PHILIPPINE COVID-19 LIVING CLINICAL PRACTICE GUIDELINES

As of 27 June 2023

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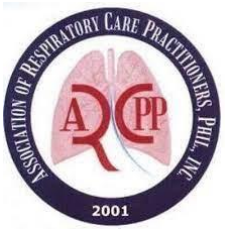
This project was implemented under the Institute of Clinical Epidemiology, National Institutes of Health (NIH), University of the Philippines Manila (UPM). It was completed with the valuable contribution of 190 people representing the different stakeholders

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 760 million confirmed COVID-19 cases have been reported globally, with 4.1 million of these cases from the Philippines as of July 2023. 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. The Philippine COVID-19 Living CPG aimed to provide up-to-date, evidence-based recommendations on the management of COVID-19 among adults and children 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.

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 from 2020 to early 2021 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). The third phase of the project was conducted from December 2022 to May 2023 and a total of 43 evidence summaries were generated. The third phase also updated and consolidated the recommendations from the Pediatric COVID-19 LCPG.

This version contains the new and updated recommendations for Phase 3 of the COVID-19 LCPG.

The Diagnosis, Screening and Preventive Interventions Task Force provided three new evidence summaries on masking, ventilation and the use of tixagevimab-cilgavimab as prophylaxis and updated nine evidence summaries with previously convened recommendations from Phase 1 and 2 of the COVID-19 LCPG.

The Treatment and Critical Care Task Force provided four new treatment evidence summaries on Nirmatrelvir-Ritonatir (Paxlovid), Tixagevimab-Cilgavimab, Sotrovimab and Metformin and two new critical care evidence summaries on pulmonary rehabilitation for long COVID and on the management of MIS-C in children. Seventeen evidence summaries with previously convened recommendations from Phase 1 and 2 of the COVID-19 LCPG were updated.

The Vaccines Task Force provided six new evidence summaries on booster doses for the pediatric population as well as recommendations on the use of the bivalent vaccines as a second booster for the general population. The task force also updated two evidence summaries with previously convened recommendations from Phase 2 of the COVID-19 LCPG.

The CPG recommendations were used in constructing management algorithms for COVID-19. Process evaluation using website analytics also revealed the average number of site visits in the last year.

The summary of the recommendations for Phase 3 are listed below:

SUMMARY OF RECOMMENDATIONS

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 Diagnosis, Screening and Preventive Interventions

Recommendations	Certainty of Evidence	Strength of Recommendation
We recommend the use of a 7-day symptom-based* test, instead of 14 days, to assess for possible COVID-19 infection among adults and children.** * Symptoms listed in the WHO Case Definition: acute onset of fever AND cough (ILI) OR acute onset of ANY THREE OR MORE of the following signs or symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, nausea/diarrhea/anorexia ***Please refer to previous recommendation on testing using RTPCR and RAT*	Very low	Strong
Among adults and children suspected to have COVID-19 who are symptomatic, we suggest the use of RAT for the diagnosis of COVID-19 as an alternative to RT-PCR.	Very low	Weak
Among adults and children exposed to COVID-19 who are asymptomatic, we suggest against the use of RAT for the diagnosis of COVID-19	Very low	Weak
We recommend the use of self-administered rapid antigen test for the diagnosis of SARS-CoV-2 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 (Studies that challenge the robustness of a diagnostic kit under various conditions of stress); AND 4. Individuals present with symptoms for less than 7 days.	Moderate	Strong
We recommend against the use of self-administered rapid antigen test for asymptomatic individuals.	Moderate	Strong
There is insufficient evidence to recommend the use of breath test in detecting COVID-19 Infection.	Low	-
There is no evidence to recommend for or against antibody testing to diagnose COVID-19 disease among vaccinated patients.	None	None
We suggest against the routine measurement of SARS-CoV-2 antibody titers after vaccination. In the rare situations where we need to determine prior COVID-19	Very low	Weak

