with atypical presentation, it would still be prudent to treat the patient especially if there is high clinical suspicion regardless of the test result. Additionally, the use of tryptase test in settings of mass vaccination poses feasibility issues because (1) the sample should be taken within 30 minutes up to two hours after the patient presents with a reaction, and (2) there is a paucity of laboratories offering the test. However, a weak recommendation was made since the test may still benefit a small subset of the population and may have more utility in the emergency department setting.

Evidence and Recommendations for the Treatment of COVID-19

Should hydroxychloroquine/ chloroquine, with or without azithromycin be used in the treatment of patients with COVID-19 infection?

As of 19 February 2021

RECOMMENDATION

We recommend against the use of hydroxychloroquine/chloroquine, with or without azithromycin among patients with COVID-19 infection. *(Moderate certainty of evidence, Strong recommendation)*

KEY FINDINGS

- Twenty-two trials [1-22] showed that hydroxychloroquine (HCQ)-containing treatment regimens did not significantly improve the outcomes of patients with COVID-19 disease compared with placebo or standard of care. Eleven (11) of these trials provided evidence of low certainty that the use of HCQ for the treatment of COVID-19 infection was significantly associated with a higher risk of adverse events (i.e., diarrhea, headache, rashes, and fatigue).
- There was limited evidence with low to very low certainty which showed that treatment with HCQ combined with azithromycin does not show any significant difference from placebo in any of the efficacy outcomes. Adverse events were more frequent with the hydroxychloroquine plus azithromycin group compared to placebo.

Should azithromycin be used in the treatment of patients with COVID-19 infection?

As of 1 December 2021

RECOMMENDATION

We recommend against the use of azithromycin among patients with COVID-19 infection. *(Moderate certainty of evidence, Strong recommendation)*

KEY FINDINGS

Based on 11 RCTs and one additional RCT [23-30] for asymptomatic to mild COVID -19 patients, there was no significant difference in clinical outcomes with the use of azithromycin compared to placebo among patients with COVID-19 across all disease severity. Likewise, there was no significant difference in serious adverse events and cardiac arrythmias among all patients but there was a noted significantly higher risk among those given azithromycin for non-serious adverse events for the asymptomatic to mild group with diarrhea being the most common adverse event. This was not noted among the moderate to severe group.

Among patients with COVID-19, should favipiravir be used for treatment?

As of 8 November 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of favipiravir among patients diagnosed with COVID-19. *(Very low certainty of evidence)*

KEY FINDINGS

- Seven (7) randomized controlled trials (RCTs) [31-37] found on the use of favipiravir among patients with COVID-19. Pooled results showed a modest benefit in clinical improvement on day 7 favoring favipiravir compared to standard of care; however, clinical improvement on day 28 showed no significant benefit. There was also significant benefit in time to clinical improvement and time to negative conversion. Incidence of viral negative conversion was not significantly different between favipiravir and standard of care.
- There was no significant difference on the incidence of adverse events and serious adverse events. Report on adverse events, although an important outcome, was not rated as a critical outcome to be included in the decision making. The overall certainty of evidence was rated low due to serious risk of bias, inconsistency, and very serious imprecision in several critical outcomes.

CONSENSUS ISSUES

Results from the study are mostly inconclusive and there are still no recommendations on the use of favipiravir outside clinical trials. There are ongoing clinical trials, including one local study currently recruiting participants. Results from these ongoing studies will help further evaluate the use of favipiravir in the treatment of COVID-19.

Should remdesivir be used in the treatment of patients with COVID-19 infection?

As of 19 February 2021

RECOMMENDATION

We suggest the addition of remdesivir to dexamethasone in patients with COVID-19 infection who have O2 saturation < 94% and/or requiring oxygen supplementation and are high risk for progression. *(Low certainty of evidence, Weak recommendation*)

**For patients who progress to invasive mechanical ventilation while on remdesivir, the drug may be continued.*

RECOMMENDATION

We suggest against the use of remdesivir in patients with COVID-19 infection who have O2 saturation ≥94% and do not require oxygen supplementation. *(Low certainty of evidence, Weak recommendation)*

RECOMMENDATION

We suggest against the use of remdesivir in patients with COVID-19 infection who are already on invasive mechanical ventilation or ECMO. *(Low certainty of evidence, Weak recommendation)*

KEY FINDINGS

- Four randomized controlled trials on the use of remdesivir as treatment for COVID-19 were found [38-41]. Low certainty of evidence shows that remdesivir has limited effect on all cause-mortality, clinical improvement, and initiation of mechanical ventilation among confirmed COVID-19 patients. However, remdesivir appears to be beneficial in the time to clinical improvement especially among cases needing supplemental oxygen but not high flow oxygen/ mechanical ventilation.
- Remdesivir did not show increased risk for serious adverse events. Availability and cost of intervention should be considered before making recommendations regarding its use locally.

CONSENSUS ISSUES

Early introduction of remdesivir in the treatment of COVID-19 is preferred because of its action on the polymerase resulting in less viral replication. Remdesivir is a relatively safe drug, but its cost should be considered. Hence, routine use of the drug is not recommended. There are 26 ongoing trials pertaining to the efficacy and safety of remdesivir for the treatment of COVID-19.

Among patients with COVID-19, should molnupiravir be used for treatment?

As of 10 January 2022

RECOMMENDATION

We suggest the use of molnupiravir within 5 days of symptom onset among non-hospitalized adult patients (18 years old and older) with mild to moderate COVID-19 infection with at least one risk factor* for progression. *(Low certainty of evidence, Weak recommendation)*

Risk factors for progression include:
age >60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, serious heart conditions or diabetes mellitus

KEY FINDINGS

- Five (5) randomized controlled trials (RCTs) [42-46] studied the effect of molnupiravir on the treatment of COVID-19 compared to standard of care and/or placebo. Molnupiravir significantly decreased the need for hospitalization at day 29. Subgroup analysis based on the severity showed significant reduction in mortality in non-hospitalized mild to moderate patients but did not show significant benefit among hospitalized mild to severe patients. For other critical outcomes, molnupiravir had no apparent effect on clinical improvement based on patient reported outcome measures (FLU-PRO), WHO COVID-19 ordinal scale, National Early Warning Score (NEWS2) and sustained recovery. Adverse events and serious adverse events were similar between molnupiravir and standard of care and/or placebo.
- The phase 2a study had randomization issues and reporting bias. The serious risk of bias and imprecision led to the downgrading of evidence to low certainty.

CONSENSUS ISSUES

Molnupiravir showed general net benefit, specifically for mortality. The drug should be given specifically within the given time period (within 5 days of symptom onset). There are still issues to consider about the availability and use since it is still limited (currently available under compassionate special permit issued by FDA).

Should baloxavir be used in the treatment of patients with COVID-19 infection?

As of 20 May 2021

RECOMMENDATION

We suggest against the use of baloxavir as treatment for patients with COVID-19 infection. (Very low certainty of evidence, Weak recommendation)

KEY FINDINGS

There was only one randomized controlled trial [47] included in this review. Treatment with baloxavir did not lead to significant reduction in the need for invasive mechanical ventilation, admission to intensive care unit, hospitalization and clinical improvement (very low quality of evidence). There was no report of mortality in any of treatment arms. Currently, there are two ongoing clinical trials on the efficacy of baloxavir as treatment for COVID-19.

CONSENSUS ISSUES

Only one small study was included in the review, which showed consistent result of no significant benefit across all the outcomes measured (i.e., need for mechanical ventilator/ ECMO, admission to ICU, hospitalization, clinical improvement at 14 days, adverse events and time to clinical improvement). It was noted that baloxavir is a repurposed drug for COVID-19 and is originally indicated for influenza. It costs Php 450 per tablet and is usually given within 48 hours from the onset of symptoms for the treatment of influenza. In terms of health equity, it was raised that since its benefit is yet to be established, resources should be allocated to more known and established drugs where the benefits are certain.

Should oseltamivir be used for the treatment of COVID-19?

As of 22 May 2021

RECOMMENDATION

We recommend against the use of oseltamivir as treatment for patients with COVID-19 infection. *(Very low certainty of evidence, Strong recommendation)*

KEY FINDINGS

Based on the five retrospective cohort studies [48-52] included in this review, oseltamivir was associated with increased risk of mortality (Odds Ratio (OR), 4.20; [95%CI 4.03, 4.38], very low certainty of evidence). Moreover, it was associated with risk of disease progression (OR 5.22; [95% CI, 2.00, 13.02], low quality of evidence) as well as longer time to viral clearance (standard mean difference (SMD) of 1.65 days longer [95% CI 1.27, 2.03], low quality of evidence). Currently, there are five ongoing clinical trials on the efficacy of oseltamivir as treatment for COVID-19.

CONSENSUS ISSUES

The panel made a strong recommendation against the use of oseltamivir noting that the mortality rate among patients given the drug is higher compared to those given standard of care (i.e., 27% vs. 6%). Likewise, results showed that the progression to severe disease is five times more likely among patients taking oseltamivir.

Should lopinavir/ritonavir be used in the treatment of COVID-19?

As of 07 April 2021

RECOMMENDATION

We recommend against the use of lopinavir/ritonavir as treatment for COVID-19 infection. *(Moderate certainty of evidence, Strong recommendation)*

KEY FINDINGS

Based on 5 randomized controlled trials [53-57] enrolling both suspected and confirmed COVID-19 patients, lopinavir/ritonavir combination did not significantly affect clinical improvement, all-cause mortality, viral negative conversion, need for mechanical ventilation, or WHO progression score level 7 or higher, when compared to standard of care. No difference in adverse events were also seen between lopinavir/ritonavir and control groups. The overall quality of evidence ranged from low to high across different outcomes.

Among patients with COVID-19, should tocilizumab be used for treatment?

As of 28 October 2021

RECOMMENDATION

We recommend the addition of tocilizumab to systemic steroids in patients showing rapid respiratory deterioration and/or requiring high doses of oxygen (high-flow nasal cannula, noninvasive or invasive mechanical ventilation) and with elevated biomarkers of inflammation (CRP). *(Moderate certainty of evidence, Strong recommendation)*

RECOMMENDATION

We recommend against the use of tocilizumab among patients with COVID-19 infection who do not require oxygen. *(Very low certainty of evidence, Strong recommendation)*

KEY FINDINGS

Fifteen (15) randomized controlled clinical trials (RCTs) [58-72] (N = 8,937) that investigated the effectiveness of tocilizumab among confirmed hospitalized COVID-19 patients compared to placebo and/or standard of care was found. Tocilizumab significantly reduced all-cause mortality, time to clinical improvement, and the need for mechanical ventilation, with no significant increase in adverse events among hospitalized patients.

CONSENSUS ISSUES

Report on adverse events, although an important outcome, was not rated as a critical outcome to be included in the decision making. The over-all assessment of the certainty of evidence is based only on critical outcomes identified by the consensus panel, hence, the quality of evidence was retained as moderate.

There is no new evidence on the use of tocilizumab among patients with COVID-19 infection who do not require oxygen. Given the lack of evidence, potential adverse effects and risks, this recommendation also considers indiscriminate use to avoid misuse or overuse of tocilizumab among patients who do not require oxygen.

Among patients with COVID-19, should baricitinib be used for treatment?

As of 21 October 2021

RECOMMENDATION

We suggest the use of baricitinib in addition to dexamethasone and remdesivir as treatment for hospitalized COVID-19 patients who require low-flow oxygen, high-flow oxygen, and non-invasive ventilation. *(Low certainty of evidence; Weak recommendation)*

RECOMMENDATION

There is insufficient evidence to recommend baricitinib as an alternative to tocilizumab as treatment for hospitalized COVID-19 patients. *(Very low quality of evidence)*

KEY FINDINGS

The evidence on the use of baricitinib comes from 2 RCTs [73-75] among hospitalized patients with moderate to severe COVID-19. Both studies found that there was a reduction in the all-cause mortalities, progression of oxygen use, and serious adverse events in the baricitinib group compared to the control group. However, there was no significant difference in the duration of hospitalization between the two groups.

CONSENSUS ISSUES

The recommendation to give baricitinib in addition to dexamethasone and remdesivir was made based on 2 randomized controlled trials wherein baricitinib was given as an add-on therapy to dexamethasone and remdesivir among hospitalized patients with moderate to severe COVID-19. At present, dexamethasone, a systemic corticosteroid, is considered standard of care for patients requiring oxygen supplementation (High quality of evidence; Strong recommendation), while remdesivir may be considered as an additional therapy for patients who require oxygen supplementation but not on invasive mechanical ventilation (Low quality of evidence, Conditional recommendation). Although remdesivir is not currently considered standard care, there are studies that show possible synergistic effect in concurrently giving an anti-viral to shorten viral clearance plus an immunomodulator to address impending cytokine storm. Addition of baricitinib is recommended only for non-intubated patients (i.e., on low-flow oxygen, high-flow oxygen, and non-invasive ventilation).

As of writing, the available evidence on baricitinib is not as robust as tocilizumab, and there is only 1 retrospective observational study, which directly compared baricitinib versus tocilizumab. As such, there is insufficient evidence to make recommendations on whether baricitinib may be used as an alternative to tocilizumab. Strategies for conservation of tocilizumab is beyond the scope of the consensus panel, and may be discussed by the local expert group working on COVID-19 treatment algorithms.

Among patients with COVID-19, should imatinib be used for treatment?

As of 8 November 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of imatinib among patients with COVID-19 infection. *(Low certainty of evidence)*

KEY FINDINGS

There is one (1) randomized controlled trial (RCT) [76] that investigated the effect of imatinib compared to placebo as treatment for hospitalized patients with COVID-19 requiring supplemental oxygen. Imatinib was associated with significant reduction in the duration of mechanical ventilation and duration of intensive care unit (ICU) stay. However, there was no significant benefit for several outcomes such as mortality at day 28, need for ICU admission, need for mechanical ventilation, discontinuation of supplemental oxygen and mechanical ventilation, discontinuation of ventilation and supplemental oxygen in 48 hours, and duration of hospital admission. There was also no significant difference in the number of adverse events. The overall certainty of evidence was rated low; evidence was downgraded for serious risk of bias and imprecision due to wide confidence intervals and small number of events.

CONSENSUS ISSUES

Further trials are needed to recommend the use of imatinib for the treatment of COVID-19.

Among patients with COVID-19, should tofacitinib be used for treatment?

As of 21 October 2021

RECOMMENDATION

We suggest against the use of tofacitinib among hospitalized COVID-19 patients. *(Low certainty of evidence, Weak recommendation)*

KEY FINDINGS

- There is one (1) randomized controlled trial (RCT) [77] that investigated the effect of tofacitinib compared to placebo as treatment for patients with COVID-19. Patients treated with tofacitinib had a significant reduction in death or respiratory failure. Tofacitinib did not show significant effect in all-cause mortality, need for mechanical ventilation or extracorporeal membrane oxygenation (ECMO), cure (defined as resolution of fever, cough, or need for ventilatory/oxygen support), length of hospitalization, length of ICU stay, and duration of mechanical ventilation.
- There was no significant increase in serious adverse events and adverse events between the tofacitinib and placebo group. However, there was a significant increase in adverse events leading to treatment discontinuation for patients given tofacitinib compared to placebo, with increase in transaminase levels and lymphopenia being the most commonly reported adverse events. The very serious

imprecision due to the limited number of events contributed to the downgrading of evidence to a low certainty of evidence.

CONSENSUS ISSUES

The recommendation against the use of tofacitinib among hospitalized patients with COVID-19 was mainly due to the drug's safety issues. Although the study showed that there was benefit in reducing death or respiratory failure, particularly among patients on low-flow supplemental oxygen, patients who received tofacitinib were three times more likely to experience adverse events leading to treatment discontinuation. Furthermore, the US FDA and Health Canada issued safety alert on the use of tofacitinib due to increased risk of serious cardiovascular-related events (heart attack, stroke), cancer (lymphoma, lung cancer), thrombosis and death.

Among patients with COVID-19, should leronlimab be used for treatment?

As of 28 October 2021

RECOMMENDATION

We suggest against the use of leronlimab as treatment for COVID-19. *(Very low certainty of evidence, Weak recommendation)*

KEY FINDINGS

Two (2) unpublished randomized controlled trial (RCTs) [78-82] investigated the effect of leronlimab compared to placebo as treatment for patients with COVID-19. There was no significant benefit in the use of leronlimab in reducing mortality, length of hospital stay, resolution of clinical symptoms, and time to symptom resolution. There was no significant difference in serious adverse events and adverse events. The overall quality of evidence was rated very low because of serious risk of bias and very serious imprecision.

CONSENSUS ISSUES

The evidences of the review are now based on unpublished randomized controlled trials (previously from case series and a case study), however, similar to the previous consensus issue, the panel agreed that further trials are needed to recommend the use of leronlimab for the treatment of COVID-19.

Among patients with COVID-19, should infliximab be used for treatment?

As of 12 October 2021

RECOMMENDATION

We suggest against the use of infliximab among patients with COVID-19 infection *(Very low certainty of evidence, Weak recommendation)*

KEY FINDINGS

There is one (1) pre-print randomized controlled trial (RCT) [83] that reported the effect of infliximab compared to standard of care as treatment for patients with COVID-19. Results of the RCT showed no significant difference in mortality, hospital discharge in 28 days, and time to improvement in the WHO clinical progression scale. The RCT suffered from lack of allocation concealment, blinding, and poor comparability of treatment groups. It was also terminated prematurely due to futility. The very serious risk of bias and imprecision contributed to the downgrading of evidence to a very low certainty of evidence.

CONSENSUS ISSUES

The recommendation against the use of infliximab among patients with COVID-19 was made based on a small, pre-print randomized controlled trial (n = 63), which did not show any benefit on mortality, hospital discharge within 28 days, and time to clinical improvement. The panel also emphasized that the infliximab arm of the study was prematurely terminated due to futility on interim analysis, explaining its small sample size.

Among patients with COVID-19, should bevacizumab be used for treatment?

As of 12 October 2021

RECOMMENDATION

We suggest against the use of bevacizumab as treatment for COVID-19. *(Very low certainty of evidence, Weak recommendation)*

KEY FINDINGS

One (1) small non-randomized clinical trial [84] investigated on the potential use of bevacizumab for treatment of COVID-19. The study showed that bevacizumab led to net potential harm with minimal potential benefit only in terms of duration of oxygen support. Evidence was inconclusive for hospital discharge. Adverse events in the bevacizumab group were elevation of liver enzymes (30%), reduced hemoglobin (19%), decreased platelet counts (15%), elevation of blood pressure (11%), elevated blood urea nitrogen (7%), and sepsis (7%).

CONSENSUS ISSUES

Currently available evidence came from one small non-randomized clinical trial with only 27 patients in the treatment group and 26 patients in the external control cohort.

Administration of bevacizumab led to net potential harm with unclear potential benefit in only 1 non-critical outcome (i.e., duration of oxygen support). Its cost and potential negative effect on equity, since the drug is also being used as treatment for lung cancer, were also considered by the consensus panel. At present, bevacizumab is not readily accessible due to its limited availability and large cost. Use of bevacizumab among COVID-19 patients when its benefit is still unclear, may lead to even greater difficulty for lung cancer patients to gain access to this drug.

Among patients with COVID-19, should ivermectin be used for treatment?

As of 6 December 2021

RECOMMENDATION

We recommend against the use of ivermectin for the treatment of patients with COVID-19 of any severity. *(Very low certainty of evidence, Strong recommendation)*

We suggest against the use of ivermectin combined with doxycycline for the treatment of patients with COVID-19. *(Very low certainty of evidence, Weak recommendation)*

We suggest against the use of ivermectin combined with doxycycline for the treatment of patients with COVID-19. *(Very low certainty of evidence, Weak recommendation)*

KEY FINDINGS

- There are 16 randomized controlled trials (RCTs) [85-113] that investigated the effects of ivermectin as treatment for patients with COVID-19. No significant overall mortality benefit was found. Subgroup analysis by disease severity also showed no significant benefit for low dose ivermectin. We cannot estimate the risk of benefit or harm associated with high dose ivermectin because no deaths were reported among the three included RCTs. Sensitivity analysis revealed that publication status and study quality did not influence our estimates.
- Treatment with ivermectin was not significantly associated with clinical deterioration, need for mechanical ventilation, clinical improvement, reduction in hospital length of stay, time to symptom resolution, and virologic clearance. The risk for serious and non-serious adverse events was not significantly different among patients who received ivermectin. Our results agree with a recent Cochrane systematic review done in May 2021.
- These results must be interpreted in the context of very low certainty of evidence. The certainty of evidence was downgraded due to varying degrees of risk of bias in most studies, inconsistency, and imprecision in several critical outcomes.

CONSENSUS ISSUES

The review showed that ivermectin has no clear benefit for mortality and all other outcomes for patients with different disease severity, hence the panel made a general recommendation for all COVID-19 patients regardless of severity (mild, moderate, severe or critical).

This update provided additional evidence ivermectin did not differ significantly from placebo in terms of critical outcomes in the treatment of COVID-19. Hence, given the ongoing misuse and abuse of the drug, the panel unanimously voted for a strong recommendation against the use of ivermectin. Other considerations included issues on the pharmacologic property of the drug, given that the drug is registered for veterinary use, the need for higher doses, and concerns regarding adverse events. The panel also considered the issue on health equity wherein other medications for COVID-19 are available, hence resources should be allocated to these more effective

and efficacious treatment with clear benefits. There are still a number of ongoing trials, including a local one, which will be considered once data is available.

There is no new evidence for ivermectin combined with doxycycline available, hence, no update was done and the previous recommendations were retained.

Among patients with COVID-19, should artesunate (artemisinin) be used for treatment?

As of 18 November 2021

RECOMMENDATION

We suggest against the use of artesunate, artemisinin or pyronaridine tetraphosphate + artesunate in the treatment of COVID-19. *(Very low certainty of evidence, Weak recommendation)*

KEY FINDINGS

There are three (3) randomized controlled trials (RCTs) [114-116] that investigate the effect of artesunate (artemisinin) compared to varying standards of care or placebo as treatment for patients with COVID-19. Artesunate showed no significant difference in mortality, clinical deterioration, improvement in chest CT scan or X-ray, time to virologic clearance, and mild and moderate-to-severe adverse effects. Two (2) studies reported shorter time to clinical improvement for artesunate. The overall certainty of evidence was rated very low due to very serious imprecision, serious risk of bias, and in some outcomes, inconsistency and indirectness.

CONSENSUS ISSUES

There may be evidence on the in vitro effect of the drug. Despite being a new drug, we have a similar drug being used for malaria (Artemether-lumefantrine). However, given that the evidences available are very limited and the effect of drug is not yet clear, the panel unanimously suggests against the use of it. We need to wait for ongoing studies and more evidence for its use and effect on COVID 19.

Among patients with COVID-19, should colchicine be used for treatment?

As of 8 November 2021

RECOMMENDATION

We suggest against the use of colchicine in the treatment of COVID-19 patients. *(Low certainty of evidence, Weak recommendation)*

KEY FINDINGS

- Five (5) randomized controlled trials (RCTs) [117-122] investigated the effect of colchicine compared to standard of care as treatment for patients with COVID-19. Colchicine showed net potential harm (significant increase in adverse events) with no significant benefit in all-cause mortality, need for mechanical ventilation, clinical improvement (defined as hospital discharge) within 28 days, need for hospitalization, and need for hemodialysis or hemofiltration.
- One large RCT reported that colchicine did not significantly shorten duration of hospitalization, while 2 smaller RCTs reported significantly shorter duration of hospitalization (data could not be pooled due to inadequate data provided). All studies had risk of bias issues as there were concerns in allocation concealment, blinding, attrition and selective reporting of outcome. The serious risk of bias and issues with inconsistency and imprecision in one critical outcome contributed to the downgrading of evidence to very low certainty of evidence.

CONSENSUS ISSUES

The addition of a large multicenter trial (RECOVERY trial) still showed that colchicine led to net potential harm (significant increase in adverse events) with no significant benefit in terms of all-cause mortality, clinical improvement (defined as hospital discharge) within 28 days, need for hospitalization, need for mechanical ventilation, and need for hemodialysis or hemofiltration. Hence, the consensus panel decided to maintain the previous recommendation against the use of colchicine in patients with COVID-19, regardless of hospitalization status.

Among patients with COVID-19, should interferon be used for treatment?

As of 6 December 2021

RECOMMENDATION

We recommend against the use of interferon in the treatment of COVID-19 patients. *(Very low certainty of evidence, Strong recommendation)*

KEY FINDINGS

Nine (9) published randomized controlled clinical trials (RCTs) [123-131] (N = 5,957) investigated the efficacy and safety of interferon in the treatment of COVID-19 compared to standard of care and/or placebo. Results showed significant benefit on viral negative conversion among patients given interferon, however, there was inconclusive evidence in terms of the critical outcomes such as all-cause mortality, clinical improvement, need for mechanical ventilation, progression to severe disease, ICU admission, adverse events, and serious adverse events.

CONSENSUS ISSUES

Recent review included more participants (close to 6,000) yet, interferon still did not show any clear benefit for all-cause mortality and other critical outcomes. There is a need to emphasize the potential harm and side effects of the drug as well as its high cost.

Among patients with COVID-19, should fluvoxamine be used for treatment?

As of 8 November 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of fluvoxamine among COVID-19. *(Low certainty of evidence)*

KEY FINDINGS

Two (2) published randomized controlled trials (RCTs) [187-188] (N = 1,649) investigated on the effectiveness of fluvoxamine compared to placebo among confirmed symptomatic non-hospitalized COVID-19 patients compared. Results showed significant reduction in emergency room visits and the need for hospitalization. There was inconclusive evidence in terms of other critical outcomes such as all-cause mortality, clinical deterioration, viral negative conversion, adverse events, and serious adverse events.

CONSENSUS ISSUES

Current evidence showed that although fluvoxamine appeared to reduce the need for emergency room visit or hospitalization, there was inconclusive evidence in terms of other critical outcomes such as all-cause mortality, clinical deterioration, adverse events, and serious adverse events. The sample size of the two randomized controlled trials may still be too small to reach a level of significance, precluding any

recommendation to be made. As of writing, there are 9 ongoing clinical trials, results of which may further elucidate on fluvoxamine's effectiveness in the treatment of COVID-19.

Among patients with COVID-19, should bamlanivimab in combination with etesevimab be used for treatment?

As of 12 October 2021

RECOMMENDATION

We suggest the use of bamlanivimab and etesevimab combination therapy as treatment for mild to moderate, non-hospitalized COVID-19 patients with at least 1 risk factor* for progression to severe disease. *(Low certainty of evidence, Weak recommendation)*

**Risk factors for severe COVID-19: age ≥65 years, body-mass index ≥35 kg/m^2, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromised conditions*

KEY FINDINGS

The evidence on the use of bamlanivimab + etesevimab combination comes from two (2) randomized controlled trials (RCTs) [154-155] among non-hospitalized patients with COVID-19. Both studies found that there was a significant reduction in COVID-19 related hospitalizations, all-cause mortalities, symptom resolution, and reduction in viral load among the participants who received the bamlanivimab + etesevimab cocktail compared to placebo. There was no significant difference in adverse events between the two groups.

CONSENSUS ISSUES

The panel favoured the use of bamlanivimab and etesevimab among non-hospitalized COVID-19 patients who are at risk for severe disease, based on the results of 2 randomized controlled trials that showed net potential benefit in terms of COVID-19 related hospitalizations and all-cause mortality, reduction in total symptom score, and number of days to symptom resolution, with no significant difference in terms of adverse events. Concern regarding the drug's effectivity against variants was raised by one of the panelists. As of writing, the drug has no emergency use authorization from the Philippine FDA, thus may only be used in the context of clinical trials.

Among patients with COVID-19, should casirivimab-imdevimab be used for treatment?

As of 20 December 2021

RECOMMENDATION

We suggest the use of casirivimab-imdevimab as treatment for symptomatic, non-hospitalized patients with at least 1 risk factor* for severe COVID-19. (*Moderate certainty of evidence, Weak recommendation)*

**Risk factors: age >50 years, obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromised conditions*

RECOMMENDATION

We recommend against casirivimab-imdevimab as treatment for hospitalized COVID-19 patients. (*Low certainty of evidence, Strong recommendation)*

RECOMMENDATION

There is insufficient evidence to recommend casirivimab-imdevimab as treatment for asymptomatic COVID-19 patients. *(Low certainty of evidence)*

KEY FINDINGS

Six (6) RCTs [156-161] evaluated the efficacy of casirivimab-imdevimab cocktail as treatment for patients with COVID-19. Among non-hospitalized patients given casirivimab-imdevimab, there was a significant reduction in combined end-point of need for invasive mechanical ventilation or death, COVID-19-related medically-assisted visits, duration of symptoms, and serious adverse events. However, evidence was largely inconclusive for hospitalized patients and asymptomatic, non-hospitalized patients. There was trend towards benefit in clinical recovery among hospitalized seronegative patients (negative for serum SARS-CoV-2 antibodies at baseline), but not for seropositive patients (positive for serum SARS-CoV-2 antibodies at baseline). There was no benefit in all-cause mortality regardless of hospitalization status.

CONSENSUS ISSUES

Addition of 2 new pre-print randomized controlled trials (RCTs) still showed that casirivimab and imdevimab cocktail is beneficial for symptomatic, non-hospitalized COVID-19 patients with at least 1 risk factor for progression to severe disease. Although there was moderate certainty of evidence, the recommendation was weak due to inconclusive evidence on all-cause mortality, large cost, need for emergency room visit for drug administration and close monitoring and equity considerations. At present, the drug is only available in private tertiary hospitals.

The evidence remained inconclusive for hospitalized COVID-19 patients. The previous update included 1 pre-print RCT (RECOVERY trial), which on subgroup analysis showed that casirivimab-imdevimab appeared to have benefit in terms of all-cause mortality, need for mechanical ventilation, and clinical recovery among hospitalized patients who were seronegative at baseline (negative for serum SARS-CoV-2

antibodies). However, addition of 1 (one) new pre-print RCT showed trend towards benefit in clinical recovery only. The panel maintained the previous recommendation against the use of casirivimab-imdevimab cocktail among hospitalized COVID-19 patients because of uncertain balance of effects in this specific subset of patients and both RCTs are still pre-print. As of writing, there are 8 ongoing clinical trials on casirivimab-imdevimab, 2 of which are among hospitalized patients. Results of these trials may further elucidate on the cocktail's effectiveness in the treatment of hospitalized COVID-19 patients.

Lastly, the only available study for asymptomatic, non-hospitalized COVID-19 patients is a small pre-print RCT with low certainty of evidence. The panel deemed that current evidence is still insufficient to make any recommendations for this subset of patients.

Among patients with COVID-19, should regdanvimab be used for treatment?

As of 20 December 2021

RECOMMENDATION

We suggest against the use of regdanvimab for the treatment of mild to moderate COVID-19. *(Very low certainty of evidence, Weak recommendation)*

KEY FINDINGS

Two (2) randomized controlled trials (RCTs) [162-163] evaluated the efficacy of regdanvimab as treatment for patients with COVID-19. The overall certainty of evidence was very low because of serious risk of bias, imprecision, and high probability of publication bias. Among patients with mild to moderate COVID-19 infection, regdanvimab showed minimal potential benefit in terms of clinical recovery at Day 14 and Day 28. There was inconclusive evidence in terms of other critical outcomes such as all-cause mortality, need for hospitalization, and oxygen therapy requirement. There was no significant difference in adverse events between patients treated with regdanvimab compared to placebo.

CONSENSUS ISSUES

Very limited evidence (2 small randomized controlled trials, one of which is still a pre-print) support the use of regdanvimab in treatment of mild to moderate COVID-19. Although regdanvimab showed potential benefit in terms of clinical recovery at Day 14 and Day 28, the evidence was inconclusive for other critical outcomes such as all-cause mortality, need for hospitalization, or clinical deterioration. Clinical recovery among patients with moderate to severe symptoms at baseline was defined as improvement of symptoms and not necessarily complete resolution of symptoms. Concern regarding the effect of possible publication bias on subjective outcomes such as clinical recovery was raised, since currently available studies were both funded by regdanvimab's manufacturing company. Hence, the panel suggested against use of regdanvimab considering its limited evidence, potentially large cost, and availability of treatment alternatives with more robust evidence that has shown benefit on more objective outcomes (e.g., all-cause mortality and need for hospitalization) among patients with mild to moderate COVID-19.

Among patients with COVID-19, should convalescent plasma be used for treatment?

As of 18 November 2021

RECOMMENDATION

We recommend against the use of convalescent plasma in patients with COVID-19 infection. *(Moderate certainty of evidence, Strong recommendation)*

KEY FINDINGS

- There are 22 randomized controlled trials (RCTs) [132-153] that compared the effect of convalescent plasma therapy against placebo and/or standard of care among confirmed COVID-19 patients. Pooled estimates of critical patient outcomes (i.e., all-cause mortality) on the use of convalescent plasma were not statistically significant. Exploratory subgroup analysis done for all-cause mortality by age, severity of disease, and timing of administration did not show any statistically significant benefit except for the subgroup of early administration (defined as within 3 days of hospitalization) of high-level titers of convalescent plasma (RR 0.42, 95% CI 0.21, 0.86; I^2 = 0%; 4 RCTS, n = 376).
- The incidence of adverse and serious adverse events (e.g., transfusion-related events) were not significantly different between the convalescent plasma group and those given standard care or placebo. The over-all certainty of evidence was retained as moderate.

CONSENSUS ISSUES

Serious adverse events and progression to respiratory distress/respiratory failure were re-rated and still considered as critical outcomes. However, the panel unanimously voted to give more value to the effect of convalescent plasma on all-cause mortality, clinical improvement, and need for invasive ventilation and ICU admission, hence, the over-all certainty of evidence was retained as moderate.

Recommendation remains strong given that convalescent plasma is no different from placebo in terms of efficacy, clinical outcomes, and harm; yet there is a lot to consider in terms of cost, value preferences, equity, and feasibility.

Should intravenous immunoglobulin (IVIG) be used for the treatment of COVID-19?

As of 18 May 2021

RECOMMENDATION

We suggest against the use of intravenous immunoglobulin as treatment for moderate to severe COVID-19. *(Very low certainty of evidence, Weak recommendation)*

KEY FINDINGS

Four (4) RCTs [164-167] that were of low to very low quality found that the use of intravenous immunoglobulin (IVIg) did not significantly reduce mortality or risk of mechanical ventilation among patients with moderate to severe COVID-19. However, one very low quality RCT found higher incidence of virologic clearance as assessed by negative RT PCR with the use of IVIg. There was also no significant increase risk of adverse events with its use in COVID-19.

CONSENSUS ISSUES

A conditional recommendation was made while waiting for the results of the 31 ongoing trials.

Should mesenchymal stem cell therapy be used for the treatment of COVID-19?

As of 29 May 2021

RECOMMENDATION

There is insufficient evidence to recommend using umbilical cord-derived mesenchymal stem cell therapy among adults with severe COVID-19 (PaO2/FiO2 ratio ≤ 300 mmHg). *(Very low certainty of evidence)*

KEY FINDINGS

We found 3 randomized controlled trials [168-170] evaluating the effectiveness and safety of mesenchymal stem cell (MSC) therapy in COVID-19 treatment. One RCT was at high risk of bias while the remaining 2 RCTs were of moderate quality. Validity issues included unclear allocation concealment, lack of blinding and incomplete outcome reporting. Based on very low certainty of evidence, umbilical cord-derived MSC (UC-MSC) therapy reduces mortality and hastens clinical improvement in adults with severe COVID-19. Limited by small sample sizes, adverse events were not significantly different between MSC and control groups.

CONSENSUS ISSUES

Although the current available evidence shows benefit in terms of mortality and time to clinical improvement, no recommendation was made due to the small sample size of the included studies. Further, more patients in the mesenchymal stem cell (MSC) therapy arm received co-interventions (i.e., remdesivir and corticosteroids) compared to the control arm which may have overestimated the true effect of MSC.

Among patients with COVID-19, should inhaled corticosteroiuds be used for treatment?

As of 18 November 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of inhaled corticosteroids in treatment of non-hospitalized COVID-19 patients. *(Very low certainty of evidence)*

KEY FINDINGS

Four (4) randomized controlled trials (RCTs) [171-174] investigated the effectiveness of inhaled corticosteroids for the treatment of COVID-19. Use of inhaled corticosteroids (e.g., budesonide and ciclesonide) among non-hospitalized patients with mild to moderate COVID-19 demonstrated benefit only for subjective outcomes such as self-reported clinical recovery or improvement at day 14 and day 28/30 but not for objective outcomes such as mortality, need for hospitalization, emergency room visit, and duration of hospitalization. There was no significant difference in serious adverse events and adverse events.

CONSENSUS ISSUES

Current evidence shows that inhaled corticosteroids (i.e., budesonide and ciclesonide) had benefit for subjective outcomes such as self-reported recovery on day 14 and day 28/30. However, evidence was inconclusive in terms of objective outcomes such as mortality, emergency room visit, need for hospitalization, duration of hospitalization, and clinical improvement (as evaluated by an assessor). Self-reported recovery may be biased since participants are not blinded, hence a more objective marker of clinical status such as oxygen saturation is more reliable. Only 1 study explicitly excluded patients with asthma or chronic obstructive pulmonary disease (COPD), and the perceived positive effect may have been due to improvement of asthma or COPD and not COVID infection. As of writing, there are 13 ongoing clinical trials, results of which may further elucidate on the effectiveness of inhaled corticosteroids in the treatment of COVID-19.

Should steam inhalation be used for the treatment of COVID-19?

As of 12 March 2021

RECOMMENDATION

We recommend against the use of steam inhalation alone in the treatment of COVID-19. *(Very low certainty of evidence, Strong recommendation)*

KEY FINDINGS

Based on a single arm observational study [175] with high risk of bias, there is currently only very low certainty of evidence showing the possible benefit of steam inhalation in the prevention of developing symptomatic COVID-19 among exposed healthy individuals and reducing symptoms and number of days to negative SARS-COV-2 RT-PCR test of COVD-19 confirmed individuals. Meanwhile, there is indirect evidence

highlighting the significant adverse effects of steam inhalation among individuals using it for symptomatic relief from the colds.

CONSENSUS ISSUES

The panel strongly recommended against the use of steam inhalation as treatment for COVID-19, despite the very low quality of evidence, because it was recognized that the potential for harm outweighs the benefit.

Should virgin coconut oil (VCO) be used in the treatment of patients with COVID-19 infection?

As of 20 February 2021

RECOMMENDATION

There is no evidence to recommend the use of VCO as treatment among patients with COVID-19 infection.

KEY FINDINGS

To date, there is no available completed clinical trial directly investigating effectiveness or safety of virgin coconut oil as an adjunct treatment for COVID-19 patients of any age or disease severity. Indirect evidence was noted from two studies of VCO on other viruses such as human immunodeficiency viruses. [178-179]

CONSENSUS ISSUES

It is important to note that this recommendation is strictly for the use of VCO in the treatment of COVID-19 infection and should not be confused with another living recommendation pertaining to the use of VCO in the adjunctive treatment of COVID-19.

The ongoing clinical trial for VCO is not yet registered with the local Food and Drug Administration, hence, the evidence that will be generated cannot be used as an additional indication for the marketing purpose of VCO.

Among patients with COVID-19, should Lianhua be used for treatment?

As of 06 December 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of Lianhua in the treatment of patients with non-severe COVID-19. *(Very low certainty of evidence)*

KEY FINDINGS

Five (5) randomized controlled trials investigated the effect of Lianhua compared to standard of care as treatment for patients with COVID-19. Lianhua showed significant benefit in preventing clinical deterioration or progression to severe disease among patients with non-severe COVID 19. There was no significant benefit in mortality, and day-14 improvement in fever, cough and fatigue. There was no significant difference

in adverse events or serious adverse events between the Lianhua and control group. The overall certainty of evidence was rated very low due to very serious risk of bias and serious imprecision in some critical outcomes.

CONSENSUS ISSUES

Although the recent review showed some benefit on the symptomatic treatment (clinical deterioration), the panel considered that the uncertainties on the quality of the evidence outweigh the trend in benefit. First, the subset of patients (percentage of mild and moderate cases) were not clearly stated in the included studies. This may actually affect the trend towards benefit since patients with mild COVID are expected to improve and have shorter time to recovery. Second, the definition of outcomes, particularly total symptom recovery may be too lax as it accounted only for at least one of the major symptoms. The panel also considered that since this is a regulated drug, there are uncertainties about the reported harm (expected adverse effects from ephedra such as hypertension and tachycardia was not assessed in the study procedures or reported in the results) and serious adverse events (unclear if the reported events were transient nor how severe the cases were). There are also inconsistencies in the direction of the clinical outcomes. While there is some benefit seen in reducing clinical deterioration, no definite benefit was seen in terms of clinical improvement of individual symptoms.

Should famotidine be used for the treatment of COVID-19?

As of 30 May 2021

RECOMMENDATION

We suggest against the use of famotidine in the treatment of COVID-19. (*Very low certainty of evidence, Weak recommendation)*

KEY FINDINGS

Very low-quality evidence from seven retrospective cohort studies [180-186] was found on the use of famotidine for the treatment of COVID-19. There was no significant reduction in the risk of mortality, mechanical ventilation, and composite outcome of mortality or mechanical ventilation. However, there was a significant increase in the risk of the composite outcome of mortality, mechanical ventilation, and intensive care unit admission. Adverse events were not examined in these retrospective cohort studies.

Should ibuprofen be used in the treatment of patients with COVID-19 infection?

As of 5 March 2021

RECOMMENDATION

We recommend against the use of ibuprofen as treatment among patients with COVID-19 infection. *(Very low certainty of evidence, Strong recommendation)*

KEY FINDINGS

Currently, there are no randomized controlled trials that assessed the efficacy of ibuprofen as a treatment for COVID-19. Based on the two observational studies (one retrospective cohort and one case series) [176-177] that have not been peer-reviewed, there is limited evidence that ibuprofen treatment could improve COVID-19 symptoms and outcomes.

CONSENSUS ISSUES

It is important to note that this recommendation is strictly for the use of ibuprofen in the treatment of COVID-19 infection and should not be confused with another living recommendation pertaining to the effect of the concurrent use of ibuprofen with other COVID-19 outcomes.

Although direct evidence of very low quality suggests a trend towards benefit, there was indirect evidence of possible harm. The benefit that was seen from the first study might not be solely because of ibuprofen given that other patients were given other medications. The severity of COVID-19 infection was not also specified in the first study and it was assumed that it included patients of all severity (i.e., mild, moderate, severe) since the information were taken from electronic health records of different hospitals.

Evidence and Recommendations for the Critical Care and Respiratory Management of COVID-19

Should intravenous corticosteroids be used in COVID-19?

As of 03 January 2022

RECOMMENDATION

We recommend the use of dexamethasone for up to 10 days among patients with severe and critical COVID-19. *(Moderate certainty of evidence; Strong recommendation)*

We recommend the use of 6mg to 12mg per day of dexamethasone among patients with severe and critical COVID-19. *(Moderate certainty of evidence; Strong recommendation)*

We suggest that steroid therapy be initiated as soon as diagnosed or categorized as severe and critical COVID-19. *(Very low certainty of evidence; Weak recommendation)*

RECOMMENDATION

We recommend against the use of corticosteroids among mild and moderate (non-oxygen requiring) COVID-19 patients*. (Moderate certainty of evidence; Strong recommendation)*

KEY FINDINGS

- Fourteen randomized controlled trials (RCTs) [1-14] provided data on the effect of different intravenous (IV) corticosteroids versus placebo or standard of care on all-cause mortality in severe and critical COVID-19 patients. Compared to placebo, only dexamethasone showed a statistically significant reduction in the risk of mortality. However, patients in this group had significantly longer duration of hospital stay. In terms of adverse events, no significant difference was found between the IV corticosteroids and control groups. No significant benefit on 28-day mortality and a tendency towards harm were observed when dexamethasone was given to COVID-19 patients who did not require oxygen therapy.
- In comparing 12mg and 6mg dosing of dexamethasone, no significant differences were found in terms of all-cause mortality and life support-free days while marginal benefits in ventilator-free days, cardiovascular support-free days, and renal replacement therapy-free days were observed in the 12mg group. No significant difference in adverse events were observed between the two dosing regimens.[15]
- Seven retrospective cohort studies [16-22] evaluated the effect in the timing of administration of different corticosteroids among severe and critical COVID-19 patients. Significant benefit was found only when systemic corticosteroids were started early within 24 hours of admission compared to non-early initiation beyond 24 hours. Mechanical ventilation was likewise significantly reduced when systemic corticosteroids were initiated within 24 hours of admission.

CONSENSUS ISSUES

Dexamethasone has a better pharmacokinetic profile (i.e., longer acting than hydrocortisone and methylprednisolone) and better anti-inflammatory effect as compared to other steroids with less corticoid effects (e.g., less water retention). Low-dose steroids (i.e., 6mg of dexamethasone) are preferred by physicians. As for other corticosteroids such as methylprednisolone and hydrocortisone, there is insufficient evidence to recommend its use in patients with COVID-19 infection who require supplemental oxygenation.

Should anticoagulation be used in treating patients diagnosed with COVID-19?

As of 26 October 2021

RECOMMENDATION

We recommend the use of prophylactic over therapeutic dose anticoagulation among hospitalized patients with moderate, severe or critical COVID-19 disease unless there are any contraindications. *(Low certainty of evidence; Strong recommendation)*

We recommend the use of standard dose prophylactic anticoagulation over intermediate dose prophylactic anticoagulation among hospitalized patients with COVID-19 disease unless there are any contraindications. *(Moderate certainty of evidence; Strong recommendation)*

KEY FINDINGS

- Eight randomized controlled trials (RCTs) [23-30] were included in this review to compare therapeutic versus prophylactic anticoagulation and to compare intermediate dose versus standard dose prophylactic anticoagulation in COVID-19 patients. Quality of evidence ranged from very low to moderate due to issues regarding risk of bias, and imprecision due to underpowered population, and wide confidence intervals.
- Comparing therapeutic and prophylactic anticoagulation (AC) [23-28], there was no significant difference over-all in terms of mortality and organ support-free days among critically ill and stable patients. There was a significantly lower over-all incidence of venous thromboembolism (VTE) for therapeutic anticoagulation but there was significantly higher risk for major and minor bleeding for therapeutic anticoagulation considering all populations. However, no significant difference was seen in the incidence of VTE among critically ill patients. There was no significant difference in major bleeding among subgroups of critically ill and stable patients but the trend pointed to a higher incidence among those undergoing therapeutic anticoagulation. For minor bleeding, there was a significantly higher observed incidence among critically ill patients.
- For the comparison of intermediate versus standard prophylactic anticoagulation dose among severely ill patients [29,30], there was no statistically significant difference in terms of mortality and incidence of venous thromboembolism. There was also no significant difference in terms of major and minor bleeding, but the trend showed higher incidence when given intermediate prophylactic dose anticoagulation.

CONSENSUS ISSUES

A strong recommendation in favor of prophylactic dose anticoagulation was unanimously given despite the low certainty of evidence to give emphasis on preventing harm, as the risk of bleeding was significantly higher with therapeutic dose anticoagulation. It was further emphasized that the duration of anticoagulation, which was not directly addressed by the studies included in this review, should be individualized based on the patient's thromboembolic and bleeding risks.

Should empiric antimicrobial coverage be given to patients with severe and critical COVID-19?

As of 15 April 2021

RECOMMENDATION

We recommend against the use of antibiotics in patients with severe and critical COVID-19 infection, unless with suspicion of secondary bacterial co-infection. For patients on empiric antibiotics, they should be assessed daily for the need for discontinuation, continuation or de-escalation based on clinical and laboratory parameters. *(Very low certainty of evidence; Strong recommendation)*

KEY FINDINGS

Very low quality of evidence from one retrospective observational report was found on the use of empiric antimicrobials for COVID-19.[31] Early administered antibiotics did not significantly impact mortality or delayed hospital acquired infections in critically ill patients with COVID-19.