disease or infection, we suggest the use of nucleocapsid antibody testing among vaccinated individuals, along with infectious disease specialist consultation.		
Among asymptomatic individuals scheduled for non-emergent/non-urgent surgery, we suggest using clinical risk assessment alone to screen for COVID-19. Among asymptomatic individuals scheduled for non-emergent/non-urgent surgery who have been diagnosed to have COVID-19 within the last 90 days, we suggest against the use of SARS-CoV-2 RT-PCR.	Very low Very low	Weak Weak
For **asymptomatic fully vaccinated adults**, or **symptomatic fully vaccinated adults with mild COVID-19**, we suggest the use of the criterion for ending isolation: ● At least 5 days have passed since the first positive COVID-19 RT-PCR test	Low	Weak
For **asymptomatic not fully vaccinated adults**, or **symptomatic not fully vaccinated adults with mild COVID-19**, we suggest the use of the criterion for ending isolation: ● At least 7 days have passed since the first positive COVID-19 RT-PCR test	Low	Weak
For **symptomatic adults with moderate COVID-19** diagnosis and **any vaccination status**, we suggest the use of the following symptom-based criteria for ending isolation: ● At least 10 days have passed since the onset of symptoms AND ● No fever during the previous 72 hours without the use of antipyretic medications AND ● There has been substantial improvement in respiratory or other symptoms of the acute illness, as applicable.	Low	Weak
For **symptomatic fully vaccinated adults with severe-to-critical COVID-19** , we suggest the use of the following symptom-based criteria for ending isolation: ● At least 20 days have passed since the onset of symptoms AND ● No fever during the previous 72 hours AND without the use of antipyretic medications AND ● There has been substantial improvement in respiratory or other symptoms of the acute illness, as applicable.	Low	Weak
For **symptomatic not fully vaccinated adults with severe-to-critical COVID-19**, we suggest the use of the following symptom-based criteria for ending isolation:	Low	Weak

● Minimum of 20 days have passed since the onset of symptoms AND ● No fever during the previous 72 hours without the use of antipyretic medications AND ● There has been substantial improvement in respiratory or other symptoms of the acute illness AND ● With multi-disciplinary consultation among relevant subspecialists		
In the community setting, we recommend the use of a face mask for preventing COVID-19 in crowded, enclosed, and poorly ventilated spaces	Low	Strong
We recommend the use of natural ventilation* in indoor spaces to prevent COVID-19 transmission, if possible and safe to do so. * *Includes opening doors and windows and electric fans*	-	Good practice statement
We recommend the use of mechanical ventilation systems with appropriate filtration systems** in indoor spaces to prevent COVID-19 transmission if *natural ventilation is not feasible or adequate*. ** *Includes HVAC systems and portable air cleaners*	Very low	Strong
We suggest the use of carbon dioxide (CO2) monitors in enclosed spaces to guide actions to improve ventilation and reduce the risk of transmission of SARS-CoV-2.	Low	Weak
We suggest against the use of casirivimab-imdevimab as post-exposure prophylaxis against COVID-19.	Low	Weak
Pre-exposure Prophylaxis We suggest against the use of AZD7442 (tixagevimab-cilgavimab) as pre-exposure prophylaxis against COVID-19.	Very low	Weak
Post-exposure Prophylaxis We suggest against the use of AZD7442 (tixagevimab-cilgavimab) as post-exposure prophylaxis against COVID-19.	Very low	Weak

Summary of Recommendations on Treatment

Recommendations	Certainty of Evidence	Strength of Recommendation
We recommend against the use of favipiravir among patients with COVID-19.	Moderate	Strong
We suggest the use of remdesivir among hospitalized adult patients with mild to moderate COVID-19 infection with at least 1 risk factor* for progression to severe disease. **60 years old or older, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity (a body-mass index [BMI; the weight in kilograms divided by the square of the height in meters] of ≥30), immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer, or sickle cell disease*	Low	Weak
We recommend the use of remdesivir among non-hospitalized adult patients with mild to moderate COVID-19 infection with at least 1 risk factor* for progression to severe disease. **60 years old or older, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity (a body-mass index [BMI; the weight in kilograms divided by the square of the height in meters] of ≥30), immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer, or sickle cell disease.*	Moderate	Strong
We suggest the use of remdesivir in children (hospitalized or ambulatory) with mild to moderate COVID-19 infection with at least 1 risk factor for disease progression.	Very low	Weak
We suggest the addition of remdesivir to dexamethasone in adult patients with COVID-19 infection requiring oxygen supplementation but do not require mechanical ventilation*. **For patients who progress to invasive mechanical ventilation while on remdesivir, the drug can be continued.*	Low	Weak
We suggest the addition of remdesivir to dexamethasone in children with COVID-19 infection requiring oxygen supplementation but do not require mechanical ventilation.	Very low	Weak