CONSENSUS ISSUES

Despite the low quality of evidence available, the panel voted for a strong recommendation against the routine use of antibiotics due to concerns on antimicrobial resistance.

Should hemoperfusion be used in patients diagnosed with COVID-19?

As of 01 December 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of hemoperfusion among patients diagnosed with COVID-19. *(Very low certainty of evidence)*

KEY FINDINGS

Presently, no randomized clinical trials have been published to provide data on the use of hemoperfusion in patients with COVID-19. Two retrospective cohort studies [32,33] showed statistically significant benefit in terms of mortality. Improvement in some clinical parameters such as respiratory rate, heart rate, and peripheral oxygen saturation, and selected markers such as C-reactive protein, erythrocyte sedimentation rate, and serum ferritin levels were also significantly observed among COVID-19 patients who received hemoperfusion. However, the benefits in clinical and laboratory parameters failed to translate to more clinically important outcomes such as decrease in the length of hospital and intensive care unit stay. Moreover, the studies were of very low certainty of evidence being non-clinical trials.

CONSENSUS ISSUES

No randomized controlled trials were available for review and the observational studies included did not adjust for confounders. With the available sparse evidence, the use of hemoperfusion can be suggested in COVID-19 patients with clinical deterioration despite standard medical therapy (including Tocilizumab). However, there is no consensus among experts in the panel on the use of hemoperfusion in COVID-19. Clinical trials are needed to be able to identify and evaluate the balance of benefits, harm, and cost for an invasive mode of treatment such as hemoperfusion especially since immunotherapy has been made available for the management of COVID-19.

Should a conservative fluid management strategy be used in mechanically ventilated adult COVID-19 patients?

As of 05 March 2021

RECOMMENDATION

We suggest the use of conservative fluid management rather than liberal fluid management strategy in mechanically ventilated adult COVID-19 patients with acute respiratory distress syndrome who have been adequately resuscitated*. *(Low quality of evidence; Weak recommendation)*

**without tissue hypoperfusion and fluid responsiveness*

KEY FINDINGS

Analysis of four randomized controlled trials [34-37], which included 1,106 hemodynamically stable mechanically ventilated patients with acute respiratory distress showed a trend towards decreased risk of mortality in the conservative fluid management strategy group. Furthermore, the use of conservative fluid management strategy resulted in significantly increased ventilator-free days, significant decrease in the length of intensive care unit stay and duration of mechanical ventilation. In terms of adverse events, the use of conservative fluid management strategy showed no significant difference in renal failure-free days and need for renal replacement therapy. The overall quality of studies included in this analysis was found to have moderate risk of bias with common issues on selection, performance, and reporting bias.

CONSENSUS ISSUES

The recommendation of initiating a conservative fluid management strategy should be employed in adequately resuscitated and hemodynamically stable mechanically ventilated patients with acute respiratory distress syndrome. Studies included in the evidence review for this clinical question excluded patients with hemodynamic instability or those with more than minimal requirement for vasopressors for septic shock. It should be emphasized that fluid resuscitation for septic shock should be prioritized in order to optimize adequate perfusion and hemodynamic stability. Fluid responsiveness should also be adequately assessed as conservative fluid management strategy must not be initiated until patient is deemed fluid or volume unresponsive.

Should side lying position be used in patients with severe to critical COVID-19?
Should self-proning be used in non-intubated patients with severe COVID-19?

As of 26 October 2021

RECOMMENDATION

We suggest self-proning position in non-intubated patients with severe and critical COVID-19. (*Very low certainty of evidence; Weak recommendation)*

RECOMMENDATION

There is insufficient evidence to recommend the use of side lying in non-intubated patients with severe and critical COVID-19. *(Very low certainty of evidence)*

KEY FINDINGS

- Among non-intubated severe patients with COVID 19 with oxygen saturation of at least 90% and oxygen requirement of less than 6 liters per minute, pooled results of 4 randomized controlled trials [38-41] showed no difference in the duration of proning and outcomes such as mortality, need for intubation and the need for intensive care.
- A case series [42] of five patients with COVID-19 associated ARDS showed that side lying accompanied with Positive End Expiratory Pressure (PEEP) titration provided a statistically significant benefit by decreasing the incidence of overdistension and lung collapse. Adverse events were not reported.
- The certainty of evidence for both side lying and proning are very low due to serious risk of bias, substantial heterogeneity and imprecision.

CONSENSUS ISSUES

Self-proning in non-intubated patients with severe and critical COVID-19 was suggested despite the lack of significant benefit in terms of mortality, need for endotracheal intubation, and need for intensive care unit stay on the basis that self-proning may still offer some benefit on improving oxygenation citing theoretical effect and personal experience, and taking into consideration the existing recommendations made by various international guidelines as well.

There was very limited evidence to recommend side lying for the same subset of patients, although it was recognized that there may be some benefit. This intervention will depend on the physician's prerogative in situations where self-proning is not possible. Potential harms such as patient discomfort and risk of accidental removal of peripheral lines and endotracheal tubes and the need for additional healthcare workers to perform proning in sedated and mechanically ventilated patients should be considered for both patient and health care worker in attempting this intervention.

Should high flow nasal cannula be used for patients with COVID-19 and acute respiratory failure?

As of 01 December 2021

RECOMMENDATION

We suggest the use of high flow nasal cannula for patients with severe to critical COVID-19 who do not respond to conventional oxygen therapy (low flow nasal cannula/face mask). *(Low certainty of evidence; Weak recommendation)*

KEY FINDINGS

Two randomized controlled trials [43,44] comparing the use of high flow nasal cannula (HFNC) versus conventional oxygen therapy (COT) in COVID-19 patients with acute respiratory failure showed significant improvement of PaO_2/FiO_2 ratio among patients who received HFNC. However, no significant benefit was found in terms of 30-day mortality, length of hospital stay, length of intensive care unit stay, and eventual tracheal intubation and intensive care unit admission. Certainty of evidence was low because of unclear to high-risk of selection and detection bias, and imprecision in most of the critical outcomes.

CONSENSUS ISSUES

The use of high flow nasal cannula should only be considered when patients fail to respond to low flow nasal cannula or face mask. It is not intended to be the immediate first line respiratory support for COVID-19 patients. It was initially promoted due to its capability to deliver high oxygen concentration, particularly when coupled with the potential harm or risk of viral aerosolization with non-invasive ventilation. The comparison of the efficacy of high flow nasal cannula and non-invasive ventilation is discussed in a separate review.

Should non-invasive ventilation be used over high flow nasal cannula for patients with severe and critical COVID-19?

As of 03 January 2022

RECOMMENDATION

We suggest the use of either high flow nasal cannula or non-invasive positive pressure ventilation in COVID-19 patients with hypoxemic respiratory failure in the absence of any indication for emergent invasive mechanical ventilation. *(Low certainty of evidence; Weak recommendation)*

KEY FINDINGS

Two randomized controlled trials [45,46] were evaluated to compare the effect of non-invasive ventilation (NIV) and high flow nasal cannula (HFNC) oxygenation in improving clinical outcomes in COVID-19 patients with respiratory failure. Direct comparison of NIV in the form of helmet and face mask CPAP with HFNC in 218 COVID-19 patients with hypoxemia showed that reduction in mortality and need for endotracheal intubation were inconclusive. Certainty of evidence was low due to serious risk of bias and serious imprecision. Indirect mixed treatment comparison of NIV in the form of helmet CPAP and HFNC among COVID-19 patients with hypoxemia also showed no significant difference in terms of in-hospital mortality, need for mechanical ventilation, intensive care unit admission, and length of hospital stay.

CONSENSUS ISSUES

The risk of aerosolization using non-invasive ventilation was not discussed in the identified studies, but case series and reports have suggested minimal risk for health care workers. Standard operating procedure includes the use of filters in the expiratory limb tubing for non-invasive ventilation and use of face masks for patients on high flow nasal cannula. Physicians must be cognizant of the indications for intubation such as continued and progressive deterioration, and signs of respiratory failure.

Should lung protective ventilation, high PEEP and driving pressure-limited strategies be used in the management of adult patients with COVID-19-associated acute respiratory distress syndrome?

As of 19 February 2021

RECOMMENDATION

We suggest the use of a lung protective ventilation strategy (tidal volume 4-8 mL/kg predicted body weight and plateau pressure less than 30 cmH2O) in patients with COVID-19 infection and ARDS. *(Very low certainty of evidence; Weak recommendation)*

RECOMMENDATION

There is insufficient evidence to recommend the use of a higher PEEP strategy. We suggest to individualize PEEP or employ a PEEP strategy based on respiratory mechanics (i.e., compliance) in patients with COVID-19 infection. *(Low certainty of evidence)*

There is insufficient evidence to recommend a driving pressure limited strategy in patients with COVID-19 infection. We suggest to keep the driving pressure ≤ 14 cmH2O. *(Low certainty of evidence)*

KEY FINDINGS

There were no clinical trials evaluating the (1) effectiveness and harms of lung protective ventilation strategy and high PEEP strategies in patients with COVID-19-associated ARDS; (2) effectiveness and harms of higher PEEP versus lower PEEP strategies in conjunction with LTVV in patients with COVID-19-associated ARDS; and, (3) effectiveness and harms of a driving pressure-limited strategy in patients with COVID-19 and ARDS.

Lung Protective Ventilation

- Higher tidal volume was associated with the same or higher risk of 28-day mortality but there was no significant difference in ventilator-free days in multivariable models.[47] A smaller case study [48] also showed that barotrauma cases were observed to have significantly lower V_T than the controls. These studies provided very low quality of evidence for this component of the review question.

Higher PEEP and Low Tidal Volume Ventilation

- Higher PEEP was not associated with differences in 28-day mortality nor ventilator-free days in adults with COVID-19-related ARDS.[47] A case-control study showed that PEEP was not statistically significantly different between patients with and without barotrauma.[48] These studies provided low quality of evidence for this component of the review question.

Driving Pressure

- There was no significant difference in 28-day mortality, in-hospital mortality, mechanical ventilation-free days, hospital stay and barotrauma were observed.[49]

These studies provided low quality of evidence for this component of the review question.

CONSENSUS ISSUES

During the early stages of the disease, COVID-19 ARDS may not be the same as the usual ARDS. In COVID-19-related ARDS, compliance can be high or normal even in patients with very low PaO2/FiO2 ratios. In these cases, the lungs are not recruitable and the use of high levels of PEEP will not lead to better oxygenation.

As the respiratory mechanics (compliance) in COVID-19 ARDS are not uniformly correlated with the severity of the hypoxemia, it is best to individualize PEEP based on compliance and driving pressure rather than titrating PEEP based on the severity of the PaO2/FiO2 ratio. Thus, a higher PEEP strategy (using the high PEEP/ FiO2 table) for moderate to severe ARDS is not recommended for all patients with COVID 19 infections due to possible complications such as barotrauma.

We suggest titrating lung volumes (tidal volume 4-8 ml/kg predicted body weight) and PEEP to maintain the plateau pressure less than 30 and to have the lowest driving pressure. A driving pressure of <14cm H20 is recommended. The driving pressure is the difference between the plateau pressure and the PEEP, or tidal volume over the respiratory system compliance.

Should rapid sequence intubation or delayed sequence intubation be used for the management of COVID-19?

As of 30 June 2021

RECOMMENDATION

We suggest the use of rapid sequence intubation for COVID-19 patients to reduce infection among healthcare workers performing the procedure. *(Very low certainty of evidence; Weak recommendation)*

KEY FINDINGS

- There were no studies directly comparing rapid sequence intubation (RSI) and delayed sequence intubation (DSI). For each modality, there were very low quality evidence, which had limitations in study design and indirectness.
- Both RSI and DSI improved the post-intubation oxygen saturations of the patients. The study on RSI [50] reported that 10.4% of the patients died within 24 hours of intubation.
- On the other hand, the study on DSI [51] reported no deaths within an unspecified time period. The study on RSI reported cardiac arrest in 2% of the patients and pneumothorax in 5.9% of the patients post intubation. Conversely, the study on DSI reported that none of the patients had cardiac arrest post intubation within an unspecified time period. The study on RSI reported that there was no evidence of cross infection in the anesthesiologists who intubated the COVID-19 patients.

CONSENSUS ISSUES

There is no direct comparison between rapid sequence intubation (RSI) and delayed sequence intubation (DSI). RSI does not pertain to the timing of intubation but rather it pertains to the sequence of events.

RSI helps prevent the aerosolization of COVID-19 particles and is safer for the healthcare workers performing RSI. RSI is done rapidly and prevents further deterioration of patients who are in need of oxygen supplementation. However, there is a potential to develop hypoxemia among patients who have undergone RSI. RSI is commonly done locally except in patients with collapsed airways. Depending on the condition, RSI may be modified to suit the patients' needs. On the other hand, delayed sequence intubation (DSI) is generally much safer for patients because it ensures that the procedure is not conducted haphazardly (patients are pre-oxygenated and sedatives and neuromuscular blockers are administered). In addition, RSI is also recommended by the other societies except for agitated patients. Additional costs for anesthesia must be considered in performing RSI.

Should extracorporeal membrane oxygenation (ECMO) be used in the management of Acute Respiratory Distress Syndrome (ARDS) among COVID-19 patients?

As of 03 January 2022

RECOMMENDATION

We suggest the use of Extracorporeal Membrane Oxygenation (ECMO) for judiciously selected COVID-19 patients with severe Acute Respiratory Distress Syndrome (ARDS) based on the ELSO criteria. *(Very low certainty of evidence; Weak recommendation)*

KEY FINDINGS

Four cohort studies on the use of ECMO in adult patients with critical COVID-19 or COVID-19 ARDS were reviewed in this evidence update.[52-55] Pooled results from four studies showed inconclusive mortality benefit with the use ECMO versus standard of care. In one study [52], occurrence of procedure-related infection reported as a serious adverse event was significantly associated with ECMO therapy. The certainty of evidence is very low because of the risk of bias attributed to lack of randomized studies, inconsistency due to significant heterogeneity, and imprecision due to small study sample sizes.

CONSENSUS ISSUES

VV-ECMO is not indicated for all severe COVID-19 patients with ARDS. The general guidelines for the use of ECMO among non-COVID patients must be followed given that there are no guidelines for the use of ECMO among patients with COVID-19. Likewise, standard selection criteria, indications and contraindications should be followed in recommending the use of ECMO. The protocol for the treatment of severe ARDS must be followed. VV-ECMO is used once other modalities (e.g., proning, mechanical ventilation and lung protective strategies) did not work and the patients are qualified for ECMO.

There is a limited number of ECMO machines that are locally available. In addition, manipulation of this machine requires manpower, training and additional medical equipment. The use of ECMO must be judicious due to the considerable concern on the high cost and local availability of ECMO. ECMO is also used for the treatment of ARDS caused by leptospirosis and cytokine adsorption among COVID patients. The use of ECMO is included in the COVID fund and it costs around Php 2,000,000.00 per day, however, the costs are not fully covered. The results of ongoing trials are needed to show that the use of ECMO is effective and safe among patients with COVID-19 infection.

Should hyperbaric oxygen therapy be used in COVID-19 patients with hypoxemia?

As of 01 December 2021

RECOMMENDATION

We suggest against the use of hyperbaric oxygen therapy for the management of COVID-19 patients with hypoxemia due to insufficient evidence. *(Very low certainty of evidence; Weak recommendation)*

KEY FINDINGS

- Two interventional studies (non-randomized and randomized controlled trials) [56,57] were included in this review update on the use of hyperbaric oxygen therapy (HBOT) among COVID-19 patients with hypoxemia. HBOT appears to have a tendency towards benefit in reducing need for mechanical ventilation (HR 0.26, 95% CI 0.07-0.98) and in increasing the proportion of patients successfully weaned from oxygen support (RR 6.33, 95% CI 2.15-18.62).
- The effects of HBOT on mortality, oxygen saturation, and clinical improvement scores were inconclusive given the wide confidence intervals. The intervention appears generally safe with only a few minor adverse events including claustrophobia (RR 1.60, 95% CI of 0.07-38.20) and ear pain (RR 4.81, 95% CI of 0.27-86.47) reported. The overall certainty of evidence was low because of non-randomization, imprecision, and presence of possible confounders.

CONSENSUS ISSUES

The potential for the use of hyperbaric oxygen therapy in COVID-19 is recognized based on some reported benefit and minimal harm. However, its large cost and limited availability are important factors to consider especially since the noted benefits are based on a singular trial with very low certainty of evidence. More clinical trials are thus needed before recommending its use in patients with COVID-19.

Should sedation and neuromuscular blockade be done in mechanically ventilated patients with COVID-19-associated acute respiratory distress syndrome?

As of 03 January 2022

RECOMMENDATION

We suggest light over deep sedation in COVID-19 patients who are mechanically ventilated and who are anxious or agitated. *(Very low certainty of evidence; Weak recommendation)*

RECOMMENDATION

We suggest against the routine use of neuromuscular blockade in mechanically ventilated patients with COVID-19 associated respiratory distress syndrome. *(Low certainty of evidence; Weak recommendation)*

KEY FINDINGS

- There are currently no available randomized clinical trials testing for the effect of sedation and neuromuscular blockade in COVID-19 patients with acute respiratory distress syndrome (ARDS). Only indirect evidence from eight studies (two randomized clinical trials (RCTs) [58,59] on the use of sedation versus no sedation in mechanically ventilated patients and six RCTs [60-65] on the use of neuromuscular blockade agent (NMBA) compared to light sedation alone or placebo with or deep sedation in mechanically ventilated patients with moderate to severe ARDS) showed no significant benefit in 90-day mortality, length of hospital stay, and ventilator free-days.
- In terms of adverse events, major thromboembolic complications were significantly observed among mechanically ventilated patients on sedation while the incidence of delirium, accidental extubation, and ventilator-associated pneumonia did not significantly differ. The use of NMBA in moderate-to-severe ARDS showed significant reduction in 28- and 90-day mortality, improvement in PaO2/FiO2 ratio at 72 hours when compared to a deep sedation strategy without NMBA. Likewise, the use of NMBA reduced the risk of barotrauma and pneumothorax compared to no NMBA.

CONSENSUS ISSUES

Light sedation for mechanically ventilated COVID-19 patients has been suggested to help in managing agitation and anxiety. Certain patients, however, who are on paralytics and prone position, as well as those who exhibit ventilator asynchrony must be considered for deep sedation. On the other hand, routine neuromuscular blockade is not recommended unless there are indications for paralysis: as supportive management to facilitate lung protective strategies or prone ventilation.

Should inhaled nitric oxide be used in patients with COVID-19?

As of 26 October 2021

RECOMMENDATION

We recommend against the use of nitric oxide among patients with COVID-19. *(Low certainty of evidence; Strong recommendation)*

KEY FINDINGS

- One open-label randomized controlled trial [66] showed that the administration of inhaled nitric oxide as an adjunct to standard-of-care among hospitalized patients with moderate COVID-19 infection had no significant difference in 28-day mortality, need for mechanical ventilation, intensive care unit length of stay, hospital length of stay, viral clearance, and two-point WHO Ordinal Scale improvement when compared to standard-of-care alone.
- The incidence of methemoglobinemia was also not significantly different among patients who were given inhaled nitric oxide compared to those who received standard-of-care. The certainty of evidence was low due to lack of allocation concealment and serious imprecision of effect estimates.

CONSENSUS ISSUES

A strong recommendation against the use of nitric oxide was unanimously given on the basis of low certainty of currently available evidence (non-peer reviewed pre-print article with small population and imprecision of effect estimates) to justify its use and the high cost of the intervention.

Should etoposide be given among patients with severe COVID-19 pneumonia in cytokine storm?

As of 15 April 2021

RECOMMENDATION

We recommend against the use of etoposide among patients with COVID-19 pneumonia in cytokine storm. *(Very low certainty of evidence; Strong recommendation)*

KEY FINDINGS

Very low quality evidence was found on the use of etoposide as treatment for severe COVID-19: one case series [67] and one case report.[68] The case series showed an improvement in PaO2-FiO2 ratio (PFR) post-treatment of etoposide. Among the 14 patients studied in both studies, three patients expired while ten patients improved and were subsequently discharged. Adverse effects of etoposide include alopecia, gastrointestinal symptoms, acute hypersensitivity reactions, myelosuppression, and rarely, secondary malignancies such as acute myelocytic leukemia.

CONSENSUS ISSUES

There is not enough high-quality evidence to show that etoposide is useful for the management of COVID-19 patients with pneumonia in cytokine storm. There are significant adverse events with the use of etoposide, namely: alopecia, nausea,

vomiting, myelosuppression, acute hypersensitivity reactions, hepatotoxicity, hypotension from rapid infusion, and secondary malignancies.

Should pulmonary rehabilitation be done among long COVID patients with residual pulmonary symptoms to improve pulmonary function and quality of life?

As of 30 June 2021

RECOMMENDATION

We recommend individualized pulmonary rehabilitation with pre-intervention medical clearance for long COVID patients who show residual respiratory symptoms. *(Moderate certainty of evidence; Strong recommendation)*

KEY FINDINGS

- We found one randomized controlled trial that investigated the effect of pulmonary rehabilitation (PR) among long COVID patients with residual respiratory symptoms.[69] The study was found to have a moderate risk of bias due to absence of blinding for both patients and outcome assessors and unclear allocation process. They also enrolled only participants above 65 years of age.
- Based on moderate quality of evidence, pulmonary function tests of those who received pulmonary rehabilitation significantly improved. Quality of life and anxiety scales also significantly differed between groups, with improvement noted in the PR group compared to no PR. There was no significant difference for depression and activities of daily living between groups and within groups before and after the intervention. The RCT did not report any adverse events; indirect evidence from PR done on COPD patients [70] likewise showed no to low number of adverse events which did not hinder the feasibility and safety of the procedure of pulmonary rehabilitation.

CONSENSUS ISSUES

The panel recommends that the start and duration of pulmonary rehabilitation of each patient should be individualized depending on the assessment of a pulmonologist. Studies showed that the assessment of pulmonary rehabilitation among long COVID patients should start at least 6 months after their hospital admission and last for as long as 6 weeks. However, recommendations on when the assessment for pulmonary rehabilitation should start differ across professional medical societies. An international task force with representation from the European Respiratory Society and the American Thoracic Society recommends that the assessment should be done 6 to 8 weeks after hospital discharge in order to identify patients who will have residual symptoms. In addition, pulmonary rehabilitation for other disease conditions lasts for 6 to 9 weeks.

Should pirfenidone versus nintedanib be used as therapy for post-COVID-19 pulmonary fibrosis?

As of 26 October 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of pirfenidone or nintedanib among patients with post-COVID-19 pulmonary fibrosis. *(Very low certainty of evidence)*

KEY FINDINGS

Limited evidence is available on the use of pirfenidone or nintedanib among patients with post-COVID-19 fibrosis, most of which are from published case reports. There are no clinical trials or observational studies among this group of patients which directly compare both anti-fibrotic agents, nor are there studies comparing each drug individually to placebo. Indirect evidence from prospective and retrospective cohort studies on the use of pirfenidone versus nintedanib among non-COVID patients with idiopathic pulmonary fibrosis [71-77 showed no difference in mortality rate, respiratory-related hospitalizations, acute exacerbation of pulmonary fibrosis and percent predicted forced vital capacity (FVC%) at 6 and 12 months of treatment; higher frequency of diarrhea and transaminitis with nintedanib; and a higher rate of discontinuation due to adverse events with pirfenidone.

CONSENSUS ISSUES

Evidence to support this recommendation is indirect as the studies included do not involve patients with post-COVID-19 pulmonary fibrosis. This is due to the paucity of available data on the use of pirfenidone and nintedanib in this population. There is no strong evidence to favor one anti-fibrotic agent over the other except for less side effects with nintedanib. Both drugs are costly, with annual expenses amounting to approximately Php 4.3M and Php 2.4M for pirfenidone and nintedanib, respectively. This may increase the inequity of treatment among those who cannot afford these drugs.

Evidence and Recommendations for the Non-Pharmacologic Interventions for Prevention and Control of COVID-19

Should cloth masks be used to prevent COVID-19 infection caused by Variants of Concern (VoC)?

As of 03 December 2021

RECOMMENDATION

We recommend the proper use of either a well-fitted cloth mask or a medical mask in the community setting. If a cloth mask will be used, we suggest that it should be made of at least two layers of cotton (e.g., t-shirt fabric) or non-woven nylon with aluminum nose bridge. *(Very low certainty of evidence; Strong recommendation)*

KEY FINDINGS

At the time of writing, there were no published nor preprint studies that directly investigated the efficacy or effectiveness of cloth masks in preventing COVID-19 infection caused by specific SARS-CoV-2 variants of concern (VoC). There was indirect evidence from two studies that investigated cloth masks for the prevention of COVID-19 in general: one was a case-control study [1] that showed no significant difference between cloth mask and medical mask, and the other was a cluster-randomized trial [2] which showed that both cloth and surgical mask reduced the proportion of people with COVID-19-like symptoms in the community. The indirect evidence from these two studies suggested that cloth masks can reduce symptomatic COVID-19 cases at the community level, albeit at a lesser degree compared to medical masks. It also suggested that community use of both surgical and cloth masks can reduce symptomatic COVID-19 cases at the community level.

CONSENSUS ISSUES

The panel unanimously recommended the proper use of either a well-fitted cloth or a medical mask in the community setting. Whether to add qualifiers or not (regarding, for instance, the type of fabric and the particular setting) to this updated recommendation, as was done in the previous one, weighed heavily on the consensus panel and was discussed extensively. Eventually, it was highlighted that regardless of the community area or situation (e.g., crowded places, close-contact settings, confined and enclosed spaces, indoors or outdoors), proper wearing of a well-fitted mask must be emphasized and is still strongly recommended.

Is a facemask with face shield more effective than facemask alone in reducing SARS COV2 transmission?

As of 05 November 2021

RECOMMENDATION

We suggest against requiring the use of face shields in addition to face masks among the general public in non-healthcare settings. *(Very low certainty of evidence; Weak recommendation)*

RECOMMENDATION

We recommend the addition of face shields to face masks among the general public in areas with sustained community transmission of SARS-CoV-2. *(Very low certainty of evidence; Strong recommendation)*

We recommend the use of face shield plus medical face mask and standard personal protective equipment among health care workers not directly involved in the care of COVID-19 patients in areas with sustained community transmission of SARS-COV2. *(Very low certainty of evidence; Strong recommendation)*

KEY FINDINGS

- There was no available direct evidence for face shield plus face mask versus face mask alone in the general public. In the initial review done in May 2021, there were three studies that were included; for this updated review (until September 2021) we found two additional case-control studies. All these five studies were conducted among health care workers: four were done in the health care setting and one in the community.
- Three case-control studies [3-5] showed a trend toward benefit with the use of face shields but this was inconclusive (OR 0.85, 95% CI 0.68-1.08). Two pre- and post-face shield use surveillance studies [6-7] showed significant benefit (OR 0.28, 95% CI 0.22-0.37 and OR 0.04, 95% CI 0.00-0.69), respectively. The overall certainty of evidence was very low as the studies were non-randomized, unadjusted for confounders and with high risk of bias as well as indirectness.

CONSENSUS ISSUES

For the first statement, which suggests against obligatory public use of face shields, the panel's primary consideration was the insufficient evidence from existing literature that were assessed to be of very low certainty. This assessment stemmed from the indirectness of the studies in which they enrolled healthcare workers – rather than the general public – in the community, and included laboratory experiments not directly involving humans, as well as studies that investigated different viral infections with varied routes of transmission. Other factors affecting the panel's decision were public preference and observed poor compliance, environmental pollution, safety issues particularly in workplaces, additional costs, increasing vaccination rates, declining COVID-19 incidence, and the individuals' capacity to assess their own risk in the

community. Despite this suggestion to rescind the mandatory use of face shields, continued proper use of well-fitted face masks is still recommended.

Due to the perceived benefit of providing an additional mechanical barrier against viral infections, the panel maintained a strong recommendation for wearing both face masks and face shields in high-risk environments such as crowded public transit, poorly ventilated spaces, and areas with high incidence of COVID-19 cases. In support of this, the panel considered the indirect evidence taken from a high-quality meta-analysis that showed a 78% reduction of risk in contracting respiratory infections from SARS-CoV-2, SARS, or MERS when an eye protector, such as face shield or goggles, was used compared with none.

There was a unanimous decision on adopting the previous recommendation on the use of face shield plus medical face mask for the healthcare workers and no concerns were mentioned.

Should copper-containing masks be used to decrease SARS-CoV-2 transmission?

As of 03 December 2021

RECOMMENDATION

There is no evidence to recommend the use of copper-containing over non-copper-containing masks to decrease SARS-CoV-2 transmission.

KEY FINDINGS

Currently, there are no clinical trials directly comparing copper-containing masks with non-copper-containing masks in terms of SARS-CoV-2 transmission except in two in-vitro studies [8-9]. One study demonstrated that the metal leaching potential of copper-containing textiles could potentially lead to adverse events attributed to inhalation or ingestion of copper. In terms of cost, copper-containing masks are more expensive than regular masks.

CONSENSUS ISSUES

Due to the absence of clinical trials on the efficacy of copper-containing masks in reducing COVID-19 transmission, the panel members opted to have no recommendation. One panelist voted against the use of copper masks because of the higher costs compared with using surgical or cloth masks and the potential harm of metal leaching from copper-containing textiles.

What is the appropriate PPE to be used use during surgeries to reduce the risk of virus transmission?

As of 30 June 2021

RECOMMENDATION

We recommend the use of appropriate PPE to include mask (N95 or higher standard), fluid repellent sealed well-fitting long gown, double gloves, apron, full face shield or goggles or visor, scrub hat, and disposable shoe covers or dedicated closed footwear among surgeons engaged in aerosol generating procedures of suspected or confirmed COVID-19 patients. *(Very low certainty of evidence; Strong recommendation)*

KEY FINDINGS

- Five observational studies (2 cohorts, 2 cross-sectional, and 1 case series) investigated the effectiveness of PPE use in reducing SARS-CoV-2 transmission among healthcare workers involved in surgical aerosol-generating procedures (AGP).[10-14]
- Very low evidence suggests the protective effect of an appropriate PPE on surgeons engaged in AGP procedures of suspected or confirmed COVID-19 patients. Consistent N95 mask use reduced the odds of SARS-CoV-2 infections significantly (OR 0.37 [95% CI 0.21, 0.67], 1 study, n=195 participants) than inconsistent N95 use among healthcare workers involved AGP. Consistent gown use significantly reduced the odds of SARS-CoV-2 infections (OR 0.59 [95% CI 0.46, 0.77] I2= 0%, 2 studies, n= 941 participants) than inconsistent gown use amongst healthcare workers performing AGP.
- Consistent glove use reduced the odds of SARS-CoV-2 significantly (OR 0.42 [95% CI 0.43, 0.55] I2=34%, 3 studies, n=978) than inconsistent glove use among healthcare workers performing AGP. Very low evidence suggests the protective effects of N95 mask, gown, gloves, face shield/goggles, apron, and scrub hat in reducing SARS-CoV-2 transmission among healthcare workers performing AGP procedures.

CONSENSUS ISSUES

Although shoe cover was not mentioned in the assessed studies and in the recommendations from other groups, the panel agreed to include this in the minimum PPE required in surgery as it is part of the standard precaution. A strong recommendation was given despite the very low quality of evidence since the enumerated PPE is the existing minimum standard protection recommended for healthcare workers directly caring for COVID-19 patients. The panel also emphasized strict adherence to protocols and the appropriate use of this minimum PPE to prevent COVID-19 infection.

What is the appropriate PPE for healthcare workers in the outpatient setting to reduce the risk of virus transmission?

As of 30 June 2021

RECOMMENDATION

We recommend the use of at least surgical face mask and face shield for protection against COVID-19 infection among healthcare workers in the outpatient setting not performing aerosol generating procedures. Additional PPEs such as medical gowns and gloves should be worn as part of standard precautions during the performance of other procedures. *(Very low certainty of evidence; Strong recommendation)*

KEY FINDINGS

- There are no available direct evidence comparing the effectiveness of N95 versus surgical mask in COVID-19 infection among healthcare workers in the outpatient setting. Meta-analysis comparing the two among healthcare workers in general showed no significant difference in their effectiveness in preventing clinical and laboratory viral infection. One RCT [15] investigated the difference of N95 and surgical mask in protecting healthcare workers in different outpatient setting from viral respiratory infection and noted no significant difference between the two.
- Indirect evidence also shows more adverse skin reactions for those wearing N95 respirators as compared to surgical masks. The use of face shield on the other hand in addition to face mask provided added protection from acquiring COVID-19 among community healthcare workers in India based on a before and after study.[7] The use of gowns and gloves are standards of care in medicine whenever handling patient's body fluids and this recommendation is still applicable in the current setting.

CONSENSUS ISSUES

The superiority of N95 over medical face masks cannot be established based on the imprecise effects noted from the evidence. The high likelihood of dermatosis or skin infections while using N95 respirators was also noted. Considering these issues, the panel deemed that medical face masks would be more cost-effective as long as only non-aerosol generating procedures are done in the outpatient setting. The use of additional PPEs may be required depending on the procedure that will be performed, consistent with the recommendation of the US Centers for Disease Control (CDC). Face shields are preferred over goggles as it offers a greater level of protection from droplets.

Despite the very low quality of evidence, a strong recommendation was formulated as the listed PPEs are already considered the minimum standard protection needed by the healthcare workers. Strict adherence to appropriate use of these PPEs is emphasized.'

What is the appropriate PPE for health care workers in the wards, ICU and emergency room to reduce the risk of virus transmission?

As of 30 June 2021

RECOMMENDATION

We recommend the use of the following PPE: disposable hat, medical protective mask (N95 or higher standard), goggles or face shield (anti-fog), medical protective clothing, disposable gloves and disposable shoe covers or dedicated closed footwear as an effective intervention in the prevention of COVID-19 among health care workers in areas with possible direct patient care of COVID-19 positive patients and aerosol generating procedures. *(Moderate certainty of evidence; Strong recommendation)*

KEY FINDINGS

Four studies and a case report were found on the use of PPE among health care workers to prevent COVID infection.[16-20] Moderate certainty evidence from three of the studies showed that the use of Level 2 PPE (disposable hat, medical protective mask (N95 or higher standard), goggles (anti-fog) or protective mask (anti-fog), medical gown clothing or white coats covered by medical protective clothing, disposable gloves and disposable shoe covers), N95 respirators and face shields protected health care workers in hospital settings from COVID-19 infections. On the other hand, very low certainty evidence showed no significant protective effect from the use of face/surgical masks, gowns, and/or disposable gloves if used individually.

CONSENSUS ISSUES

Direct patient care is defined as hands on, face-to-face contact with patients for the purpose of diagnosis, treatment and monitoring. This recommendation was made by the panel as it prioritized giving the best available protection to the healthcare workers. Whenever possible, hospital administrators should invest in these PPEs. Strict adherence to the appropriate use of PPEs must be observed even if healthcare workers have already been vaccinated against COVID-19.

Should ionizing air filter be used in the prevention and control of COVID-19 infection in public spaces with sustained community transmission?

As of 30 June 2021

RECOMMENDATION

We recommend against the use of ionizing air purifier to reduce COVID-19 transmission in the community. *(Low certainty of evidence; Strong recommendation)*

KEY FINDINGS

- No direct evidence was found assessing the effectiveness of ionizing air filters in reducing SARS-CoV-2 infections. Five experimental studies [21-24] reported using an ionizing air purifier in reducing airborne particles, mostly in uninhabited laboratory settings. Ionizing air purifiers can efficiently remove the fine and ultrafine particles. However, its effectiveness in eliminating airborne organisms for infection control is lacking. Ozone, a dangerous respiratory irritant produced by some ionizing air purifiers, is a health risk to users.
- Overall quality: Most of the studies were at high risk of bias, with common issues on selecting tested ionizing air purifiers and the assessor's blinding.

CONSENSUS ISSUES

One of the studies noted that when an area is inhabited, reducing the particulate matter becomes insignificant once people move within the household, which consequently makes the ionizing air purifier ineffective. The panel also recognized that the harm caused by this intervention outweighs its benefit because one of the apparent disadvantages of ionizers is the emission of ozone, a powerful oxidant that may inflict health hazards through long-term or high-dose exposure.

Should foot baths be used in the prevention and control of COVID-19 infection?

As of 30 June 2021

RECOMMENDATION

We recommend against the use of foot baths for prevention and control of COVID-19 transmission. *(Very low certainty of evidence; Strong recommendation)*

KEY FINDINGS

No evidence was found evaluating the effectiveness of footbaths in preventing or controlling COVID-19 infections.

Should misting tents or disinfection chambers be used in preventing and controlling COVID-19 transmission?

As of 30 June 2021

RECOMMENDATION

We recommend against the use of misting tents or disinfection chambers for preventing and controlling COVID-19 transmission. *(Very low certainty of evidence; Strong recommendation)*

KEY FINDINGS

There are no existing or ongoing studies investigating the effectiveness and safety of sanitation tents for preventing and/or controlling COVID-19 infections. Indirect evidence from a rapid systematic review [26] of 6 laboratory studies and 1 in-vitro case control study showed effective viral inactivation after application of various cleaning products. However, disinfecting substances pose significant health risks, especially when used outside their manufacturer's recommendation or with repeated, prolonged exposure.

CONSENSUS ISSUES

The strong recommendation was based on the intrinsic irritant properties of the chemicals used in disinfection. Although some health facilities have implemented misting tents, evidence was not established to show their effectiveness to prevent and control COVID-19 transmission. Likewise, it was noted that aerosols are not actually recommended because the contact time is not enough to kill the microorganism.

Should ultraviolet (UV) lamps be used in the prevention and control of COVID-19 infection in public spaces in locations with sustained community transmission?

As of 30 June 2021

RECOMMENDATION

We recommend against the use of UV lamps or other UV devices in any place outside of a controlled clinic or hospital setting to prevent and control COVID-19 transmission. *(Low certainty of evidence; Strong recommendation)*

KEY FINDINGS

- No direct evidence was found evaluating the effectiveness of ultraviolet lamps in the prevention and control of COVID-19 infections in public spaces in locations with sustained community transmission.
- Indirect evidence of low quality showed some benefit in reducing the incidence of viral infection in a hospital ward.[25-31] However, the evidence for its potential harm such as skin erythema, ocular itching, blurring and conjunctival injections, was more significant.

CONSENSUS ISSUES

A strong recommendation was made based on the potential adverse reactions and the risks associated with UV lamps. Although the panel recognizes the germicidal effect of UV light in clinical settings, emphasis was made to limiting its use only in controlled environments (i.e., without the presence of human beings) with trained staff to minimize its potential health hazards. Since the use of personal UV lamps and devices in households has also become widespread following advertisements, the public must be appropriately informed that misuse of these devices may cause harmful, long-term effects on health.

Should high efficiency particulate air (HEPA) filters be used in the prevention and control of COVID-19 infection in public spaces and locations with sustained community transmission?

As of 30 June 2021

RECOMMENDATION

We suggest the use of HEPA filter as an option to improve air quality for COVID-19 prevention and control in indoor spaces with inadequate ventilation. *(Low certainty of evidence; Weak recommendation)*

KEY FINDINGS

No direct evidence was found assessing the effectiveness of HEPA filters in preventing and controlling COVID-19 infection in public spaces and locations with sustained community transmission. Low quality evidence from 3 laboratory experiments and 1 case series [32-35] demonstrated that HEPA filters appear to significantly improve air quality.

CONSENSUS ISSUES

A weak recommendation was made because of indirect evidence showing the benefit of HEPA filter in improving air quality. HEPA filters may be useless in public spaces with uncontrolled airflow and should be used only in areas where air exchange is compromised. To ensure that HEPA filters serve their purpose, the amount of air that can be filtered per hour by the machine must be matched with the size of the room. Proper installation and regular maintenance are likewise important to avoid contaminated air from recirculating back to the room and to maximize the machine's lifespan. In spite of the use of HEPA filters, minimum health standards should still be observed.

Should carbon dioxide (CO2) monitors be used to reduce transmission of COVID-19?

As of 05 November 2021

RECOMMENDATION

We recommend the use of carbon dioxide (CO2) monitors in enclosed spaces to guide actions to improve ventilation and reduce transmission of SARS-CoV-2. *(Moderate certainty of evidence; Strong recommendation)*

KEY FINDINGS

- We found no studies that directly answered the question on whether carbon dioxide level determination can be used to prevent SARS-CoV-2 infection. There were observational studies [36-38] that reported no infection when there was increased air ventilation and the CO2 levels were low. In these studies, many factors affecting CO2 levels were considered simultaneously real-time, such as use of personal protective equipment (PPEs), activity of persons in the room, duration of stay in the room, and size of the room, among others. The CO2 levels, as detected by carbon dioxide sensors, were correlated with air ventilation and in most studies, the CO2 level was designated to be a surrogate or proxy to COVID-19 risk of transmission. Indirect evidence showed that people exposed to a room with more than or equal to 1000 parts per million (ppm) of carbon dioxide in the air, as measured by a CO2 monitor, had as high as 16x higher risk of contracting tuberculosis, compared to those in a room with lower CO2 levels.[39]
- The other studies [40-42] investigated the presence of the virus in air (aerosol and droplets), and as fomites. Although there was a disagreement existed among the studies, as two studies were able to isolate the virus in the air, while the other was able to isolate the virus only as fomites, it may be possible that the negative growth of the virus may not mean that it is absent.

CONSENSUS ISSUES

The panel made a strong recommendation for the use of carbon dioxide (CO2) monitors because of the moderate certainty of evidence based on an indirect study that showed much higher risk of contracting tuberculosis when exposed to a room whose air reached 1000 parts per million (ppm) of carbon dioxide. The panel believed CO2 monitors could serve as a real-time guide to initiate activities that improve air ventilation (such as promoting distancing, opening windows, or turning on electric fans). However, two panelists still voted for a weak recommendation due to (1) unknown accuracy of various commercial monitors in detecting CO2 levels and (2) concerns regarding the actual use of industrial-grade monitors (training of personnel, number of monitors needed, calibration, preventive maintenance) in different institutions. Even with the use of CO2 monitors, the public must continue to observe the precautionary measures of handwashing, wearing face masks, and observing physical distancing to avoid infection with COVID-19.

What are effective decontamination techniques for N95 reuse?

As of 30 June 2021

RECOMMENDATION

In situations where there is shortage of filtering facepiece respirators (FFR), we suggest the use of Hydrogen Peroxide Vapor (HPV), Ultraviolet Germicidal Irradiation (UVGI), moist heat and peracetic acid dry fogging system (PAF) as options for N95 mask decontamination as recommended by the manufacturer based on their ability to reduce SARS-COV-2 load and infectivity while still maintaining N95 mask integrity. *(Low certainty of evidence; Weak recommendation)*

RECOMMENDATION

We recommend against the use of autoclave and alcohol as these methods alter filtering facepiece respirator's (N95) integrity and degrade filtration efficacy. *(Very low certainty of evidence; Strong recommendation)*

KEY FINDINGS

Eight quasi-experimental studies reported the effects of six decontamination techniques (i.e., alcohol, autoclave, moist heat, HPV, PAF, UVGI) on SARS-CoV-2 laden N95 masks.[43-50] There is low evidence on use of Hydrogen Peroxide Vapor (HPV), Ultraviolet Germicidal Irradiation (UVGI), moist heat and peracetic acid dry fogging system (PAF) as options for N95 mask decontamination. These decontamination methods resulted in ≥4.79 $\log_{10}$ reductions in SARS-CoV-2. Except for autoclave, they preserved the quality fit of N95 masks after 10 decontamination cycles. There is very low evidence against the use of autoclave and alcohol for N95 mask decontamination as these methods alter N95 integrity and degrade filtration efficacy.

CONSENSUS ISSUES

Reuse of N95 masks should be considered only in cases of shortages and not during times of normal supply. It is important to specify the maximum number of cycles by which the decontamination techniques can still preserve the functional and physical integrity of the N95 mask: (1) autoclave- up to 2 cycles; and (2) moist heat, HPV and PAF- up to10 cycles.

Regarding local availability, some noted that HPV is usually not affordable in resource-limited settings, making UVGI the preferred option due to its lower cost. In practice, however, HPV is considered more effective in decontamination. Its mist can reach all the spaces once halo fogging is done, which is beneficial to N95 mask since it has many pores. In contrast, UVGI can only disinfect the area reached by the UV light. Although HPV is available in the country, its use will entail the need for a special decontamination room and a machine. Some noted that HPV is usually not affordable in resource-limited settings. The panel also stressed the importance of checking the condition of the N95 mask before decontamination and not just solely rely on the

manufacturer's recommendation. Likewise, the proper procedure before decontamination should also be emphasized.

On the recommendation against the use of autoclave, it was clarified that although it can destroy the virus, the physical and functional integrity of the N95 mask are affected. In terms of the other decontamination techniques, no study was found on the effectiveness of air dry alone, exposure to sunlight, soap and water, 0.5% chlorine solution, and for other disinfecting agents such as benzalkonium chloride.

Should protective physical barriers be used to prevent COVID-19?

As of 30 June 2021

RECOMMENDATION

We suggest against the use of protective physical barrier enclosures (ex. aerosol box) for the prevention of COVID-19 among health care providers who perform aerosol generating medical procedures*. *(Very low certainty of evidence; Weak recommendation)*

**Proper PPEs should be used by health care providers when performing aerosol-generating procedures.*

RECOMMENDATION

We suggest the use of protective physical barriers in the prevention of COVID-19 in areas where social distancing cannot be adhered to (e.g., offices, reception desk). *(Very low certainty of evidence; Weak recommendation)*

***Adequate ventilation, physical distancing, use of facemasks and personal hygiene should still be maintained to prevent COVID-19 infections. Regular cleaning and disinfection of physical barriers should be practiced.*

KEY FINDINGS

- Two case series reported that there were no COVID-19 infections among health care providers who used protective barrier enclosures during aerosol generating procedures on COVID-19 patients.[51,52] One systematic review reported that barrier devices were effective at either preventing or reducing the number of particles escaping the system only when negative pressure suction was applied.[53]
- As for physical barriers (i.e., sneeze guards), we did not find any studies on its efficacy in preventing COVID-19 infections. Two computational fluid-particle dynamics (CFPD) simulation studies, however, showed that physical barriers could potentially reduce aerosol transmission within shared spaces such as classrooms or airplane cabins.[54,55]

CONSENSUS ISSUES

Protective physical barrier enclosures refer to passive protective barriers that were used to protect the health care workers during the early stages of the pandemic when PPE supplies were limited. The physical barrier enclosure can be used as an

additional layer of protection in situations where the HCP does not have adequate PPE for aerosol generating procedures. However, these barriers should be used with suction or negative pressure devices to reduce the risk of transmission from secondary aerosols that are trapped underneath the plastic barrier. Previous studies showed that aerosols can still escape a physical barrier enclosure. In addition, concerns related to efficiency and usability of such barriers have also been reported, such as: (1) longer intubation time; (2) difficulty in maneuvering the arms because of the rigidity of the box; (3) view of the anesthesiologist or ER doctor is blocked by the plastic or acrylic box). The Philippine Society of Anesthesiologists (PSA) also no longer recommends the use of physical barrier enclosures.

The use of physical barriers is not mandatory, but an option in areas where social distancing cannot be maintained. The proper disinfection of these barriers is emphasized. It was noted that the World Health Organization and Centers for Disease Control and Prevention have specifications and instruction for disinfection of barriers.

Should surfaces be disinfected to prevent COVID-19 infection?

As of 30 June 2021

RECOMMENDATION

We recommend the practice of cleaning and disinfecting surfaces using the appropriate disinfecting chemical agents such as 0.5% sodium hypochlorite solution (bleach) or 70% alcohol to prevent COVID-19 infection. (*Low certainty of evidence; Strong recommendation*)

For high touch surfaces and high traffic areas, such as in the workplace, disinfection should be done before shift, intermittently during, and after the shift.

For household disinfection, once daily disinfection on high touch surfaces is recommended.