We suggest against the use of remdesivir among adult patients with COVID-19 infection who are already on non-invasive or invasive mechanical ventilation.	Low	Weak
We suggest against the use of remdesivir among children with COVID-19 infection who are already on non-invasive or invasive mechanical ventilation.	Very low	Weak
We suggest the use of molnupiravir within 5 days of symptom onset in adult patients with COVID-19 infection who are non-oxygen requiring and with at least one risk factor* for progression. **Risk factors for progression include:* *age >60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, serious heart conditions, or diabetes mellitus*	Very low	Weak
We suggest against the use of molnupiravir among children with COVID-19.	Very low	Weak
We recommend the use of nirmatrelvir+ritonavir within 5 days of symptom onset among unvaccinated symptomatic adult patients with high risk* for progression to severe disease. *Risk factors include any of the following: ≥60 years of age; BMI >25kg/m^2; cigarette smoking; immunosuppressive disease (including HIV infection with CD4 cell count <200mm^3 and viral load <400 copies/mL) or prolonged iatrogenic immunosuppression; chronic lung, cardiovascular, kidney, or sickle cell disease; hypertension; diabetes; cancer; neurodevelopmental disorders or other medically complex conditions; or medical-related technological dependence	Moderate	Strong
We suggest the use of nirmatrelvir+ritonavir among unvaccinated, symptomatic pediatric patients 12 years of age and older weighing at least 40kg with high risk for progression to severe disease.	Low	Weak
We recommend the use of baricitinib in addition to corticosteroids among critical COVID-19 patients on high-flow nasal cannula oxygenation, noninvasive ventilation, or invasive mechanical ventilation.	Moderate	Strong
We suggest against the use of baricitinib among pediatric patients with COVID-19.	Very low	Weak

We suggest against use of tofacitinib among adult patients with COVID-19.	Low	Weak
We suggest against use of tofacitinib among children with COVID-19.	Very low	Weak
We recommend against the use of ivermectin in the treatment of children and adults with COVID-19 regardless disease severity.	Very low	Strong
We recommend against the use of colchicine in the treatment of COVID-19 patients.	Very low	Strong
We suggest against the use of fluvoxamine among adult patients with COVID-19 infection.	Very low	Weak
We suggest against the use of fluvoxamine among children and adolescent patients with mild to moderate COVID-19 infection.	Very low	Weak
We suggest against the use of bamlanivimab and etesevimab combination therapy as treatment COVID-19 patients.	Low	Weak
We suggest the use of casirivimab-imdevimab as an alternative to anitivirals* among symptomatic, non-hospitalized COVID-19 adult patients with risk factor for severe disease,** only when the predominant circulating variant is not Omicron SARS-CoV-2. **When other drugs (i.e. molnupiravir and paxlovid [nirmatrelvir-ritonavir]) are contraindicated* ***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.*	Very low	Weak
We recommend against the use of casirivimab-imdevimab as treatment for hospitalized COVID-19 patients.	Very low	Strong
We recommend against the use of casirivimab-imdevimab as treatment for asymptomatic, non-hospitalized patients.	Very low	Strong
We recommend against the use of casirivimab-imdevimab in children with COVID-19.	Very low	Strong
We suggest the use of tixagevimab-cilgavimab as treatment for unvaccinated non-hospitalized patients with mild to	Very low	Weak

moderate COVID-19 with at least 1 risk factor* for progression to severe disease. **Risk factors for severe COVID-19: age ≥65 years, body-mass index ≥35kg/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*		
We suggest the use of tixagevimab-cilgavimab as treatment for unvaccinated hospitalized COVID-19 patients in addition to standard of care.	Low	Weak
We suggest against the use of tixagevimab-cilgavimab among children with COVID-19.	Very low	Weak
We suggest against the use of sotrovimab among children and adult patients with COVID-19.	Very low	Weak
We suggest the use of Lianhua in the symptomatic relief of adult patients with non-severe COVID-19.	Very low	Weak
We suggest against the use of Lianhua in children with COVID-19.	Very low	Weak
We suggest against the use of metformin as treatment for COVID-19.	Low	Weak