KEY FINDINGS

No randomized controlled studies were found directly addressing this question. Indirect evidence from a rapid systematic review [26] of 7 studies, 5 laboratories, 1 case control, and 1 experimental provided data on the effects of cleaning products on SARS-CoV-2 inactivation. Indirect evidence from laboratory studies showed that SARS-CoV-2 is inactivated by common disinfectants within 1 minute when used according to their manufacturer's specifications and precautionary measures. However, disinfectants such as 0.1% sodium hypochlorite and 70% alcohol are potential irritants to the skin, ocular tissue, and respiratory tract and should be handled with proper protection and precaution.

CONSENSUS ISSUES

The panel noted that alcohol is actually recommended for use on skin but is now also being used in the environment because of its accessibility. As for sodium hypochlorite solution, the DOH Department Memorandum 2020-0157 (“Guidelines on Cleaning and Disinfection in Various Settings as an Infection Prevention and Control Measure Against COVID-19”) provides instructions on its dilution and appropriate use.

Evidence and Recommendations for the Vaccines and Prophylactic Interventions for COVID-19

Among persons at risk, what is the clinical efficacy, effectiveness and safety of BBIBP-CorV (Sinopharm) in the prevention of SARS-CoV-2 infection?

As of 02 December 2021

RECOMMENDATION

We recommend the use of BBIBP-CorV (Sinopharm), given as 200U (WIV04) or 4ug (HBO2) in 0.5 ml in 2 doses, 21 days apart, to prevent symptomatic and asymptomatic COVID-19 infection among healthy adults (18 to 59 years old). *(Moderate certainty of evidence; Strong recommendation)*

We suggest the use of BBIBP-CorV to prevent severe COVID-19 infection among healthy adults (18 to 59 years old). *(Low certainty of evidence; Weak recommendation)*

We suggest the use of BBIBP-CorV to prevent symptomatic COVID-19 infection in the following:

a. Adults with comorbidities (*Very low certainty of evidence; Weak recommendation)*
b. Older persons (60 years and older) (*Very low certainty of evidence; Weak recommendation)*

RECOMMENDATION

There is insufficient evidence to recommend for or against the use of BBIBP-CorV to prevent COVID-19 infection among the following:

1. Children (3-17 years old) (*Very low certainty of evidence)*
2. Immunocompromised population (*Very low certainty of evidence)*
3. Pregnant and lactating women (*Very low certainty of evidence)*

In areas where the SARS-CoV-2 variants of concern are prevalent, there is insufficient evidence to recommend for or against the use of BBIBP-CorV to prevent COVID. (*Very low certainty of evidence)*

KEY FINDINGS

The evidence base for the clinical efficacy, effectiveness, and safety of BBIBP-CorV (Sinopharm), as of October 29, 2021 included one network meta-analysis[3], four randomized controlled trials[4-7], 14 observational studies and two regulatory authority reports[8-24]. Trial results showed that BBIBP-CorV, particularly the HB02 formulation, provided sufficient protection against symptomatic and asymptomatic COVID-19 infection, within a follow up period of 77days. Limited information was available regarding effectiveness against severe infection and on protection for the older population. Immunologic studies show that the vaccine is immunogenic even

among children[7]. Limited information from observational studies on the effectiveness of the vaccine for the immunocompromised suggested some protection and immunogenicity. Available safety data shows acceptable safety profile with no adverse event of interest reported.

CONSENSUS ISSUES

The decision of the Panel to defer any recommendation for the use of BBIBP-CorV on children and the immunocompromised was based on the limited evidence of efficacy. As no correlate of protection has been established for COVID-19 vaccines, the Panel did not feel that immunogenic response was sufficient to make a recommendation, especially from studies with a small number of participants. The same issue was considered in withholding a recommendation with the use of BBIBP-CorV against the SARS-COV-2 variants of concern.

Is CoronaVac (Sinovac) effective and safe in the prevention of COVID-19-infections?: A Rapid Review (Update)

As of 28 October 2021

RECOMMENDATION

We recommend the use of the CoronaVac (Sinovac), given as (given as 0.5 mL (600SU) to prevent symptomatic SARS-CoV-2 infection in:

- Healthy Adults *(Low certainty of evidence; Strong recommendation)*
- Pregnant women in their first trimester after consultation with a physician *(Very Low certainty of evidence; Strong recommendation)*
- Pregnant women in their 2nd and 3rd trimester and lactating women *(Very Low certainty of evidence; Strong recommendation)*
- Adults who have medical comorbidities *(including chronic respiratory disease and infection, cardiovascular disease, chronic kidney disease, cerebrovascular disease, diabetes mellitus, obesity, neurologic disorder, chronic liver disease and others like sickle cell disease, thalassemia, or Down's syndrome, as per DOH guidelines dated April 5, 2021 on the A3 Priority Group) (Low certainty of evidence; Strong recommendation)*
- Immunocompromised patients after medical clearance from a physician *(the immunocompromised include those diagnosed with HIV, hepatitis B and C, those with cancer undergoing chemotherapy, transplant patients receiving immunosuppression) (Low certainty of evidence; Strong recommendation)*

In areas where Delta is the predominant variant of concern, we recommend the use of CoronaVac (Sinovac) *(Very Low certainty of evidence; Strong recommendation)*

For immunocompromised patients who received primary CoronaVac (Sinovac) vaccination, we recommend for heterologous booster vaccination *(Very Low certainty of evidence; Strong recommendation)*

RECOMMENDATION

We suggest the use of CoronaVac (Sinovac) to prevent SARS-CoV-2 infection in older adults (>60 years old). *(Low certainty of evidence; Weak recommendation)*

RECOMMENDATION

We suggest against the use of CoronaVac (Sinovac) to prevent SARS-CoV-2 infection in children (3 to 17 years old) *(Very Low certainty of evidence; Weak recommendation)*

Under the current context of low vaccine coverage and inadequate vaccine supply, we recommend against booster vaccination using CoronaVac (Sinovac) in the healthy, adult population (18 years old and above) *(Low certainty of evidence; Strong recommendation)*

KEY FINDINGS

The updated search on September 7, 2021 provided additional real-world evidence on the clinical effectiveness of CoronaVac in the general, as well as the immunocompromised population, in whom immune response to the vaccine is diminished. One trial showed that CoronaVac was immunogenic and safe among children aged 3 to 17 years old[30]. Studies among the immunocompromised population showed reduced immunologic responses after CoronaVac vaccination[42, 44, 60]. Additional evidence showed sufficient protection against COVID-19 infection by the Delta variant despite decreased immunologic response elicited by CoronaVac against the variant of concern [61,62]. However, available evidence suggests escape from immunity against the Gamma variant after CoronaVac vaccination[63]. It is also uncertain whether a booster results in additional protection against infection in terms of clinical outcomes[28, 69-71]. Studies suggest declining immunologic marker levels over time with concomitant decreased vaccine effectiveness in the older population[34]. The effect of booster vaccination in providing additional protection is limited[28].

CONSENSUS ISSUES

In the light of new evidence since the last version of the guidelines, the panel revised the wordings and updated the strengths of the recommendations accordingly.

The panel members were divided and could not reach consensus regarding homologous booster vaccination for CoronaVac. Despite three rounds of voting and additional evidence search followed by a Delphi and a fourth round of voting, no consensus was reached. The arguments for and against homologous boosting of these 4 vaccines in the immunocompromised are as follows:

FOR:

1. The immunocompromised are vulnerable and at risk of severe COVID-19 infection and should be given the necessary protection from effective vaccination.

2. Primary vaccination has been found to result in poor immunogenic response in this population. Without a third/additional dose, these patients remain relatively unprotected and would likely have breakthrough infections.
3. Majority of the local population, and this likely includes the immunocompromised, received either ChAdOx1 or CoronaVac as their primary vaccination. Hence, despite the lack of a strong evidence of efficacy/effectiveness, giving them a booster using the same vaccine is better than not giving one.

AGAINST:

1. Homologous boosting using these vaccines for this population may turn out to be a waste of precious resources, given the lack of evidence that demonstrates clinical or even immunologic effectiveness and safety.
2. Ongoing trials and continued evidence generation may soon provide the necessary answer to the question and it may be prudent to wait for their results.
3. Heterologous boosting may be a better option, considering the current evidence of a satisfactory benefit/harm ratio.

The panel gave a strong recommendation for heterologous booster vaccination despite the low certainty of the evidence because of its significantly better immunogenic response compared to homologous boosting combined with the acceptable safety profile. More importantly, with the inconsistent supply of vaccines, and the need for the provide an effective vaccination regimen to the immunocompromised, the heterologous booster vaccination may be the only available option at this time

Is vaccination with BBV152 (Covaxin/Bharat) effective and safe in the prevention of COVID-19 infections?: A Rapid Review

As of 21 October 2021

RECOMMENDATION

We recommend the use of BBV152 (Covaxin/Bharat), 0.5 mL/dose, in a two-dose regimen, 28 days apart for the prevention of symptomatic COVID-19 infection in healthy adults*. (Moderate certainty of evidence; Strong recommendation)*

RECOMMENDATION

We suggest the use of BBV152 (Covaxin/Bharat), 0.5 mL/dose, in a two-dose regimen, 28 days apart for the prevention of symptomatic COVID-19 infection:

e. Adults who have stable medical co-morbidities and are at high risk for severe infection *(Low certainty of evidence; Weak recommendation)*
f. Healthy, older adults (>60 years old) *(Low certainty of evidence; Weak recommendation)*
g. Pregnant and lactating women, after discussing with a physician *(No direct evidence; Weak recommendation)*
h. Immunocompromised patients, after discussing with a physician *(No direct evidence; Weak recommendation)*

RECOMMENDATION

We suggest against the use of BBV152 (Covaxin/Bharat) for the prevention of COVID-19 in children and adolescents. *(No evidence; Weak recommendation)*

We recommend against the use of BBV152 (Covaxin/Bharat) in individuals who have known allergies to its contents/excipients. *(Best practice statement).*

KEY FINDINGS

The search performed on September 20, 2021 included one (1) randomized controlled clinical trial (RCT) (n=25,798)[77] and seven (7) observational studies[78-84], which provided evidence on the efficacy, effectiveness, and safety of BBV152 (Covaxin/Bharat) in the prevention of SARS-CoV-2 infection, including those due to the variants of concern.

Is NVX-Cov2373 (Novavax) effective and safe in the prevention of COVID-19 infection?

As of 27 December 2021

RECOMMENDATIONS

We suggest the use of NVX-CoV2373 (Novavax), given as 5ug (with 50ug Matrix M1 adjuvant) two doses, intramuscular, 21 days apart, for the prevention of symptomatic and severe SARS-CoV-2 infection in healthy adults. *(Low certainty of evidence; Weak recommendation)*

We suggest the use of NVX-CoV2373 (Novavax), given as 5ug (with 50ug Matrix M1 adjuvant) two doses, intramuscular, 21 days apart, for the prevention of symptomatic SARS-CoV-2 infection in older adults (>65 years old). *(Low certainty of evidence; Weak recommendation)*

We suggest the use of NVX-CoV2373 (Novavax), given as 5ug (with 50ug Matrix M1 adjuvant) two doses, intramuscular, 21 days apart, for the prevention of symptomatic SARS-CoV-2 infection in adults with comorbidities. *(Moderate certainty of evidence; Weak recommendation)*

In areas where the Alpha variant is predominant, we suggest the use of the NVX-CoV2373 (Novavax) given as 5ug (with 50ug Matrix-M1 adjuvant), two doses, intramuscular, 21 days apart, to prevent symptomatic SARS-CoV-2 infection. *(Low certainty of evidence; Weak recommendation)*

RECOMMENDATIONS

We suggest against the use of NVX-CoV2373 (Novavax), for the prevention of symptomatic SARS-CoV-2 infection in the immunocompromised population (specifically HIV positive individuals). *(Very low certainty of evidence; Weak recommendation)*

We suggest against the use of NVX-CoV2373 for the prevention of symptomatic SARS-CoV-2 infection among pregnant and lactating women. (*No direct evidence; Weak recommendation)*

In areas where the Beta variant is predominant, we suggest against the use of the NVX-CoV2373 (Novavax) to prevent symptomatic SARS-CoV-2 infection. *(Low certainty of evidence; Weak recommendation)*

We recommend against the use of the NVX-CoV2373 (Novavax) in individuals who have known allergies to its contents/excipients, such as Matrix-M1. *(Best practice statement)*

RECOMMENDATION

There is insufficient evidence to recommend for or against the use of NVX-2373 for the prevention of symptomatic SARS-CoV-2 infection among children.

KEY FINDINGS

The evidence base on the efficacy and safety of NVX-Cov2373, as of November 12, 2021, includes five RCTs and one comparative cohort study[86, 88-92]. Results show that the vaccine provides excellent protection against symptomatic COVID-19 among healthy adults, among older persons above 65 years of age, among high-risk groups and those with comorbidities. The vaccine is highly immunogenic. Effectiveness is preserved against the Alpha variant, but one study showed potential loss of effect against the Beta variant. The vaccine is reactogenic.

CONSENSUS ISSUES

The Panel highly considered equity issues in the recommendations for the use of NVX-2373 in the prevention of SARS-CoV-2 infection. However, in the case of populations who were at high risk of severe infection and are immunocompromised such as the HIV positive individuals and in the pregnant and lactating women, the Panel took into consideration the lower efficacy estimates and the wide confidence interval with the lower border breaching the 30% threshold combined with the signal of additional harm with the higher adverse reaction risk so that a recommendation against the use of the vaccine was given.

Are vaccines effective and safe in the prevention of COVID-19 infections?

As of April 23, 2021

RECOMMENDATIONS

We recommend the use of the following vaccines to prevent symptomatic SARS-CoV-2 infection in adults: *(Moderate certainty of evidence; Strong recommendation)*

a. **BNT162b2 (Pfizer/BioNTech)** given as 0.3ml (30ug) intramuscular injections, in 2 doses, 21 days apart
b. **mRNA-1273 (Moderna)** given as 0.5ml (100ug) intramuscular injections, in 2 doses, 28 days apart
c. **ChAdOx1 (AstraZeneca)** given as 0.5 ml (5×10^6 vp) intramuscular injections, in 2 doses, **at least 12 weeks** apart
d. **Gam-COVID-Vac (Gamaleya)** given as rAd-26 0.5ml intramuscular injection, then rAd-5S 0.5 ml intramuscular injection 21 days after
e. **Ad26.COV2.S (Janssen/Johnson&Johnson)** given as 0.5ml single dose intramuscular injection

We recommend the use of CoronaVac (Sinovac) (given as 0.5ml (600SU) intramuscular injection, in 2 doses, at 28 days apart) to prevent symptomatic SARS-CoV-2 infection among adults: *(Low certainty of evidence; Strong recommendation)*

CONSENSUS ISSUES

It was noted that ChAdOx1 was originally designed for a 21-day dosing interval, but because of some problems in logistics during the trial, different dosing intervals were implemented and the vaccine efficacy per dosing interval was recorded. The above recommendation, i.e., at least 12 weeks, reflects the dosing interval with the highest observed vaccine efficacy of 81.3% (95% CI 60.3-91.2).

With regard to Coronavac, a strong recommendation was made despite the low certainty of evidence because the panel considered its availability and the very high vaccine efficacy in preventing severe COVID-19. Although a 14-day dosing interval was utilized in the trial, it was noted that the recommendation on a 28-day dosing interval was based on the submission of the manufacturer to the Hongkong Food and Health Bureau. It was assumed that a longer duration may have better vaccine efficacy based on the immunogenicity data (seroconversion on 14-days versus 28-days) and the result of the subgroup analysis (<21 days versus >21 days). It was likewise explained that in general, increasing the interval between the doses of vaccines will provide better immunogenicity because it will give ample time for the population of lymphocytes in the lymph nodes to be replenished, thus resulting in a more robust immune response.

RECOMMENDATIONS

We recommend the use of BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya) and Ad26.COV2.S (Janssen/ Johnson&Johnson) vaccines to prevent symptomatic SARS-CoV-2 infection in older adults (>64 year old). *(Low certainty of evidence; Strong recommendation)*

We recommend the use of these vaccines in pregnant and lactating women after consultation with a physician. *(Very low certainty of evidence; Weak recommendation)*

RECOMMENDATION

There is insufficient evidence to recommend the use of CoronaVac to prevent symptomatic SARS-CoV-2 Infection in older adults (>60-year-old). *(Very low certainty of evidence)*

CONSENSUS ISSUES

The strength of recommendation was changed from weak to strong because, although the certainty of evidence is low, the benefits of vaccinating the elderly who are at risk of severe disease outweigh the harm as reported in the evidence presented, which showed lower adverse event rates in the said population compared to the younger group.

The panel agreed not to recommend CoronaVac due to the very low certainty of evidence wherein the interim analysis showed imprecision because of the very wide confidence interval for symptomatic COVID-19. Moreover, there was no disaggregation of data into mild, moderate or severe COVID-19 in older adults ≥60 y/o. There was also no data on harm.

RECOMMENDATION

We recommend the use of these vaccines in pregnant and lactating women after consultation with a physician. *(Very low certainty of evidence; Weak recommendation)*

CONSENSUS ISSUES

The certainty of evidence was changed from low to very low given that there was no evidence on either efficacy or safety in pregnant and lactating women because they were excluded from the trials. Regarding the risk of COVID-19 infection in the fetus, there is no evidence to date of vertical transmission, but there is increased incidence of premature birth and other complications arising from the pregnancy itself. There is also lack of evidence on transmitting COVID-19 infection through breastmilk. The risk of horizontal transmission in the household versus from the mother is the same provided that infection prevention and control (IPC) measures are observed. It was emphasized that the discussion with a physician should involve informing these women of the benefits and risks of vaccination, specific to the timing of its administration during the pregnancy. Physicians should be educated on these risks and benefits for the delivery of proper advice.

There was a discussion on the registry involving Pfizer and Moderna vaccines, where pregnant women who get vaccinated can volunteer to join and report their outcomes. This real world analysis showed that there was no difference in the incidence of early trimester complications. Moreover, it was mentioned that the WHO report already included eight (8) pregnancies after the J&J vaccination, which noted the following results: one (1) spontaneous abortion, one (1) elective abortion, while the rest had no reported congenital anomalies.

RECOMMENDATIONS

We recommend the use of BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya) and Ad26.COV2.S (Janssen/ Johnson&Johnson) vaccines to prevent SARS-CoV-2 infection in adults who have stable medical comorbidities and those who are at risk for severe infection. *(Moderate certainty of evidence; Strong recommendation)*

We suggest the use of CoronaVac to prevent SARS-CoV-2 infection in adults who have stable medical comorbidities and those who are at risk for severe infection. *(Very low certainty of evidence; weak recommendation)*

CONSENSUS ISSUES

A weak recommendation was made for Coronavac because the panel took into account the absence of any estimate of vaccine efficacy specific for this subgroup. Although the Brazilian trial included healthcare workers with stable medical comorbidities, the proportion of this subgroup as well as the vaccine efficacy for this specific population are unknown. As such, the panel considered the estimates of vaccine efficacy for the entire trial population as indirect evidence to support its use on those with comorbidities.

RECOMMENDATIONS

We recommend the use of these vaccines to prevent SARS-CoV-2 infections in immunocompromised patients (i.e., diagnosed with HIV, hepatitis B and C, those with cancer undergoing chemotherapy, transplant patients receiving immune-suppression) after medical clearance from a physician. *(Low certainty of evidence; Strong recommendation)*

CONSENSUS ISSUES

Despite the low certainty of evidence, a strong recommendation was made because the benefits of vaccination outweigh any potential harm. It was noted that there are no specific subgroup results for the immunocompromised patients and the expected vaccine efficacy would be lower, but then the vaccine will still give them protection against COVID-19. The panel also emphasized that a medical clearance from any physician should be sufficient to facilitate the vaccination.

RECOMMENDATIONS

We recommend against the use of these vaccines in children to prevent SARS-CoV-2 infection: *(Weak recommendation)*

- BNT162b2: <16 years old
- ChAdOx1: <18 years old

There is no evidence on the use of mRNA-1273, GamCOVID-Vac, Ad26.COV2.S and CoronaVac in children to prevent SARS-CoV-2 infection.

CONSENSUS ISSUES

A weak recommendation was made for BNT162b2 and ChAdOx1 because these are the only vaccines that included children in the trial protocol, the results of which are still pending. It was clarified that the recommendation against its use was not because of safety issues.

Based on the existing protocols, children are excluded in the clinical trials of mRNA-1273, GamCOVID-Vac, Ad26.COV2.S and CoronaVac. There is no statement of planned recruitment for the younger population.

RECOMMENDATIONS

We recommend against the use of particular vaccines in individuals who have known allergies to the contents/excipients of that vaccine, such as polysorbate (ChAdOx1, Gam-COVID-Vac and Ad26.COV2.S) and polyethylene glycol or PEG200 DMG (BNT162b2 and mRNA-1273). *(Moderate to high certainty of evidence; Strong recommendation)*

CONSENSUS ISSUES

It was clarified that the recommendation was specific for polysorbate and PEG because these two (2) excipients are notorious for hypersensitivity reactions based on different regulatory authorities. CoronoVac does not contain any of these, but the Philippine Society of Allergy, Asthma and Immunology (PSAAI) has been receiving reports on allergic reactions to CoronaVac and this is currently being investigated.

OTHER CONSENSUS ISSUES

The panel agreed to place in a separate document (i.e., guidance or standard operating procedure) the recommendations on (1) advising the recipients regarding adverse reaction and adverse events as well as the (2) implementation of a pharmacovigilance program and regular evidence review upon vaccine use.

KEY FINDINGS

As of April 23, 2021, interim trial data on the safety and efficacy of six COVID-19 vaccines have been made publicly available [95-196]. The BNT162b2 (Pfizer/BioNTech), the mRNA-1273 (Moderna), the ChAdOx1 (AstraZeneca), the

Gam-COVID-Vac (Gamaleya), and the Ad26.Cov2.S (Janssen/Johnson&Johnson) vaccines demonstrated satisfactory vaccine efficacy against symptomatic COVID-19 infection among adults in the short term with moderate certainty. Limited available information provides low certainty evidence that the CoronaVac (Sinovac) vaccine also provides satisfactory protection against symptomatic COVID-19 infection among adults. Data on the efficacy against severe COVID-19 infection and asymptomatic COVID-19 infection are still inconclusive, except for Ad26.CoV2.S, which demonstrated, with moderate certainty, good efficacy in preventing moderate and/or severe COVID-19 infection and acceptable protection against asymptomatic COVID-19 infection 28 days after vaccination. Efficacy data on preventing death from COVID-19 infection are still inconclusive. Very limited Phase 3 trial data are available to inform vaccine efficacy against the different variants of SARS-CoV-2.

Administration of these vaccines was associated with higher proportions of adverse reactions compared with the control, although serious adverse event rates were comparable. These adverse events, mostly from reactions to the vaccines, were mild to moderate and of short duration. Long term efficacy and safety data are still lacking.

Real world evidence supports clinical trial findings on the efficacy of BNT162b2, mRNA-1273, ChAdOx1, Gam-COVID-Vac and CoronaVac. A rare phenomenon, the vaccine-induced thrombotic thrombocytopenia has been found to have a possible link with the use of ChAdOx1 and Ad26.COV2.S. However, regulatory authorities have maintained a positive benefit-ratio for its continued use. No safety signals have been identified with the mRNA vaccines. Cases of anaphylaxis have been reported with the mRNA vaccines and with ChAdOx1 but they remain in very low numbers. Deaths after vaccination are also rare and often assessed as not related.

Is rAd26 (Sputnik Light) effective and safe in the prevention of COVID-19 infections?: A Rapid Review

As of 04 November 2021

RECOMMENDATION

We suggest the use of the rAd26 (Sputnik Light), given as 10^{11}vp per 0.5ml, single dose, intramuscularly to prevent symptomatic SARS-CoV-2 infection in:

d. Healthy adults *(Low certainty, Weak recommendation)*
e. Older adults (60 years and older) *(Low certainty, Weak recommendation)*
f. Adults with comorbidities *(Low certainty, Weak recommendation)*

In areas where Alpha, Beta or Delta is the predominant variant of concern, we suggest the use of rAd26 (Sputnik Light) to prevent COVID-19 infection. *(Very Low certainty, Weak recommendation)*

RECOMMENDATION

We suggest against the use of rAd26 (Sputnik Light) to prevent symptomatic SARS-CoV-2 infection in:

d. Children (3-17 years) *(No evidence, Weak recommendation)*
e. Pregnant and lactating women *(No evidence, Weak recommendation)*
f. Immunocompromised *(No evidence, Weak recommendation)*

KEY FINDINGS

Five observational studies [209-213] provided low to very low certainty evidence on the effectiveness and safety of rAd26 (Sputnik Light) against COVID-19 infection. Immunogenicity studies showed that rAd26 induced significant humoral and cellular response against SARS-COV-2 and its variants. Observational studies found rAd26 to provide sufficient protection against COVID-19 infection, hospitalization and death, particularly for the older person and those with comorbidities. Associated adverse events were mostly due to reactogenicity and were mild and transient. No evidence was found on the effect of rAd26 on children, pregnant women and the immunocompromised.

Among adults who received the standard full doses of any COVID-19 vaccine, what is the clinical and immunologic efficacy and effectiveness and safety of a booster?

As of 27 December 2021

RECOMMENDATION

We suggest the following homologous booster vaccination regimen for the general adult population:

g. BNT162b2 *(Low certainty of evidence; Weak recommendation)*
h. mRNA-1273 *(Low certainty of evidence; Weak recommendation)*
i. ChAdOx1 *(Very low certainty of evidence; Weak recommendation)*
j. Ad26.Cov2.S *(Very low certainty of evidence; Weak recommendation)*
k. CoronaVac *(Very low certainty of evidence; Weak recommendation)*
l. BBIBP-CorV *(Very low certainty of evidence; Weak recommendation)*

We suggest the following heterologous booster vaccination regimen for the general adult population:

k. BNT162b2 primary, mRNA-1273 booster *(Very low certainty of evidence; Weak recommendation)*
l. BNT162b2 primary, Ad26.CoV2.S booster *(Very low certainty of evidence; Weak recommendation)*
m. mRNA-1273 primary, BNT162b2 booster *(Very low certainty of evidence; Weak recommendation)*
n. mRNA-1273 primary, Ad26.CoV2.S booster *(Very low certainty of evidence; Weak recommendation)*
o. ChAdOx1 primary, BNT162b2 booster *(Very low certainty of evidence; Weak recommendation)*
p. Ad26.COV2.S primary, BNT162b2 booster *(Very low certainty of evidence; Weak recommendation)*
q. Ad26.COV2.S primary, mRNA-1273 booster *(Very low certainty of evidence; Weak recommendation)*
r. CoronaVac primary, BNT162b2 booster *(Very low certainty of evidence; Weak recommendation)*
s. CoronaVac primary, ChAdOx1 booster *(Very low certainty of evidence; Weak recommendation)*
t. BBIBP-CorV primary, BNT162b2 booster *(Very low certainty of evidence; Weak recommendation)*

We suggest the following homologous booster vaccination for the immunocompromised population:

a. BNT162b2 *(Very low certainty of evidence; Weak recommendation)*
b. mRNA-1273 *(Low certainty of evidence; Weak recommendation*

We suggest the following heterologous booster vaccination regimen for the immunocompromised population:

f. an mRNA vaccine primary, another mRNA vaccine *booster (Very low certainty of evidence; Weak recommendation)*
g. an mRNA vaccine primary, ChAdOx1 booster *(Low certainty of evidence; Weak recommendation)*
h. BNT162b2 primary, mRNA-1273 booster *(Very low certainty of evidence; Weak recommendation)*
i. BNT162b2 primary, Ad26.CoV2.S booster *(Very low certainty of evidence; Weak recommendation)*
j. mRNA-1273 primary, Ad26.CoV2.S booster *(Very low certainty of evidence; Weak recommendation)*

RECOMMENDATION

There is insufficient evidence to recommend the following homologous booster vaccination in the general population:

a. Gam-COVID-Vac
b. BBV152

There is insufficient evidence to recommend the use of the heterologous booster vaccination regimens other than the combinations included above in the general adult population.

There is insufficient evidence to recommend the following homologous booster vaccination for the immunocompromised population:

g. ChAdOx1
h. Ad26.CoV2.S
i. CoronaVac
j. Gam-COVID-Vac
k. BBV152
l. BBIBP-CorV

There is insufficient evidence to recommend the use of the heterologous booster vaccination regimen other than the combinations included above in the immunocompromised population.

KEY FINDINGS

Fifty-one studies [216-265] are now included in the review, including: 8 randomized trials; 16 studies involving immunocompromised population; and 20 studies on heterologous booster vaccination. Clinical outcomes of booster vaccination remain to be available only for BNT162b2 homologous vaccination from three observational studies and from on study which included BBIBP-CorV. A new study provides vaccine effectiveness estimates for BNT162b2 homologous vaccination. Immunogenicity studies among the general population comparing pre- and post-boost humoral response consistently show significant increases titers and seropositivity rates regardless of the booster regimen. Available data on cellular response after boosters

among the general population is limited and suggests increased response. Immunogenic response after boosters among the immunocompromised showed inconsistency. Low certainty evidence suggests booster vaccination to be safe, with heterologous booster vaccination associated with higher adverse reaction rates compared with homologous booster vaccination.

CONSENSUS ISSUES

The main considerations in the recommendations of the Panel were the positive benefit/harm ratio of the administration of a booster compared with no boosters and increasing vaccine equity, providing flexibility, and optimizing available vaccines by recommending the use of vaccine booster regimen despite low certainty of evidence and for those with comparatively lower efficacy (compared to other combinations).

Among adults, what is the clinical and immunologic efficacy and effectiveness and safety of heterologous COVID-19 vaccination compared to standard homologous COVID-19 vaccination in preventing COVID-19 infection?

As of 22 October 2021

RECOMMENDATION

We recommend the use of heterologous COVID-19 vaccination for those with serious adverse event to the first dose. *(Very low certainty of evidence; Strong recommendation)*

We suggest the use of heterologous COVID-19 vaccination in the event of the unavailability of the second dose in the recommended schedule. *(Very low certainty of evidence; Weak recommendation)*

KEY FINDINGS

Three RCTs, 18 observational studies, and 1 case report[275-295] investigated the use of heterologous vaccination using the following vaccines: BNT162b2, ChAdOx1, mRNA1273, CoronaVac, BBV152, Ad5-nCoV. No study was found using Gam-COVID-Vac, NVX-CoV2373, and BBIBP-CorV as a component of the vaccination regimen.

The overall certainty of evidence for efficacy/effectiveness is very low due to the study design (i.e. observational studies with a lack of control for confounding factors), the use of surrogate outcomes (immunogenicity), missing outcomes, and short follow up. The overall certainty of evidence for safety is low because of the study design (i.e. observational studies), unclear to lack of blinding, and the short follow-up.

Only one retrospective population-based cohort study[283] with ChAdOx1/BNT162b2 or mRNA-1273 as the heterologous regimen showed clinical efficacy against SARS-CoV-2 infection, hospitalization, and death.

Current evidence shows that heterologous primary vaccination is immunogenic and results in acceptable adverse reaction rates. Different combinations and regimen perform differently.

CONSENSUS ISSUES

The panel decided to give a strong recommendation, despite the very low certainty of evidence, on the use of heterologous vaccination among those with serious adverse event to the first dose. This is because of the need to provide the sufficient protection afforded by the second dose, especially for the vulnerable and at-risk populations. The importance of informed consent was emphasized by the panel, particularly on the benefits and harms of the administration of heterologous vaccination versus delayed administration of the second dose in the context of vaccine unavailability.

Are COVID-19 vaccines efficacious in preventing COVID-19 infections caused by the B.1.617.2 (Delta) Variant?

As of 28 October 2021

RECOMMENDATION

In areas where the Delta variant is the predominant circulating variant, we recommend for the use of the following vaccine to prevent symptomatic and severe COVID-19:

e. 2 doses of BBV152 (Covaxin/Bharat)
(Moderate certainty of evidence; Strong recommendation)
f. 2 doses of BNT162b2 (Pfizer)
(Low certainty of evidence; Strong recommendation)
g. 2 doses of mRNA-1273 (Moderna)
(Low certainty of evidence; Strong recommendation)
h. 2 doses of ChAdOx1 (Astra Zeneca)
(Low certainty of evidence; Strong recommendation)
i. 2 doses of CoronaVac (Sinovac)
(Very low certainty of evidence; Strong recommendation)

In areas where the Delta variant is the predominant circulating variant, we suggest the use of the following vaccines to prevent symptomatic and severe COVID-19:

c. Ad26.CoV2 (Janssen)
(Low certainty of evidence; Weak recommendation)
d. Gam-COVID-Vac (Sputnik V)
(Low certainty of evidence; Weak recommendation)

CONSENSUS ISSUES

The panel agreed that all vaccines may be used in for protection against the infections caused by the Delta variant, despite some reduction in vaccine effectiveness. The panel's decisions on the strength of recommendation were based mainly on the certainty of evidence supporting the effectiveness. Vaccines with clinical evidence of effectiveness were given strong recommendations for use, whereas vaccines with only immunologic evidence of effectiveness were given weak recommendations.

Among children <18 years old, what is the efficacy/effectiveness and safety of COVID-19 vaccines compared to placebo in preventing COVID-19?

As of 21 October 2021

RECOMMENDATION

We recommend the use of the BNT162b2 (Pfizer/BioNTech) vaccine, [given as 0.3 mL (30 ug) intramuscular injections, in 2 doses, 21 days apart] for children 12-15 years old to prevent symptomatic SARS-CoV-2 infection. *(Moderate certainty of evidence; Strong recommendation)*

We suggest the use of the mRNA-1273 (Moderna) vaccine, [given as 0.5 mL (100 ug) intramuscular injections, in 2 doses, 28 days apart] for children 12-17 years old to prevent symptomatic SARS-CoV-2 infection. *(Low certainty of evidence; Weak recommendation)*

RECOMMENDATION

We suggest against the use of Coronavac (Sinovac), [given as 0.5 mL (600 SU) intramuscular injection, in 2 doses, 28 days apart] for children 3-17 years old to prevent symptomatic SARS-CoV-2 infection. *(No evidence; Weak recommendation)*

KEY FINDINGS

This review provides the evidence on the use of COVID-19 vaccines in children based on one (1) systematic review, three (3) randomized controlled trials (RCTs), two (2) real world effectiveness studies, five (5) case series/reports, and six (6) regulatory agency reports[330-345]. Findings show that BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) provide sufficient protection against COVID-19 infection among adolescents who are at least 12 years old. More reactogenicity events were noted but adverse events were generally non-severe. Higher immunogenicity responses were also seen with children compared to adults. CoronaVac (Sinovac) was found to be immunogenic among children aged 3-17 years old.

Real world evidence on the use of mRNA vaccines in children supported the findings in the clinical trials. Myocarditis was detected among children after mRNA vaccination, although rare.

CONSENSUS ISSUES

The issue of myocarditis associated with the mRNA vaccines in children was a major consideration in the recommendation, particularly with the mRNA-1273 (Moderna) vaccine. Despite the low incidence of post-vaccination myocarditis, some Panel members considered it significant enough, especially when normal children are concerned, to weigh heavily on the benefit risk ratio. The suspension of the use of mRNA-1273 among children in some countries due to the myocarditis issue was also raised, resulting in the cautious recommendation given for this vaccine. The Panel emphasized that warnings should be given to the parents and caregivers of the

vaccine recipients to consult immediately in case of symptoms occurring after vaccination, which may suggest the development of myocarditis.

Is COVID-19 vaccination effective and safe among pregnant and lactating individuals and their infants in the prevention of COVID-19 infections?

As of 27 Decermber 2021

RECOMMENDATION

We suggest the use of following vaccines, after the first trimester, for the prevention of COVID-19 infection in pregnant and lactating women.

h. BNT162b2 (Pfizer) *(Low certainty of evidence; Weak recommendation)*
i. mRNA-1273 (Moderna) *(Low certainty of evidence; Weak recommendation)*
j. ChAdOx1 (AstraZeneca) *(No direct evidence; Weak recommendation)*
k. Ad26.CoV2.S (Janssen/Johnson&Johnson) *(No direct evidence; Weak recommendation)*
l. CoronaVac (Sinovac) *(No direct evidence; Weak recommendation)*
m. BBIBP-CorV (Sinopharm) *(No direct evidence; Weak recommendation)*
n. BBV152 (Covaxin) *(No direct evidence; Weak recommendation)*

RECOMMENDATION

We suggest against the use of the following vaccines for the prevention of COVID-19 infection in pregnant and lactating women:

c. Gam-CoV-Vac (Sputnik V) *(No direct evidence; Weak recommendation)*
d. NVX-2373 (Novavax) *(No direct evidence; Weak recommendation)*

KEY FINDINGS

The current evidence base includes forty-two reports [357-394] that investigated the effectiveness, immunogenicity, and safety of COVID-19 vaccination among pregnant and lactating women and their infants. Three were systematic reviews and 39 were observational studies. Available evidence demonstrates that COVID-19 vaccination provides sufficient protection against COVID-19 disease for pregnant and lactating women, with transfer of antibody protection to the newborn, without significant increase in the risk of maternal and neonatal adverse events nor adverse pregnancy and delivery outcomes.

CONSENSUS ISSUES

The Panel took into consideration that pregnant and lactating women are at a higher risk for severe COVID infection and are a particularly vulnerable population to recommend COVID-19 vaccination for them. Despite the absence of direct evidence of the efficacy of some vaccines for this population, the Panel still recommended their use using indirect evidence of efficacy and safety from the other vaccines and from the general adult population. The decision to recommend against the use of Gam-COVID-Vac (Sputnik V) was made based on the manufacturer's restriction of their

product among pregnant women, in the absence of direct evidence of its effect. On the other hand, the decision to recommend against the use of NVX-2373 for pregnant women was mainly due to its low efficacy seen in the immunocompromised population and a higher risk of adverse reaction.

Is BCG vaccination effective and safe in the prevention of COVID-19 infections?

As of 09 April 2021

RECOMMENDATION

We suggest against the use of BCG vaccine for the prevention of COVID-19 infection. *(Very low certainty of evidence; weak recommendation)*

KEY FINDINGS

A systematic review of the literature on April 2, 2021 did not yield any completed randomized trial on the efficacy and safety of BCG vaccination in the prevention of COVID-19 infection. Five retrospective cohort studies and one case control study[403-407] were included in this review and all showed high risk of bias and conflicting results. As of March 6, 2021, 22 studies that address this issue have been registered, 21 of which are randomized controlled trials.

CONSENSUS ISSUES

A weak recommendation against the use of BCG vaccination for COVID-19 prevention was made by the Panel in consideration of the following issues. Most of the evidence included in the review are retrospective cohorts and one case control. Among the articles, the timing of BCG administration is variable or unclear and the outcomes were self-reported and not necessarily RT-PCR confirmed. Also, although an RCT was recently completed in Greece on the potential utility of BCG vaccine as prophylaxis for COVID-19, it is still a preprint and not yet included in the review. There is also clinical trial evidence in the elderly that it improves outcomes for other respiratory viral infections. Furthermore, it is relatively inexpensive and there is no evidence of serious harm. It was discussed that BCG vaccine is usually given among children to prevent disseminated or miliary tuberculosis.

It was also discussed in the panel meeting that the Philippines has a policy on birth doses for BCG within 24-hours of delivery; however, this is not fully implemented in health centers since it is available as a multi-dose vial, they do not administer this if there is only one infant. On the other hand, it was noted that there is no national policy on BCG vaccination among adults.

Among close contacts of COVID-19 patients, should casirivimab + imdevimab cocktail be used as post-exposure prophylaxis?

As of 04 November 2021

RECOMMENDATION

We suggest the subcutaneous use of casirivimab + imdevimab as day 4 post-exposure prophylaxis for COVID-19 close contacts*, ages 12 years and above weighing at least 40 kilograms, who are at risk for severe disease or hospitalization**. *(Moderate certainty of evidence; weak recommendation)*

**The definition of close contacts is the same as in the Living COVID CPG guidelines.*
***This includes the following people: elderly; BMI >25; those with chronic diseases such as hypertension, diabetes, and chronic kidney disease; those who are not expected to mount an adequate immune response to the vaccine due to immunosuppressive therapy or those in an immunocompromised state.*

KEY FINDINGS

There was 1 randomized controlled trial[414] that investigated casirivimab + imdevimab cocktail as post-exposure prophylaxis for RT-PCR SARS-CoV-2 negative close contacts of COVID-19 patients. The results showed a significant decrease in symptomatic and asymptomatic COVID-19 infection. Among those who developed infection, casirivimab + imdevimab resulted in significant decrease in duration of infection. There was no significant difference in serious adverse events between those given casirivimab + imdevimab and placebo. The overall certainty of evidence was rated moderate due to imprecision in 1 critical outcome.

CONSENSUS ISSUES

Despite moderate certainty of evidence, the panel decided on a weak recommendation for prophylactic use of casirivimab + imdevimab cocktail given the following factors related to equity: (1) prohibitive cost (PHP 25,000-30,000), (2) potential problems with accessibility, (3) limited supply, (4) EUA mandate last October 2021 specifically allowing its use for treatment only and (5) issues on applicability.

The recommendation is based on a single multi-center, randomized controlled trial that was done in the United States. There is a very limited window to administer the drug therefore, the poor contact tracing and the delayed release of test results are issues in our setting that compromises the applicability of the results of this study. The vaccination status of the participants as well as the prevalent viral strains during the time of the trial were considerations of the panel. While neither of the two were discussed in the study, the study was implemented from June 2020 to March 2021.

Should melatonin be used in the prevention of COVID-19 infection?

As of 26 February 2021

RECOMMENDATION

We recommend against the use of melatonin as prevention for COVID-19 infection. *(Very low certainty of evidence; Strong recommendation)*

KEY FINDINGS

One observational study [426] reported lower odds of getting a positive test result for COVID-19 among those taking melatonin compared to those who were not. The study was found to be with serious risk of bias because of absence of randomization and allocation concealment and the lack of details which precluded assessment of blinding and follow-up. For safety, one systematic review[427] reported that overall, melatonin supplements have a good safety profile. However, there are some adverse effects that are dose- and timing-related, and one study stated that caution should be exercised in the use of melatonin in patients with hypertension [428].

CONSENSUS ISSUES

It was discussed that among the limitations of the efficacy study was the lack of information on the dose administered and the duration of intake; hence, the panel could not compare it against the usual dose used for sleep disorder, which is one (1) 3-mg capsule a day for at least a month. The cost per capsule ranges from Php 16.00 to 20.00. Regarding melatonin's adverse effects, it was noted that indirect studies were evaluated (i.e., use of 2 mg to 10 mg melatonin for different indications); hence, the observation of excessive sleepiness may be dose-related. The panel raised a concern on the potential for its misuse or overuse considering that it may be marketed as prophylaxis for COVID-19, which is an off-label indication. Likewise, its potential adverse effects from long-term use are unknown.

Considering that the certainty of evidence to support the use of melatonin is very low, and in the context of potential adverse events as well as cost considerations, the panel decided to strongly recommend against its use for COVID-19 infection.

Should Vitamin D supplementation be used in the prevention of COVID-19 infection?

As of 18 March 2021

RECOMMENDATION

We recommend against the use of Vitamin D supplementation to prevent COVID-19 infection. *(Very low certainty of evidence; Strong recommendation).*

KEY FINDINGS

A retrospective cohort study on frail, elderly nursing home residents (N=66)[437] reported that fewer patients died among those who received 80,000 IU of Vitamin D during the week following the diagnosis of COVID-19, or within one month prior to diagnosis, when compared to patients who received other medications. There was no direct evidence on the safety of Vitamin D supplementation as prevention for COVID-19.

CONSENSUS ISSUES

It was pointed out that although the study by Jollife et al. found that Vitamin D supplementation reduced the risk of acute respiratory infection (ARI) overall, this systematic review was done prior to the COVID-19 pandemic, hence the population assessed did not include COVID-19 patients. In relation to the preventive effect of Vitamin D against ARI, it was noted that the duration of the trials in the systematic review ranged from 7 weeks to 12 months, and such a duration for effect to be seen is not deemed beneficial since vaccines will soon be available. Overall, the panel recognized that all the studies evaluated on its efficacy and safety were indirect evidence.

Should zinc supplementation be used in the prevention of COVID-19 infection?

As of 18 March 2021

RECOMMENDATION

We recommend against the use of zinc supplementation to prevent COVID-19 infection. (*Very low certainty of evidence; Strong recommendation).*

KEY FINDINGS

No direct published evidence was found on the use of zinc supplements in the prevention of COVID-19. Among non-COVID adult participants, zinc acetate doses of 100 to 150 mg/day taken for months had few adverse effects. Excessive intake of zinc may lead to gastrointestinal disturbances. When taken together with other supplements, zinc may reduce copper and iron levels in the body.

CONSENSUS ISSUES

A concern was raised that the recommendation may be misconstrued that zinc supplementation is not needed, but it was clarified that this will be specific only for COVID-19 infection.

Should hydroxychloroquine/ chloroquine be used in the prevention of COVID-19?

As of 12 March 2021

RECOMMENDATION

We recommend against the use of HCQ for pre-exposure prophylaxis in adults who are at high risk of exposure to COVID-19 cases. *(Moderate certainty of evidence; Strong recommendation)*

We recommend against the use of HCQ for post-exposure prophylaxis in adults who are exposed to COVID-19 cases. *(Low certainty of evidence; Strong recommendation).*

KEY FINDINGS

Two randomized controlled clinical trials on the use of hydroxychloroquine (HCQ) as pre-exposure prophylaxis for COVID-19 showed tendency for reduction in the risk of developing COVID-19 infection. However, there was significant increase in the risk of adverse events. Three RCTs were found on the use of HCQ for post-exposure prophylaxis for COVID -19 no significant reduction in the risk of developing COVID-19 infection and a trend toward increase in the risk of adverse events. [474-478] Most of the studies were found to be at risk for bias with common issues in ascertainment bias and one study without blinding.

CONSENSUS ISSUES

For pre-exposure prophylaxis, HCQ will only have 2% benefit considering the worst-case scenario. With regard to its safety profile, there is clear harm in terms of gastrointestinal (e.g., diarrhea, abdominal cramps, nausea and vomiting) and neurological (e.g., dizziness) adverse events, which are incapacitating to health workers if they are to use this as prophylaxis.

For post exposure prophylaxis, the low-quality evidence showed no significant benefit of HCQ, and a trend toward increase in the risk of adverse events was likewise observed.

Should lopinavir/ritonavir be used as prophylaxis for the prevention of COVID-19?

As of 12 March 2021

RECOMMENDATION

We recommend against the use of lopinavir/ritonavir for chemoprophylaxis in individuals exposed to COVID-19 patients. *(Very low certainty of evidence; Strong recommendation)*

KEY FINDINGS

There is currently no available direct evidence on the use of lopinavir/ritonavir in the prevention of COVID-19 among healthy individuals, particularly those exposed to confirmed COVID-19 individuals. There is very low-quality indirect evidence of lopinavir/ritonavir as post-exposure prophylaxis for an outbreak of MERS-CoV [481].

CONSENSUS ISSUES

The panel strongly recommends against the use of lopinavir/ritonavir for chemoprophylaxis because of the very low certainty of evidence. The drug combination is not commercially available and can only be availed of through the HIV program. In addition to the limited accessibility, there might also be competition with HIV patients who need it as a regular regimen. Given the limited supply in the country, it is not deemed to be a feasible intervention for prophylaxis since a large quantity of lopinavir/ritonavir will be required in such cases.

Should ivermectin be used as COVID-19 prophylaxis for the general population?