Summary of Recommendations on Critical Care

Recommendations	Certainty of Evidence	Strength of Recommendation
We recommend the use of dexamethasone for up to 10 days among adult patients with severe and critical COVID-19.	Moderate	Strong
We suggest the use of methylprednisolone 1-2mg/kg/day for 5 to 10 days as an alternative to dexamethasone among adult patients with severe and critical COVID-19.	Very low	Weak
We suggest the use of dexamethasone at 0.15mg/kg/day or a maximum dose of 6mg per day for up to 10 days among pediatric patients with severe and critical COVID-19.	Very low	Weak
We recommend the use of standard-dose dexamethasone at 6mg to 12mg per day among adult patients with severe and critical COVID-19.	Moderate	Strong
We recommend against the use of corticosteroids among mild and moderate (non-oxygen requiring) COVID-19 patients.	Moderate	Strong
We suggest that steroid therapy be initiated as soon as diagnosed or categorized as severe and critical COVID-19.	Very low	Weak
We suggest the use of prophylactic over therapeutic dose anticoagulation among hospitalized adults with moderate, severe or critical COVID-19 disease unless there are any contraindications.	Low	Weak
We suggest the use of standard dose prophylactic anticoagulation over intermediate dose prophylactic anticoagulation among hospitalized adults with moderate, severe, or critical COVID-19 disease unless there are any contraindications.	Low	Weak
We suggest against the routine use of any anticoagulation among adults with mild COVID-	Low	Weak

19 in the outpatient setting unless there is a pre-existing non-COVID indication.		
We suggest the use of oral anticoagulation after hospital discharge among adults admitted for moderate, severe, or critical COVID-19 and who are suspected to have a high risk for VTE at-or-near hospital discharge.	Low	Weak
We suggest the use of prophylactic dose anticoagulation among hospitalized pregnant patients with moderate, severe, or critical COVID-19 disease unless there are any contraindications.	Very low	Weak
We suggest prophylactic dose anticoagulation among hospitalized pediatric patients more than 12 years of age with moderate, severe, or critical COVID-19 or MIS-C unless there are any contraindications.	Very low	Weak
We suggest awake prone positioning or self-proning in non-intubated adult patients with severe and critical COVID-19.	Very low	Weak
We suggest prone positioning among intubated adult patients with critical COVID-19 in ARDS.	Very low	Weak
We suggest the use of side lying in non-intubated adult patients with severe and critical COVID-19 who cannot tolerate proning.	Very low	Weak
We suggest the use of high flow nasal oxygen therapy for patients with severe to critical COVID-19 who do not respond to conventional oxygen therapy (low flow nasal cannula/face mask).	Low	Weak
We suggest the use of either high flow nasal oxygenation therapy or non-invasive positive pressure ventilation in patients with severe to critical COVID-19 who do not respond to conventional oxygen therapy in the absence of any indication for emergent invasive mechanical ventilation.	Very low	Weak
We suggest the use of high flow nasal oxygen therapy for children with severe to critical COVID-19 who do not respond to conventional	Very low	Weak

oxygen therapy (low flow nasal cannula/face mask).		
We recommend the use of a lung protective ventilation strategy (tidal volume 4-6mL/kg ideal body weight, plateau pressure less than 30cmH_2O, and an appropriate PEEP) among mechanically ventilated adult patients with COVID-19-associated ARDS.	Very low	Strong
We suggest against the routine use of high PEEP strategy among mechanically ventilated adult patients with COVID-19-associated ARDS. We further suggest to individualize PEEP or employ a PEEP strategy based on respiratory mechanics (i.e., compliance) in patients with COVID-19 infection.	Very low	Weak
We suggest to maintain the driving pressure less than 15cmH_2O among mechanically ventilated adult patients with COVID-19-associated ARDS.	Very low	Weak
We suggest to offer the use of extracorporeal membrane oxygenation for judiciously selected adult COVID-19 patients with acute respiratory distress syndrome refractory to optimal mechanical ventilation based on the ELSO or NHS England criteria. **after careful consideration of cost, resources, expertise available*	Very low	Weak
We suggest to offer the use of extracorporeal membrane oxygenation for judiciously selected pediatric COVID-19 patients with acute respiratory distress syndrome refractory to optimal mechanical ventilation based on the ELSO criteria. **after careful consideration of cost, resources, expertise available*	Very low	Weak
We suggest individualized pulmonary rehabilitation with pre-intervention medical clearance for patients with long COVID syndrome who show residual pulmonary symptoms to improve pulmonary function and quality of life.	Very low	Weak

We suggest the use of steroids (methylprednisolone) among children diagnosed with multisystem inflammatory syndrome in children.	Very low	Weak
We suggest to offer the use of IVIg in combination with steroids among children diagnosed with multisystem inflammatory syndrome associated with significant organ involvement*. *Based on six cohort studies, patients with MIS-C who received combination of steroids and IVIg had more severe initial presentation, with more frequent initial acute left ventricular dysfunction, ICU care upon admission, and requirement of hemodynamic support upon admission; higher troponin levels, and higher need for inotropes upon admission; high proportion of patients with abnormal inflammatory mediators on admission; lower mean ejection fraction at baseline, lower platelet counts, and higher CRP and ferritin; significantly more extensive organ involvement (higher frequency of respiratory, ocular and cardiovascular involvement); and higher cases of severe MIS-C, lower platelet and lymphocyte count, and higher CRP.	Very low	Weak

Summary of Recommendations on Vaccines

Recommendations	Certainty of Evidence	Strength of Recommendation
Among the **immunocompromised**, we suggest the use of the following COVID-19 vaccines as **homologous booster** at least two months after the primary series. a. monovalent BNT162b2 (Pfizer-BioNTech) b. monovalent mRNA-1273 (Moderna)	Very low Low	Weak
Among the **elderly**, we suggest the use of the following COVID-19 vaccines as homologous booster at least two months after the primary series: a. monovalent BNT162b2 (Pfizer-BioNTech) b. AdCOV2.S (Janssen)/ AdCOV2.S (Janssen)	Very low	Weak
Among **immunocompromised population** we suggest the following heterologous booster vaccination regimen: a. mRNA-based / mRNA-based b. mRNA-based / ChAdOx1 **(AstraZeneca) booster** c. BNT162b2 (Pfizer-BioNTech) / **monovalent mRNA-1273 (Moderna) booster** d. mRNA-based / Ad26.CoV2.S (**J&J) booster** e. AstraZeneca first dose, CoronaVac second dose / **monovalent Moderna or Pfizer booster** f. **AstraZeneca / monovalent Moderna or Pfizer booster** g. CoronaVac / **monovalent Pfizer booster** Among the **immunocompromised population, there is insufficient evidence to recommend** the following heterologous booster vaccination regimen due to insufficient evidence: a. Janssen / **monovalent Moderna or Pfizer booster** b. CoronaVac primary **/ monovalent *Moderna***	Very low	Weak
Among the **elderly population**, we suggest the		

following heterologous COVID-19 booster vaccination regimen: a. ChAdOX (AstraZeneca) Primary / **mRNA-based** b. BNT162b2 (Pfizer BioNTech) or mRNA1273 (Moderna) or ChAdOx1Oxford-AstraZeneca or Ad26CoV2 (J&J) / **mRNA-based** c. mRNA-based vaccine / **mRNA-based booster** d. CoronaVac Primary / **monovalent BNT162b2 (Pfizer-BioNTech)** e. CoronaVac Primary / **ChAdOX (AstraZeneca)**	Very low Low Very low Very low Very low	Weak
We suggest the preferential use of the following bivalent vaccines over monovalent mRNA vaccines as 2nd homologous booster among the general population: a. BNT162b2 Bivalent (Pfizer-BioNTech) b. mRNA-1273.214 (Moderna)	Very low	Weak
We suggest the administration of the following second heterologous booster vaccination in the general population: a. BNT162b2 (Pfizer monovalent) b. mRNA-1273 (Moderna monovalent) c. ChAdOx1 (AstraZeneca)	Very low	Weak
There is no recommendation on the use of the following vaccines as a second homologous booster vaccination in the general population due to insufficient evidence: a. CoronaVac (Sinovac) b. NVX-CoV2373 (Novavax)	Very Low Low	None
We recommend the use of the homologous monovalent BNT162b2 (Pfizer-BioNTech) as second booster dose to prevent symptomatic COVID-19 infection in healthcare workers.	Very low	Strong
We recommend the use of the heterologous mRNA-1273 (Moderna) as a second booster dose to prevent COVID-19 infection in healthcare workers.	Very low	Strong
No recommendation can be made on the use of a third booster dose of COVID-19 vaccine (to complete 5 vaccine doses) for the high-risk population because there is no available evidence.	No Evidence	None
Among adult individuals with previous COVID-19 infection who received standard doses of COVID-	Very low	Weak