As of 17 April 2021

RECOMMENDATION

We recommend against the use of ivermectin as COVID-19 prophylaxis for the general population. *(Very low certainty of evidence; Strong recommendation)*

We recommend against the use of ivermectin for COVID-19 as post-exposure prophylaxis for household contacts of confirmed COVID-19 patients. *(Very low certainty of evidence; Strong recommendation)*

We recommend against the use of ivermectin for COVID-19 as prophylaxis for healthcare workers. *(Very low certainty of evidence; Strong recommendation)*

KEY FINDINGS

Four very low quality randomized controlled trials[493-496] were found on the use of ivermectin as COVID-19 prophylaxis. All RCTs were found to have very serious risk of bias in terms of lack of blinding, analysis of incomplete outcome data, and selective reporting. One RCT showed lower rates of developing COVID-19 related symptoms. Moreover, two RCTs showed lower RT-PCR-confirmed COVID-19 infection rates in

the ivermectin group compared to non-intervention group. However, one of these two RCTs administered a co-intervention in the ivermectin group, which poses serious validity issues. Lastly, one cluster RCT showed inconclusive RT-PCR-confirmed results for ivermectin. Mild adverse events were reported such as gastrointestinal upset, fatigue, sleepiness, pruritus, numbness, and burning sensation, all of which did not necessitate discontinuation of therapy.

CONSENSUS ISSUES

The studies included in the review had very serious or high risk of bias. In particular, the study by Elgazzar et al. (2021) had a very low overall certainty of evidence due to the risk of bias and serious imprecision from the wide 95% confidence interval (CI). Using the WHO Considerations for Evaluation of COVID-19 Vaccines as reference for efficacy of prophylaxis or preventive therapy, the upper end of the computed CI exceeded the threshold for primary efficacy endpoint estimate 0.70 (30% efficacy). The Shoumann et al. (2021) study also has a serious validity issue due to the premature termination of the control group, and lack of pretermination protocol, thus leading to selective reporting. Lastly, the results of the Chahla et al. (2021) study also have validity issues due to the presence of a co-intervention in the treatment arm.

The panel recognized the great potential for its misuse or overuse. The panel also stressed that there is a need to have concrete evidence on safety, as well as on the appropriate dose and dosing frequency, which the current very low quality evidence did not provide. Another issue raised was that only a compassionate special permit (CSP) has been granted to two specific hospitals that applied for the permit, despite the current registration of ivermectin products as veterinary treatment for internal and external animal parasites. Hence, there may be legal implications when a positive recommendation to use it as a prophylaxis is issued. The human-grade ivermectin, on the other hand, is still applying for emergency use authorization (EUA) from the Philippine Food and Drug Administration. Considering the vaccine hesitancy of the public, a concern was raised by the panel that if a recommendation to an alternative to the vaccine as prophylactic agent will be made, then people will most likely opt not to get vaccinated, undermining the national vaccination program of the government.

Should saline nasal irrigation be used for the prevention of COVID-19?

As of 12 March 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of saline nasal irrigation (SNI) to prevent COVID-19 in healthy individuals. *(Very low certainty of evidence)*

KEY FINDINGS

There are no direct studies assessing the benefit or harm of saline nasal irrigation use among healthy individuals as a preventive strategy for COVID-19. Only indirect evidence from an observational study[508] using saline spray compared to no nasal spray in the prevention of common colds showed shorter duration of symptoms of nasal blockage and discharge but no difference in number of respiratory infections.

CONSENSUS ISSUES

The panel did not provide a recommendation on SNI because of the very low certainty of evidence on the use of nasal spray to prevent the common cold.

Should steam inhalation be used for the prevention of COVID-19?

As of 12 March 2021

RECOMMENDATION

We recommend against the use of steam inhalation in the prevention of COVID-19. (*Very low certainty of evidence; Strong recommendation)*

KEY FINDINGS

Based on two single arm observational studies[516-517] with high risk of bias, there is currently only very low certainty evidence showing the possible benefit of steam inhalation in the prevention of developing symptomatic COVID-19 among exposed healthy individuals and reducing symptoms and number of days to negative SARS-COV-2 RT-PCR test of COVD-19 confirmed individuals. Meanwhile, there is indirect evidence highlighting the significant adverse effects of steam inhalation among individuals using it for symptomatic relief from colds.

CONSENSUS ISSUES

The panel strongly recommended against the use of steam inhalation as prevention for COVID-19, despite the very low certainty of evidence, because it was recognized that the potential for harm outweighs the benefit.

Should aspirin be used for prophylaxis against COVID-19-induced coagulopathy in patients with COVID-19?

As of 02 June 2021

RECOMMENDATION

There is insufficient evidence on the use of aspirin as prophylaxis against COVID-19-induced coagulopathy among patients with COVID-19. *(Very low certainty of evidence*)

KEY FINDINGS

Very low quality evidence from one retrospective cohort study [526] was found on the use of aspirin prophylaxis for COVID-19 induced coagulopathy among COVID-19 patients. There was a significant reduction in the risk of mortality. COVID-19 induced coagulopathy and adverse events were not examined in this study.

Evidence and Recommendations for the Adjunct Interventions for Prevention and Control of COVID-19

Should zinc be used as adjunctive treatment for COVID-19 infection?

As of 21 December 2021

RECOMMENDATION

There is insufficient evidence to recommend zinc as adjunctive treatment for COVID-19 infection. *(Low certainty of evidence)*

KEY FINDINGS

This updated review [1-6] showed inconclusive results on the efficacy of zinc as adjunctive treatment for COVID-19 for the outcomes of in-hospital mortality and hospitalization of outpatients. There was a significantly higher number of adverse events in the group that received zinc compared to control.

CONSENSUS ISSUES

Despite the risk of adverse events (i.e., infusion site irritation and gastrointestinal side effects), the panelists agreed that the evidence of benefit and harm of zinc as an adjunct therapy for COVID-19 still poses uncertainty. From their experience with the use of oral zinc for prevention of other illnesses, there had been no significant events reported to identify oral zinc as a cause for concern. Its potential for benefit was still given high consideration, particularly pending the results of ongoing studies. One voted against its use due to the signal for harm (i.e., hospitalization) among ambulatory patients and the risk of adverse events in the zinc group.

Should B Vitamins be used as an adjunct in the treatment of COVID-19?

As of 30 June 2021

RECOMMENDATION

We suggest against the use of B vitamins as adjunct in the treatment of patients with COVID-19. *(Very low certainty of evidence; Weak recommendation)*

KEY FINDINGS

There was one cohort study on the use of vitamin D/magnesium/vitamin B12 (DMB) supplementation on patients with COVID-19 infection.[7] Likelihood of subsequent oxygen therapy including ICU support was significantly less for those taking DMB. However, there was no significant difference when looking at oxygen therapy alone or ICU support alone. There were no adverse events directly attributed to DMB use in the cohort study. There is very low certainty of evidence that suggests an association between excessive levels of Vitamin B12 and poorer outcomes in COVID-19 patients.[8] Overall, there is very low certainty of evidence due to risk of bias based on the observational design, as well as issues with directness (DMB was given in combination with vitamin D and magnesium) and imprecision (due to limited sample size).

CONSENSUS ISSUES

Vitamin B plays an important role in cell functioning and boosting the immune system. Therefore, there is a need to assess the potential of Vitamin B as an adjunct treatment for COVID-19.

There were no studies that assessed the use of Vitamin B alone as an adjunct treatment for COVID-19 but there are still ongoing studies that can provide a clear picture on the use of Vitamin B as adjunct treatment. There were also no studies found that assessed the correlation of Vitamin B deficiency and cytokine storm. However, a prospective study that investigated the levels of Vitamin B12 and folate plasma level among patients admitted for COVID-19 pneumonia until they were transferred to ICU or death ensued suggested that there was a potential association between high plasma levels of Vitamin B12 and increased risk of mortality.

Should vitamin C be used in the adjunctive treatment of COVID-19?

As of 21 December 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of vitamin C as adjunctive treatment for patients with COVID-19. *(Low certainty of evidence)*

KEY FINDINGS

There are eight RCTs included in this review but only four, that used intravenous vitamin C for hospitalized patients with moderate to severe COVID-19, were pooled.[9-12] For the outcome of mortality, there was a trend towards benefit with small negligible harm. There was no significant benefit and inconclusive results for length of hospital stay, length of ICU stay and need for mechanical ventilation. One RCT using oral vitamin C in the outpatient setting [13] and three RCTs using Vitamin C in addition to other adjunctive treatments [14-16] showed inconclusive results. Adverse events reported were flushing, headache, nausea, vomiting, stomach pain, and diarrhea.

CONSENSUS ISSUES

The evidence still posed low certainty in terms of efficacy (i.e., reduction in length of hospital and ICU stay, need for mechanical ventilation for hospitalized patients, and mortality among both hospitalized and non-hospitalized patients) and safety. The panel could not suggest against the use of vitamin C since only one study for non-hospitalized patients showed inconclusive effects on mortality and adverse events.

Among patients with COVID-19, should Vitamin D be used as adjunctive treatment?

As of 03 December 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of Vitamin D supplementation as an adjunct treatment for patients with COVID-19 infection. *(Very low certainty of evidence)*

KEY FINDINGS

We found eight randomized controlled trials of COVID-19 patients who were given vitamin D as adjunctive treatment.[17-24] We found no significant benefit for the following outcomes: mortality, ICU admission, need for mechanical ventilation, hospital length of stay, clinical improvement, and virologic clearance. Subgroup analysis revealed that vitamin D status did not significantly change our estimates. These results must be interpreted in the context of very low certainty of evidence due to serious risk of bias, serious inconsistency, and serious imprecision among the included studies.

CONSENSUS ISSUES

The panel members perceived that the quality of evidence, showing negligible benefit, is still very low. A panel member voted against using Vitamin D as an adjunct due to (1) the possibility of it being prescribed despite the inconclusive evidence of benefit, (2) additional expenses that would be incurred if prescribed, and (3) probable drug interactions with other medications.

Should melatonin be used in the adjunctive treatment of COVID-19?

As of 30 June 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of melatonin as adjunct treatment for patients with COVID-19 infection. *(Very low certainty of evidence)*

KEY FINDINGS

There was only one very low quality RCT that compared melatonin with standard treatment [25], and it showed significant reduction in cough, dyspnea, and fatigue, and significantly shorter hospital stay and return to baseline health in those given melatonin. There was no significant difference in the proportion of patients discharged on day 14. No adverse events were observed in the use of melatonin among COVID-19 patients.

Should virgin coconut oil be used in the adjunctive treatment of COVID-19?

As of 30 June 2021

RECOMMENDATION

There is no evidence to recommend the use of VCO as treatment among patients with COVID-19 infection.

KEY FINDINGS

Virgin coconut oil (VCO) is rich in lauric acid and pharmacologically active metabolite monolaurin. In vitro studies have found that VCO has anti-inflammatory, antioxidant, antibacterial, antifungal, and antiviral properties. In a clinical trial involving HIV and AIDS patients, VCO treatment led to an increase in CD4+ and lymphocyte counts as well as reduction in viral load. Currently, there are no published studies assessing the efficacy and safety of virgin coconut oil as an adjunctive treatment for COVID-19.

Should Lagundi (Vitex negundo) be used as adjunctive treatment for COVID-19 infection?

As of 29 October 2021

RECOMMENDATION

There is no evidence to recommend Lagundi *(Vitex negundo)* as adjunctive treatment for patients with COVID-19 infection.

KEY FINDINGS

Lagundi (*Vitex negundo*), a medicinal herbal cough remedy widely used in the Philippines, was considered a potential adjunctive treatment for COVID-19. We found no published studies on *Vitex negundo* on patients with COVID-19 but there is one completed local clinical trial [26] whose full results are not yet available.

CONSENSUS ISSUES

Considerations of the panel were the lack of completed studies to date and the possibility of misinterpretation, stemming from anecdotal accounts of relief of symptoms, which could lead to its use even without definite benefits.

Should Tawa-tawa (Euphorbia hirta) be used as adjunctive treatment for COVID-19 infection?

As of 29 October 2021

RECOMMENDATION

There is no evidence to recommend Tawa-tawa *(Euphorbia hirta)* as adjunctive treatment for patients with COVID-19 infection.

KEY FINDINGS

Tawa-tawa (*Euphorbia hirt*a) is a medicinal herb widely used for febrile illness in the Philippines; it is considered as a potential adjunctive treatment for COVID-19. We found no published studies on *Euphorbia hirta* in patients with COVID-19. There is one ongoing local clinical trial.

CONSENSUS ISSUES

Due to the lack of evidence, the panel decided not to make a recommendation for the use of Tawa-tawa as adjunctive treatment for COVID-19. One panelist opted to abstain from the vote because her inclination was to suggest against the use of Tawa-tawa. While it has been used in the treatment of dengue, it has no proven benefits for COVID-19 infection and may cause harm.

Should oral fatty acid supplements be used as adjunct treatment for patients with COVID-19?

As of 30 June 2021

RECOMMENDATION

There is insufficient evidence to recommend the use of fatty acid supplements as adjunct treatment for patients with COVID-19. *(Low certainty of evidence)*

KEY FINDINGS

There is low certainty of evidence based on one RCT (N=128) that compared omega-3-fatty acid supplementation of high-protein enteral feeding versus high-protein enteral feeding alone in hospitalized patients with COVID-19 [27], which showed significant reduction in mortality (available case analysis, RR 0.85, [0.73, 0.99]). The RCT did not report adverse events. Indirect evidence on adverse events from two meta-analyses of RCTs on critically-ill ICU patients (non-COVID), mostly with ARDS, given fatty acid supplementation versus control, showed that gastrointestinal adverse events were common but did not differ significantly between groups (RR 1.04, 95% CI 0.96-1.13; moderate certainty of evidence).

CONSENSUS ISSUES

There were no reported adverse events in the study that assessed the effect of addition of 1000mg omega-3-fatty acid supplementation to enteral feeding of hospitalized patients with COVID-19. There was no significant difference in reported adverse events between groups given fatty acid supplementation or placebo in critically-ill ICU patients (non-COVID).

In terms of cost, a capsule of 1000mg omega-3-fatty acid may cost less than Php 20.00 in the market. It was also remarked that patient preference may be a factor because of the fishy taste.

Should N-acetylcysteine be used as an adjunct treatment for patients diagnosed with COVID-19?

As of 30 June 2021

RECOMMENDATION

We recommend against the use of intravenous N-acetylcysteine as adjunct treatment for patients with COVID-19 infection. *(Moderate certainty of evidence; Strong recommendation)*

KEY FINDINGS

One randomized controlled trial comparing NAC to placebo with 135 participants [28] was found to have no significant difference compared to control for mortality, invasive mechanical ventilation, ICU admission, length of hospital and ICU stay. A case series of ten respirator-dependent patients who responded to IV NAC showed reduction in inflammatory markers wherein six patients rebounded once NAC was discontinued and eight were discharged while two remained hospitalized.[29] Indirect evidence in a low-quality systematic review of NAC vs placebo in patients with Acute Respiratory Distress Syndrome failed to show any difference in the mortality, but significantly reduced ICU stay. [30]

CONSENSUS ISSUES

The panel distinguished between the oral and intravenous (IV) preparations of N-acetylcysteine (NAC), noting in part the cost of the IV agent.

A study included in this review which compared NAC and placebo among suspected or confirmed COVID-19 patients found no significant difference on its primary and secondary outcomes (i.e., mortality, invasive mechanical ventilation and ICU admission). However, NAC may essentially still be used for its other clinical indications (i.e., as mucolytic) on patients with COVID-19, but not necessarily for the treatment of COVID-19.

There were also a few studies included in the review that compared IV-NAC and placebo among ARDS patients, and although it was also noted that NAC has no ancillary role on the treatment of ARDS, it is used for intubated patients for its mucolytic and immunomodulating properties.

Should RAAS blockers be continued in patients with COVID-19?

As of 30 June 2021

RECOMMENDATION

We recommend continuing maintenance RAAS blockers for hypertension among patients with COVID-19 infection. *(Moderate certainty of evidence; Strong recommendation)*

KEY FINDINGS

Based on two RCTs (N=811) with moderate certainty of evidence [31,32], there is probably little or no significant reduction in the risk of deaths and severe disease for patients with hypertension and COVID-19 who continued RAAS blockers compared to those who discontinued RAAS blockers.

Should statins be used as adjunctive treatment in patients with COVID-19?

As of 29 October 2021

RECOMMENDATION

There is insufficient evidence to recommend statins as adjunctive treatment in patients with COVID-19. *(Very low certainty of evidence)*

KEY FINDINGS

Statins are lipid-lowering drugs known to have pleiotropic effects against inflammation and thrombosis. Very low quality of evidence from two randomized clinical trials [33-35] showed that among COVID-19 patients admitted to the ICU, the only significant finding was a decrease in hospital stay. There was no significant benefit for the following outcomes: composite risk for adjudicated venous or arterial thrombosis, the risk for ECMO treatment, the risk for all-cause mortality, or the individual components of adjudicated venous thromboembolism, all-cause mortality, or need for mechanical ventilation.

CONSENSUS ISSUES

Due to perceived risk of harm, two panelists were inclined to suggest against the use of statins as adjunctive treatment in patients with COVID-19.

Does the concurrent use of Ibuprofen worsen COVID-19 outcomes?

As of 30 June 2021

RECOMMENDATION

We suggest that Ibuprofen may still be used as symptomatic treatment of patients with COVID-19 infection if clinically warranted. Concurrent use of ibuprofen is not associated with worsening of COVID-19 outcomes. *(Very low certainty of evidence; Weak recommendation)*

KEY FINDINGS

There has been concern on the use of ibuprofen in COVID-19. Fang et al. reported that the point of entry for SARS-COV-2 is through angiotensin- converting enzyme 2 receptor, which is believed to be upregulated by ibuprofen. Based on six observational studies assessed [36-41], there was no significant association between ibuprofen use and worse COVID-19 outcomes: composite outcome (death, acute respiratory distress syndrome, ICU admission, shock) OR 1.06 (95% CI 0.81-1.40), Death OR 1.07 (95% CI 0.35-3.24), and progression of symptoms after propensity score matching. Five clinical trials on Ibuprofen use in COVID-19 are still on-going.

Should aspirin, taken as maintenance therapy for underlying medical conditions, be discontinued in patients with COVID-19?

As of 30 June 2021

RECOMMENDATION

There is insufficient evidence to recommend discontinuation of aspirin as maintenance therapy for underlying medical conditions in patients with COVID-19. *(Very low certainty of evidence)*

KEY FINDINGS

Very low-quality evidence from three retrospective cohort studies [42-44] was found on the continuation of aspirin as maintenance for underlying medical conditions among patients with COVID-19. There was no significant decrease in the odds of mortality in the use of aspirin. However, there was a significant increase in the odds of the composite outcome of mortality or discharge to hospice with continuation of aspirin. Thromboembolic and adverse events were not examined in these studies.

CONSENSUS ISSUES

Further studies are needed for the panel to make a recommendation on the discontinuation of aspirin as maintenance therapy in patients with COVID-19. There is certainty of benefit for continuing aspirin for underlying medical conditions. However, the benefit of its use among patients with COVID-19 is still uncertain.

Should antiseptic mouthwashes/gargles be used be as adjunctive treatment for COVID-19 infection?

As of 21 December 2021

RECOMMENDATION

We recommend against the use of any antiseptic mouthwash as an adjunctive therapy for patients with COVID-19. *(Very low certainty of evidence; Strong recommendation)*

RECOMMENDATION

We recommend against the use of any antiseptic mouthwash to prevent COVID-19 in healthy individuals. *(Very low certainty of evidence; Strong recommendation)*

KEY FINDINGS

There were no studies that directly investigated antiseptic mouthwash for the prevention of COVID-19 in people without the infection. Seven randomized controlled trials (RCTs) on the use of antiseptic mouthwashes as adjunctive therapy in patients with COVID-19 were found.[45-51] Of these, six RCTs studied the effect of antiseptic mouthwashes on the SARS-CoV-2 viral load or cycle threshold. The studies, which used different agents, showed no clear clinical benefit. Only one RCT, which used hydrogen peroxide mouthwash, investigated symptom relief and found no significant benefit. Increased risk of thyroid dysfunction with povidone iodine mouthwash and nasal powder exposure was reported in one RCT. Another RCT reported increased risk of burning throat sensation with hydrogen peroxide mouthwash. For both adjunctive treatment and prevention of COVID-19, there was evidence for harm and no clear benefit with the use of antiseptic mouthwash.

CONSENSUS ISSUES

The panelists voted unanimously to recommend against the use of antiseptic mouthwash as an adjunctive treatment mainly due to the unclear clinical benefit based on the surrogate outcomes and the risk of harm among patients with COVID-19 from the very low certainty evidence. The evidence of harm on using mouthwash, which came from the studies used for adjunctive treatment, led the panel to also formulate a strong recommendation against its use for the prevention of COVID-19 infection in healthy individuals. They considered the probable risk of harm from long-term exposure to particular mouthwash components if used as a preventive strategy. Their strong recommendations also took into account individuals with possible or suspected thyroid problem. A panelist expressed that mouthwashes are unnecessary because people breathe in virus-containing particles that are likely to settle in their nasal passages. Furthermore, these antiseptic gargles could result in wasteful spending.

Should nasal sprays be used in the prevention and treatment of COVID-19 infection?

As of 03 December 2021

RECOMMENDATION

We suggest against the use of nasal spray as an adjunct to treatment of COVID-19 infection. *(Low certainty of evidence; Weak recommendation)*

RECOMMENDATION

There was no consensus on the use of nasal spray in addition to other preventive interventions such as vaccination, proper use of personal protective equipment, and adherence to quarantine and isolation protocols to prevent COVID-19 infection.

KEY FINDINGS

As an adjunct to prevention, two randomized controlled trials on healthy asymptomatic healthcare workers providing direct care to COVID-19 patients showed that the use of iota-carrageenan or dimethylsulfoxide ethanol nasal spray provided significant benefit in reducing the risk of COVID-19 infection compared to routine care with or without saline placebo.[52,53] The risk of adverse events and discontinuation of the intervention due to intolerance, comparing treatment and control groups, was inconclusive. Nasal sprays in these trials were used as an adjunct to proper personal protective equipment and universal precautions. Overall certainty of evidence was low.

As an adjunct to treatment, nine randomized controlled trials on patients with mild and moderate COVID-19 [54-62] showed that the use of nasal sprays containing different active agents (one study each for glycerol, hydrogen peroxide, nitric oxide, ivermectin, momethasone and triamcinolone; povidone iodine in three studies) did not result in significant benefit in terms of viral clearance and showed inconsistent benefit in terms of symptomatic relief. Furthermore, the risk for adverse events (mostly minor, such as sensation of nasal and throat burning, frequent sneezing, altered taste sensation, and minor epistaxis) was significantly higher in the nasal spray arm compared to placebo. Overall certainty of evidence was low.

CONSENSUS ISSUES

The statement suggesting against the use of nasal spray as an adjunct to treatment was unanimously approved by the panel members due to the high certainty of the risk of adverse events and the uncertain benefits from the use of glycerol- and hydrogen-peroxide-based nasal sprays. For the panel, the statement warranted a weak recommendation because (1) it is not a primary intervention and (2) despite the risk of harm, it may not necessarily result in overuse, unlike other drugs such as antibiotics.

The decision regarding the statement on the use of nasal spray as an adjunctive to other preventive interventions reached an impasse. The panel members who were inclined towards its use despite possible added costs based their arguments on the risk reduction of developing COVID-19, its availability in the local market, and its

authorization from the Philippine Food and Drug Administration as a medical device intended for short-term use. They also claimed that it could be a weak recommendation and that it would not be a replacement for any existing recommended intervention. However, other panel members who voted against its use placed a greater value on the benefit of vaccinations. A panel member also voiced opposition because the word “suggest” implied a strong recommendation for use despite the fact that only two small trials demonstrated benefit and several clinical trials are still underway. Another posited that glycerol-based sprays, which can be oily, might obstruct breathing when used with masks.

Evidence and Recommendations for the Screening and Diagnosis of COVID-19

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DISCUSSION

Outputs of the Philippine COVID-19 Living CPG Project

CLINICAL PRACTICE QUESTIONS

COVID-19 management issues and questions were collected from the Steering Committee members and Consensus Panelists during the organizational meetings and consensus panel meetings. Management trends and new issues were added to this list as they emerge or as suggested by health policymakers. The topics were reviewed and prioritized regularly. Priority topics were then assigned to the evidence reviewers for new evidence reviews or updating of existing reviews. A total of 139 priority topics were identified.

CONSENSUS MEETINGS, EVIDENCE SUMMARIES, AND RECOMMENDATIONS

For the first phase (December 2020 to May 2021) there were a total of 90 evidence summaries presented with 136 recommendations generated in 26 consensus panel meetings.

For the second phase (October to December 2021), there were a total of 70 evidence summaries presented and 139 recommendations generated during 25 consensus panel meetings. 36 evidence summaries were new reviews while 34 were updates of the Refer to Appendix D for the schedule of panel presentations.

Continued surveillance for new evidence and succeeding updates will be covered by the next phase of the living CPG.

Applicability Issues

The members of the Consensus Panels provided information on the facilitators, barriers, and resource implications for the implementation of the recommendations. They used their expertise and experience to identify these issues, which were discussed in more detail in the *Consensus Issues* section of each evidence summary. These were considered in the final wording of the recommendations. The following subsections summarize the overall discussion of the panelists.

ORGANIZATIONAL CONSIDERATIONS TO IMPLEMENTATION

The availability of testing kits and medical equipment for the screening and diagnostic tests for COVID-19 would likely vary at the regional, provincial, or even municipal/ city level. These issues were especially relevant to RT-PCR testing, rapid antibody, and antigen testing, chest imaging (X-ray, CT-Scan, and ultrasound), and laboratory parameters (LDH, CRP, Ferritin, D-dimer). Clinical risk assessment and using the 14-day symptom test were useful tools for screening for COVID-19, especially if there was a limitation in the availability of screening tests. Specially trained personnel were needed to do the more specialized tests, such as pooled testing using RT-PCR.

Aside from the availability of various testing modalities, there would be some limitations in the availability of treatment and critical care interventions also, most especially those investigational drugs only being accessible through the public via FDA's emergency use authorization. Medical specialists, especially those from infectious diseases, pulmonary medicine, and critical care medicine, were important to effectively lead in the use of these treatments for the management of COVID-19 patients. These limitations would be further compounded by the limitations in available isolation beds, hospital ward beds, and ICU beds.

For non-pharmacologic interventions and proven prophylactic interventions (such as vaccines) for COVID-19, one potentially major barrier was the public's perceptions of these interventions and their actual compliance. This was evident in many instances of violations of the minimum public health standards set by DOH: wearing of face mask and face shields, physical distancing, and hand hygiene. In addition to these, there were rising trends in the use of non-proven prophylactic interventions (such as ivermectin), ineffective medical devices (such as ionizing air filters), and the anti-COVID vaccine movement.

RESOURCE IMPLICATIONS

As a low-middle-income country, our limited resources needed to be allocated and used efficiently. The cost of the tests and interventions being done for COVID-19 management was one important consideration discussed in the panel meetings, especially the investigational drugs (such as remdesivir, tocilizumab) and the highly sophisticated interventions (such as ECMO, hyperbaric oxygen therapy). Health technology assessment should be a key gatekeeping mechanism to ensure that all payments by the government (through PhilHealth) are cost-effective.

Implementation Tools

Selected recommendations from the Philippine COVID-19 Living CPG have been used as a reference to the Unified COVID-19 Algorithms, specifically on testing and management. These algorithms were developed collaboratively by 15 professional organizations and stakeholder institutions. Their complete algorithms were published on the PSMID website (https://www.psmid.org/unified-covid-19-algorithms-5/). Healthcare providers, patients, and the public are encouraged to access these algorithms on the main webpage.

Process Evaluation

Using the native website tools and Google analytics, the PSMID website administrator was able to gather various metrics on website visits for the Philippine COVID-19 Living CPG: click trends and download trends. Since the release on March 31, 2021, there have been 246,982 total clicks on the website. Most of these visits from the initial launch were from the National Capital Region, Central Visayas (Region VII), and Davao Region (Region XI), which reflected the areas that had the greatest number of new cases and active cases during the project duration (Figure 7 and Table 6). Furthermore, the list of top evidence summaries clicks revealed the possible topics that CPG users needed the most guidance on (Table 7).

Figure 6. Geographical location of website visitors of the Philippine COVID-19 Living CPG.

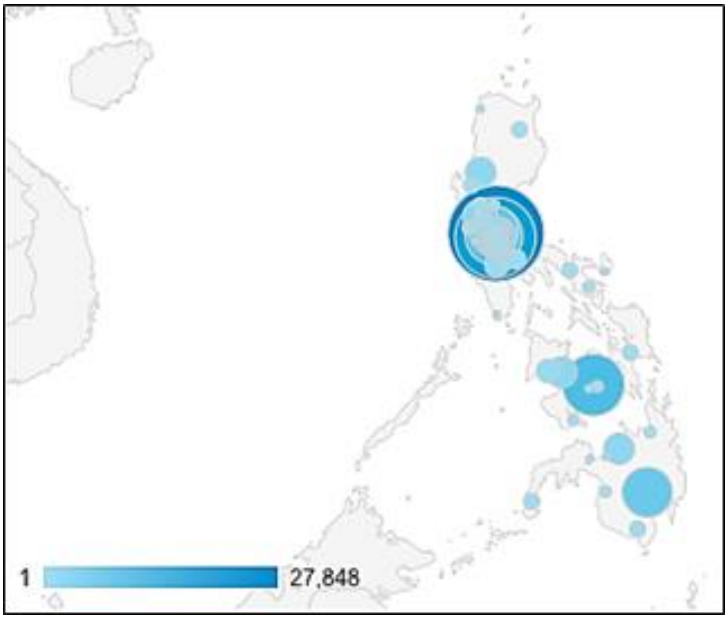

Table 6. Top locations of website visitors of the Philippine COVID-19 Living CPG. (as of June 30, 2021)

City	n	Percentage
Quezon City	27,848	18.77
Makati	20,202	13.61
Cebu City	11,112	7.49
Manila	9,706	6.54
Meycauayan	7,994	5.39
Davao City	7,249	4.89
Pasig	3,944	2.66
Paranaque	3,772	2.54
Angeles	3,376	2.28
Antipolo	3,092	2.08
Others	10,191	7.14

Table 7. Top evidence summaries downloaded from the Philippine COVID-19 Living CPG (as of August 8, 2022)

Topic	n
Ivermectin as treatment	4061
Hemoperfusion	4049
Face Shield	3090
Remdesivir	2170
Ivermectin as prophylaxis	2086
Saliva RT-PCR	1980
Lianhua	1815
Rapid Antigen Test	1321
Tocilizumab	1221
14 Day Symptom Based Test	1188

Research Implications

The novel coronavirus, now known as SARS-CoV-2, brought about a disease condition that is new to everyone. Despite the rapidly evolving evidence on COVID-19, many research gaps need to be filled in the management, prevention, and control of this disease. These were identified during the evidence reviews done in this CPG and were documented in the evidence summaries. The following discussion presents a synthesis of these research gaps.

As expected in a novel disease condition, many of the recommendations were answered with low to very low certainty of evidence. These areas are directed to a need for further primary research to be conducted.
While existing studies on the investigational treatment interventions have been able to identify the subset of patients that would benefit best, there is still a need for further studies on dosing, frequency of administration, combinations with other drugs, etc. Aside from the successful experimental drugs, additional research on those drugs showing early promise is urgently required.

Diagnosis and treatment were sometimes overemphasized in the management of COVID-19. Recommendations on vaccination were highly anticipated due to the vaccine roll out, including vaccination for the special populations (i.e. children and pregnant/lactating women) as well as booster vaccination. Equally important were the other prophylactic and non-pharmacologic interventions that are more proximal steps in the national strategy of prevention, detection, isolation, treatment, and reintegration. These studies were also crucial to prove the lack of effectiveness of several interventions that many subscribe to.

Finally, the living CPG methodology used in this project was the first local adoption known to the project team. Research into streamlining the living CPG process is important to make it more efficient. The impact measurement of this living CPG, as described in the *Monitoring and Auditing Criteria* subsection, would be another first study to formally demonstrate the effects of CPG implementation in the country.

Conclusions and Recommendations

Phase 2 of the Philippine COVID-19 Living CPG identified 70 priority questions on COVID-19 management, infection prevention, and control, generated 69 evidence summaries, and came up with 139 recommendations. Thematic areas included in this CPG were screening and diagnosis, treatment, critical care, and respiratory management, non-pharmacologic interventions, vaccines and prophylactic interventions, and adjunct interventions. The CPG recommendations were used in the construction of testing and management algorithms for COVID-19. Process evaluation using website analytics revealed that the CPG recommendations were mostly accessed in regions with the greatest number of new cases and active cases. Furthermore, a list of top evidence summaries accessed indicated topics that CPG users needed the most guidance on, or that remain to be contentious as of the present date.

The main challenges in doing a living CPG for a new disease condition in a pandemic setting were the rapidly evolving evidence and the need to come out with point in time recommendations for clinicians and policymakers. Consensus panels needed to balance the quality and totality of the evidence with the net benefit and the contextual factors related to the implementation of the interventions, i.e., cost, equity, acceptability, and feasibility. Flexibility and adaptability are key in developing a Living CPG, especially in the context of the pandemic. Given this project experience, we recommend the following for the succeeding updating of the Philippine COVID-19 Living CPG:

1. Retain consensus panel members who wish to continue contributing their time and expertise to the COVID-19 Living CPG and to ensure patient representation among all panels.
2. Continue holding capacity building workshops on CPG development, systematic reviews, and evidence-based medicine to increase the pool of skilled evidence reviewers.
3. Allow a longer project cycle for the implementation of the Living CPG development. This will ensure that adequate preparation is done by the task forces and consensus panelists prior to the en banc meeting.
4. Continue the practice of employing one technical coordinator, technical assistant and copy editor per task force to ensure the timely submission of quality evidence summaries and other deliverables.
5. Create an independent oversight committee to oversee that all task forces are complying with the accepted recommendations and a subcommittee to manage the COIs of all task force members. The review and management of conflicts of interest of all project members takes a considerable amount of time hence should be given consideration in the project timeline.
6. Involvement of stakeholders, including policy makers, especially identifying priority topics to be covered by the CPG is highly encouraged.

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APPENDICES

Appendix A. Members of the Philippine COVID-19 Living CPG Task Force

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Appendix B. Decisions of the Oversight Committee – Review of Conflict of Interest

CPG Panel on COVID – 19 Critical Care		
Jeah Alvarez Sabillo	Manageable A	Founder, President & Author/Lead Respiratory Therapy Academy for Critical Care Phils., Respiratory therapist – PHC
Pauline Convocar	Manageable A	Board member – Asian Society of Emergency, Immediate Past Pres. of PCEM
Shirley Whisenhunt	Manageable A	Chairman – CPD of PNA
Juan Javier Lichauco	Manageable A	PI for clinical trials: Infliximab, Tocolizumab, Secukinumab, Cenerimod, Evobrutinib, Speaker for Roche - Cytokine storm webinar, President – PRA, with stocks in Urology Center of the Phils.
Phorenice Francisco	Manageable A	PCP, PSAAI
Rey San Luis	Manageable A	Treasurer- PSGIM, VP – Las Pinas Medical Society, with stocks in Pope John Paul II Hosp.
Reynaldo de Castro	Manageable A	Unit Head Center for Hemoglobinopathies- UP NIH, Chairman- Thalassemia TWG, VP- Phil. Society of Pediatric Hematology, PI for Hemoglobinopathies study
Joseph Adrian Buensalido	Manageable A	Chair TWG – Sepsis CPG, Training officer & Asso. Prof. – UP-PGH, PEDER TF – MMC, Board member – PSMID, Infection Prevention & Control Chair – AHMC, author of haemophilus Influenza Infections in Medscape, stocks in New Sinai MDI Hosp & Makati Med Ctr
Rowena Marie Samares	Manageable A	TWG- Hospice Palliative DOH, Board member – Phil. Society of Hospice, VP – Phil. Acad. Of family Physicians, stocks in COL)
Jonathan Lim	Manageable A	vaccine lectures -Pfizer, Sanofi, MSD, clinical trial PI & Sub I for multinational studies, Treasurer-PPS
Albert Rafanan	Disqualified for (1) inhaled nitric oxide, (2) high flow nasal cannula, (3) hyperbaric oxygen therapy; Manageable A for the other questions	VP- Baga Inc.: med. & lab. Equipment; President- RED Medical Foundation, board member PCCP
Charito delos Santos	Manageable B	>0.1% stocks Binangonan Lakeview Hosp. & Rizal Doctors)
Maaliddin Biruar	Manageable B	Senior Medical Director – Parexel
Imelda Mateo	Manageable B	Amang Rodriguez Medical Center Chief – DOH, Expert Panel CLCPG – Diagnosis & Screening, VP- PCCP

CPG Panel on COVID – 19 Adjunctive Therapies, Non-Pharmaceutical Interventions, Infection Control		
Anthony Cortez	Manageable A	MHO- Bambang, Nueva Vizcaya
Maria Tricia Cariño	Manageable A	PI in collaboration with CDC, ongoing research on COVID serologic assessment, PI for vaccine studies, lecturer for MSD vaccines, Med Sp. III RITM)
Joan Oliveros	Manageable A	member-PAFP
Dominga Gomez	Manageable A	former DOH TWG- infection control, Faculty – DOH training of trainors for infection prevention control, Council of advisers-PHICNA & PHICS
Victoria Isla Ching	Manageable A	Adviser-PHICNA, VP & Faculty - PHIC
Elmer Bondoc	Manageable A	Governor – PNA, Trustee-PREO
Radela Yvonne Ramos-Cortes	Manageable A	Intermed Marketing for Immunomax
Roberto Razo II	Manageable A	Secretary-PSGIM
Maria Sonia Salamat	Manageable A	Co-investigator – Solidarity Trial, TWG Pneumonia CPG, lecturer for COVID-19 diagnostics & therapeutics, Med Sp. III- UP-PGH, member Board of Councils-PSMID)
Vivien Fadrilan-Camacho	Manageable A	Research on host responses in severely COVID, Asst. Prof – CPH-UP, member-HPAAC, technical consultant for 3 private companies – not related to topic
Regina Berba	Manageable A	DOH & WHO studies on COVID, Infection control lectures, Med. Sp. III- UP PGH, Chair-Pharamacovigilance Comm. of PCP, board member-PSMID, stocks in TMC
Anna Sofia Victoria Fajardo	Manageable A	Speakers bureau- PMA, PCOM, PFAP and other companies, Medical Director- PHMC Binan, National Sec.-PCOM
Camille Angelica Banzon	Manageable B	Angelicare Pharmacy owned by spouse
Gerard Belimac	Manageable B	DOH Division Chief- DPCB

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Marysia Stella Recto	Manageable B	Technical Adviser-Philippine FDA
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Julie Christie Visperas	Manageable A	Board member- Society of Physiologists
Edmyr Macabulos	Manageable A	Research on Awareness & Attitudes to improve Vaccination in Children, Adviser- Rotary Club, President- Phil. Society of HPN Central Luzon, National Pres. PCOM 2019
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Aretha Gacutan Liwag	Manageable A	grant for MRNA vaccine from Tigermed Inc., Med Sp III- West Visayas State Univ Med Center, Board-UPV
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Appendix C. General Search Strategy for COVID-19

SEARCH STRATEGY FOR COVID-19:

((("COVID-19" [Supplementary Concept] OR "COVID-19 diagnostic testing" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [Supplementary Concept] OR "COVID-19 vaccine" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR "2019-nCoV" OR "2019nCoV" OR "cov 2" OR "Covid-19" OR "sars coronavirus 2" OR "sars cov 2" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus 2" OR "COVID 19" OR "COVID-19" OR "2019 ncov" OR "2019nCoV" OR "corona virus disease 2019" OR "cov2" OR "COVID-19" OR "COVID19" OR "nCov 2019" OR "nCoV" OR "new corona virus" OR "new coronaviruses" OR "novel corona virus" OR "novel coronaviruses" OR "SARS Coronavirus 2" OR "SARS2" OR "SARS-COV-2" OR "Severe Acute Respiratory Syndrome Coronavirus 2") OR ((19[tiab] OR 2019[tiab] OR "2019-nCoV" OR "Beijing" OR "China" OR "Covid-19" OR epidem*[tiab] OR epidemic* OR epidemy OR new[tiab] OR "novel"[tiab] OR "outbreak" OR pandem* OR "SARS-CoV-2" OR "Shanghai" OR "Wuhan") AND ("Coronavirus Infections"[Mesh] OR "coronavirus"[MeSH Terms] OR coronavirus*[all] OR corona-virus*[all] OR cov[tiab] OR pneumonia-virus*[tiab]))) AND 2019/12/1:3000/12/31[PDAT])

SEARCH FILTER FOR RANDOMIZED CONTROLLED TRIALS:

(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])

SEARCH FILTER FOR SYSTEMATIC REVIEWS AND META-ANALYSES:

(((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt]

Appendix D. Breakdown of Consensus Meetings for Phase 2 of the Philippine COVID-19 Living Clinical Practice Guidelines

CONSENSUS PANEL MEETINGS	
Critical Care (3)	October 26, 2021
	December 1, 2021
	January 3, 2022
Adjunctive Therapies, Non-Pharmaceutical Interventions, Infection Control (4)	October 29, 2021
	November 5, 2021
	December 3, 2021
	December 21, 2021
Treatment (7)	October 12, 2021
	October 21, 2021
	October 28, 2021
	November 8, 2021
	November 18, 2021
	December 6, 2021
	December 20, 2021
Vaccines and Prophylaxis (6)	October 21, 2021
	October 22, 2021
	October 28, 2021
	November 4, 2021
	December 2, 2021
	December 27, 2021
Screening and Diagnosis (5)	November 11, 2021
	November 22, 2021
	November 29, 2021
	December 13, 2021
	December 17, 2021

Appendix E. AGREE Reporting Checklist

This checklist is intended to guide the reporting of clinical practice guidelines.

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
DOMAIN 1: SCOPE AND PURPOSE		
1. OBJECTIVES *Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.*	☒ Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) ☐ Expected benefit(s) or outcome(s) ☒ Target(s) (e.g., patient population, society)	1
2. QUESTIONS *Report the health question(s) covered by the guideline, particularly for the key recommendations.*	☒ Target population ☒ Intervention(s) or exposure(s) ☒ Comparisons (if appropriate) ☒ Outcome(s) ☒ Health care setting or context	See relevant sections
3. POPULATION *Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.*	☒ Target population, sex and age ☒ Clinical condition (if relevant) ☒ Severity/stage of disease (if relevant) ☒ Comorbidities (if relevant) ☐ Excluded populations (if relevant)	1-2
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
4. GROUP MEMBERSHIP *Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and individuals involved in formulating the final recommendations.*	☒ Name of participant ☐ Discipline/content expertise (e.g., neurosurgeon, methodologist) ☒ Institution (e.g., St. Peter's hospital) ☐ Geographical location (e.g., Seattle, WA) ☒ A description of the member's role in the guideline development group	227-238
5. TARGET POPULATION PREFERENCES AND VIEWS *Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.*	☒ Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) ☒ Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) ☐ Outcomes/information gathered on patient/public information ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	11
6. TARGET USERS *Report the target (or intended) users of the guideline.*	☒ The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) ☒ How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	2
DOMAIN 3: RIGOUR OF DEVELOPMENT		

7. SEARCH METHODS *Report details of the strategy used to search for evidence.*	☒ Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) ☒ Time periods searched (e.g., January 1, 2004 to March 31, 2008) ☒ Search terms used (e.g., text words, indexing terms, subheadings) ☒ Full search strategy included (e.g., possibly located in appendix)	8, 287
8. EVIDENCE SELECTION CRITERIA *Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.*	☒ Target population (patient, public, etc.) characteristics ☒ Study design ☒ Comparisons (if relevant) ☒ Outcomes ☒ Language (if relevant) ☐ Context (if relevant)	8
9. STRENGTHS & LIMITATIONS OF THE EVIDENCE *Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.*	☒ Study design(s) included in body of evidence ☒ Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) ☒ Appropriateness/relevance of primary and secondary outcomes considered ☒ Consistency of results across studies ☒ Direction of results across studies ☒ Magnitude of benefit versus magnitude of harm ☒ Applicability to practice context	8
10. FORMULATION OF RECOMMENDATIONS *Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.*	☒ Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) ☒ Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) ☒ How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)	9-15
11. CONSIDERATION OF BENEFITS AND HARMS *Report the health benefits, side effects, and risks that were considered when formulating the recommendations.*	☒ Supporting data and report of benefits ☒ Supporting data and report of harms/side effects/risks ☒ Reporting of the balance/trade-off between benefits and harms/side effects/risks ☒ Recommendations reflect considerations of both benefits and harms/side effects/risks	9

12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE *Describe the explicit link between the recommendations and the evidence on which they are based.*	☒ How the guideline development group linked and used the evidence to inform recommendations ☒ Link between each recommendation and key evidence (text description and/or reference list) ☒ Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	See relevant sections
13. EXTERNAL REVIEW *Report the methodology used to conduct the external review.*	☒ Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) ☒ Methods taken to undertake the external review (e.g., rating scale, open-ended questions) ☒ Description of the external reviewers (e.g., number, type of reviewers, affiliations) ☒ Outcomes/information gathered from the external review (e.g., summary of key findings) ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)	16
14. UPDATING PROCEDURE *Describe the procedure for updating the guideline.*	☒ A statement that the guideline will be updated ☒ Explicit time interval or explicit criteria to guide decisions about when an update will occur ☒ Methodology for the updating procedure	17
DOMAIN 4: CLARITY OF PRESENTATION		
15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS *Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.*	☒ A statement of the recommended action ☒ Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) ☒ Relevant population (e.g., patients, public) ☒ Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) ☒ If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	See relevant sections
16. MANAGEMENT OPTIONS *Describe the different options for managing the condition or health issue.*	☒ Description of management options ☒ Population or clinical situation most appropriate to each option	See relevant sections

17. IDENTIFIABLE KEY RECOMMENDATIONS *Present the key recommendations so that they are easy to identify.*	☒ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms ☒ Specific recommendations grouped together in one section	See relevant sections and Executive Summary (ix)
DOMAIN 5: APPLICABILITY		
18. FACILITATORS AND BARRIERS TO APPLICATION *Describe the facilitators and barriers to the guideline's application.*	☒ Types of facilitators and barriers that were considered ☒ Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) ☒ Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) ☒ How the information influenced the guideline development process and/or formation of the recommendations	225
19. IMPLEMENTATION ADVICE/TOOLS *Provide advice and/or tools on how the recommendations can be applied in practice.*	☒ Additional materials to support the implementation of the guideline in practice. For example: ○ Guideline summary documents ○ Links to check lists, algorithms ○ Links to how-to manuals ○ Solutions linked to barrier analysis (see Item 18) ○ Tools to capitalize on guideline facilitators (see Item 18) ○ Outcome of pilot test and lessons learned	222-223
20. RESOURCE IMPLICATIONS *Describe any potential resource implications of applying the recommendations.*	☒ Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) ☒ Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) ☒ Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course)	223 and other relevant sections

	☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	
21. MONITORING/ AUDITING CRITERIA *Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.*	☒ Criteria to assess guideline implementation or adherence to recommendations ☒ Criteria for assessing impact of implementing the recommendations ☒ Advice on the frequency and interval of measurement ☒ Operational definitions of how the criteria should be measured	16, 260
DOMAIN 6: EDITORIAL INDEPENDENCE		
22. FUNDING BODY *Report the funding body's influence on the content of the guideline.*	☒ The name of the funding body or source of funding (or explicit statement of no funding) ☒ A statement that the funding body did not influence the content of the guideline	17
23. COMPETING INTERESTS *Provide an explicit statement that all group members have declared whether they have any competing interests.*	☒ Types of competing interests considered ☒ Methods by which potential competing interests were sought ☒ A description of the competing interests ☒ How the competing interests influenced the guideline process and development of recommendations	17-18, 239

From: Brouwers MC, Kerkvliet K, Spithoff K, on behalf of the AGREE Next Steps Consortium. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. *BMJ* 2016;352:i1152. doi: 10.1136/bmj.i1152.

For more information about the AGREE Reporting Checklist, please visit the AGREE Enterprise website at http://www.agreetrust.org.


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DEPARTMENT OF HEALTH