19 vaccine primary series, we suggest the use of a homologous first booster dose of monovalent mRNA vaccines.		
Among adult individuals with previous COVID-19 infection who received standard doses of COVID-19 primary vaccine series, there is no recommendation for the use of a heterologous first booster dose of monovalent mRNA vaccines due to insufficient evidence.	Very low	None
We suggest the use of the BNT162b2 (Pfizer-BioNTech) vaccine, [given as 0.3mL (30ug) intramuscular injections, in 2 doses, 21 days apart] for healthy children 12 to 17 years old to prevent symptomatic SARS-CoV-2 infection.	Low	Weak
We suggest the use of the mRNA-1273 (Moderna) vaccine, [given as 0.5mL (100ug) intramuscular injections, in 2 doses, 28 days apart] for children 12 to 17 years old to prevent symptomatic SARS-CoV-2 infection.	Low	Weak
There is insufficient evidence to recommend the use of the following for children 12 to 17 years old to prevent symptomatic SARS-CoV-2 infection: a. ChAdOx1 (AstraZeneca b. CoronaVac (Sinovac) c. BBIBP-CorV (Sinopharm-Beijing) d. Recombinant Adenovirus	 Very low Low Low Low	None
There is insufficient evidence to recommend BNT162b2 in immunocompromised children 12 to 17 years to prevent symptomatic SARS-CoV-2 infection.	Very low	None
We suggest the use of monovalent mRNA-1273 (Moderna) vaccine in children 6 months to 4 years to prevent SARS-CoV-2 infection.	Very low	Weak
We suggest the use of CoronaVac (Sinovac) vaccine in children 3 to 5 years to prevent SARS-CoV-2 infection.	Very low	Weak
There is no recommendation on the use of the following vaccines in children 6 months to 2 years to prevent SARS-CoV-2 infection due to lack of evidence. a. CoronaVac (Sinovac) b. BBIBP-CorV (Sinopharm-Beijing) c. WIBP-CorV (Sinopharm-Wuhan)	No Evidence	None
There is no recommendation on the use of the following vaccines in children 3 to 5 years to	Low	None

prevent SARS-CoV-2 infection due to insufficient evidence. a. BBIBP-CorV (Sinopharm-Beijing) b. WIBP-CorV (Sinopharm-Wuhan)		
There is no recommendation on the use of BNT162b2 (Pfizer-BioNTech) in children 6 months to 4 years to prevent SARS-CoV-2 infection due to insufficient evidence.	Very low	None
We suggest the use of monovalent BNT1262b2 mRNA (Pfizer-BioNTech) vaccine as booster in healthy children 12 to 17 years old who received standard full doses of primary series to prevent SARS-CoV-2 infection* *After optimal coverage in the high-risk priority groups have been achieved.	Very low	Weak
There is no recommendation being made this time on booster administration in healthy children 5 to 11 years old who received standard full doses of primary series to prevent SARS-CoV-2 infection due to lack of evidence.	None	None

INTRODUCTION

The coronavirus disease 2019 (COVID-19) has grown into a pandemic and global crisis infecting more than 767 million people worldwide and causing more than six million deaths since the first reported case in December 2019 [1]. As of July 6, 2023, the number of cases in the Philippines has reached more than 4.1 million with 66,574 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 has more than 78 million fully vaccinated individuals with more than 23 million receiving at least 1 booster dose as of March 2023. The rise of variants with increased transmissibility posed challenges in epidemiologic projections throughout the pandemic which included evolution of vaccine protection and reduced effectivity of pharmacological and non-pharmacological strategies.

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 policymakers, there was a need for evidence-based guidelines for the effective management and control of the spread of this disease. Existing international guidelines and living systematic reviews on COVID-19 were 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 and children 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 to Filipinos of all age groups 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 specific phases of the CPG development process are as follows:

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 task forces of the Philippine COVID-19 Living CPG.

   The SC, together with the TWG and other key stakeholders, finalized the health questions to be addressed in the CPG. The SC selected the members of the Consensus Panel based on their knowledge and experience, and potential conflicts of interest in consultation with the heads of the professional medical societies and stakeholder organizations. The Consensus Panel is composed of multi-sectoral representatives such as practitioners, both specialists and non-specialists, and patient advocates. The panel members were selected from the designated representatives of the relevant specialty groups. Some stakeholders, such as nurses, acted as patient advocates to reflect patients' and public's views and preferences.

   Several orientation sessions were conducted for the technical reviewers and consensus panel members on the COVID Living 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 generate 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. They are composed of members with one or more of the following experts: methodologists, clinical epidemiologists, evidence-based practitioners, etc. They have attended previous training on CPG development and evidence synthesis, or have previous experience on CPG development.

For each health question, a systematic literature search was done. All eligible studies were critically appraised independently by the assigned reviewers. Evidence tables and evidence summaries were generated by the TWG using the GRADE approach. Draft recommendations were formulated based on the certainty of the evidence. All these steps were done by at least two independent reviewers.

During this stage of development, four 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 Consensus Panel were conducted wherein the evidence summaries and draft recommendations were presented for discussion and consensus voting. Prior to each meeting, panelists were requested to respond to a survey form to complete the Evidence to Decision framework wherein apart from looking at the benefit and harm of the interventions, factors such as resource implication, feasibility, and acceptability are also considered. The Consensus Panel ranked the 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. In 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. Grading of the strength of recommendations are based on the overall certainty of the evidence, trade-offs between benefits and harms, values and preferences of patients, resource implications and impact on equity. A skilled facilitator moderated the discussions during this meeting.

   Each member voted on the draft recommendation as follows: yes, no or abstain. 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 is reached. Any issues left unsettled after the en banc meeting were finalized through a modified Delphi activity.

4. **Living CPG Process** – From the standard guideline development process above, several recommendations were prioritized to a *living status* according to the following: priority for decision making, reasonable chance that new evidence changes the existing recommendation, and likelihood of new research evidence [8]. Members of the EREs working on living recommendations (1) performed continual surveillance of literature to update the living systematic review with new evidence and (2) updated the Evidence Summary tables and draft recommendations for panel discussion. The Steering Committee reviews the updated evidence summary and determines if the update will be presented to the Consensus Panel again. If so, the Consensus Panel is convened in an online meeting to discuss the new evidence and any changes in the living recommendation. The Living CPG Development Process is summarized in the figure below:

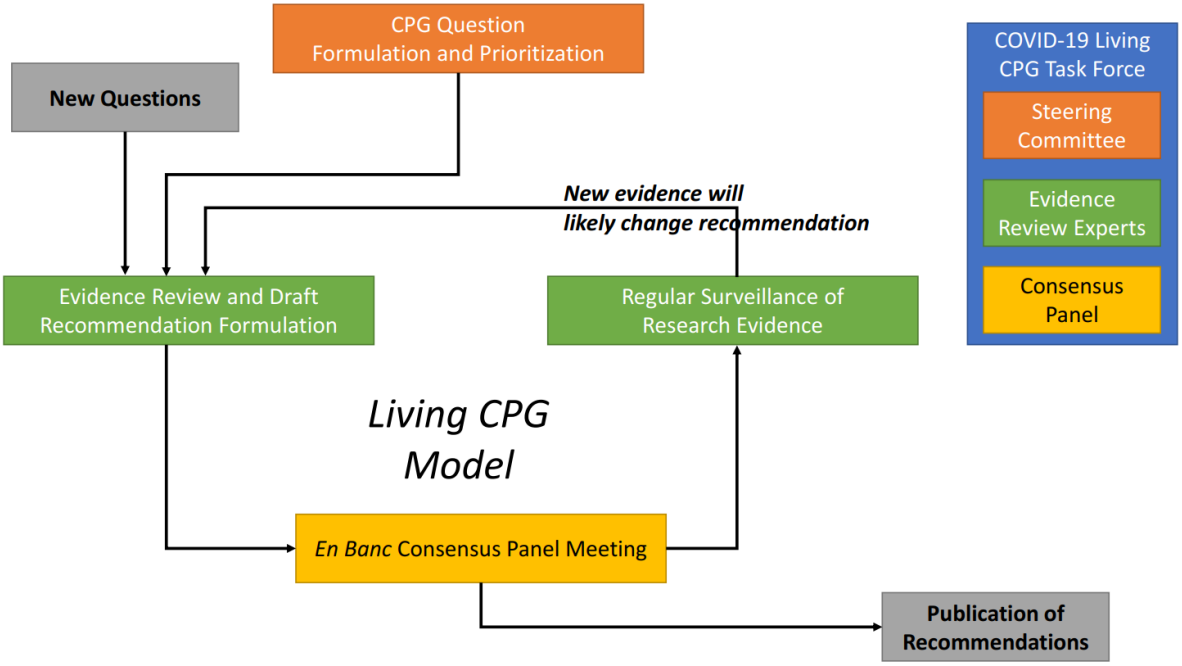


Figure 1. Philippine COVID-19 Living CPG Development Process.

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

Phase 3 of the Philippine COVID-19 Living CPG merged the six central themes in the previous phases of the COVID-19 LCPG and created three task forces that were led by 2-3 task force heads. The three task forces are the following:

1. Screening, Diagnosis and Preventive Interventions
2. Treatment, Critical Care and Adjunctive Therapy
3. Vaccines

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 Phase 3

Diagnosis, Screening and Preventive Interventions	• Return from Isolation • 14 Day Symptom Check • Self Administered Rapid Antigen Tests • Breath Tests • Clinical Risk Assessment for Surgery • Rapid Antigen Tests • Antibody Testing for Seroprevalence • Masking • Ventilation • Casirivimab-imdevimab prophylaxis • Tixagevimab-cilgavimab prophylaxis • Carbon Dioxide monitors
Treatment	• Sotrovimab • Nirmatrelvir-Ritonavir • Tixagevimab-cilgavimab • Remdesivir • Molnupiravir • Bamlanivimab • Casirivimab-imdevimab • Baricitinib • Tofacitinib • Favipiravir • Ivermectin • Fluvoxamine • Lianhua • Colchicine • Metformin
Critical Care	• Systemic Corticosteroids • Anti-coagulation • High flow nasal cannula • Mechanical Ventilation • Pulmonary Rehabilitation for Long COVID • Proning and Side-lying • ECMO • MISC
Adjunctive Therapy	• *No evidence summaries updated for this phase*
Vaccines	• First booster for 12-17 years old • First booster for 5-11 years old • Primary series for 6 months to 4 years old • Second booster for the General Population • Second booster for health care workers • Third booster for high risk groups • First booster for the COVID recovered • First booster for high risk groups • Primary series for 12-17 years old

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 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
Diagnosis and Screening	• Sensitivity and Specificity • Positive and Negative Predictive Value • Positive and Negative Likelihood Ratios • Resource Savings • Number or RT-PCR positive samples • Mortality • False Positive and False Negative Rates	• Psychological effects of testing • Physical harm of testing
Preventive Interventions	• Incidence of COVID-19 Disease of any severity • Incidence of Severe COVID-19 disease • Incidence of hospitalization among patients with COVID-19 disease • Incidence of mechanical ventilation among patients with COVID-19 disease • Deaths due to COVID-19 • Serious Adverse Events • Adverse Events	
Treatment and Critical Care – Outpatients and Mild to Moderate COVID Patients	• All cause Mortality • Clinical Improvement • Clinical Deterioration (WHO Progression Score) • Hospitalization • Progression to severe COVID • Serious Adverse Events • Need for Mechanical Ventilation	• Respiratory Distress • Viral negative conversion • Time to negative PCR • Viral Clearance • Time to clinical cure • Duration of hospitalization • ICU admission • Improvement in Chest Xray/CT Scan • Need for supportive oxygen therapy • Duration of mechanical ventilation • Adverse events

Treatment and Critical Care – Severe to Critical COVID Patients	• All Cause Mortality • Clinical Improvement • Serious Adverse Events • Respiratory Distress • Clinical Deterioration (WHO Progression Score) • Time to clinical cure • Duration of hospitalization	• Viral negative conversion • Time to negative PCR • Viral Clearance • ICU admission • Improvement in Chest Xray/CT Scan • Need for supportive oxygen therapy • Duration of mechanical ventilation 4. Adverse events
Treatment and Critical Care – Any COVID severity	• All Cause Mortality • Clinical Deterioration (WHO Progression Score) • Serious Adverse Events • Need for ICU Admission • Clinical Improvement • Respiratory Distress • Progression to Severe COVID	• Viral negative conversion • Time to negative PCR • Viral Clearance • Time to clinical cure • Hospitalization • Improvement in Chest Xray/CT Scan • Need for supportive oxygen therapy • Need and duration of mechanical ventilation • Adverse events
Vaccines	• serious adverse events • Deaths due to COVID-19 • Incidence of ICU admission among patients with COVID-19 disease • Need for mechanical ventilation among patients with COVID-19 disease • Incidence of hospitalization among patients with COVID-19 disease • Incidence of severe COVID-19 disease • Adverse events • Immunogenicity	• Incidence of COVID-19 disease of any severity

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.

Guideline Dissemination

Three methods were used in the dissemination of the Philippine COVID-19 Living CPG: (1) online webpage, (2) Living Recommendations Quick Guide, 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.

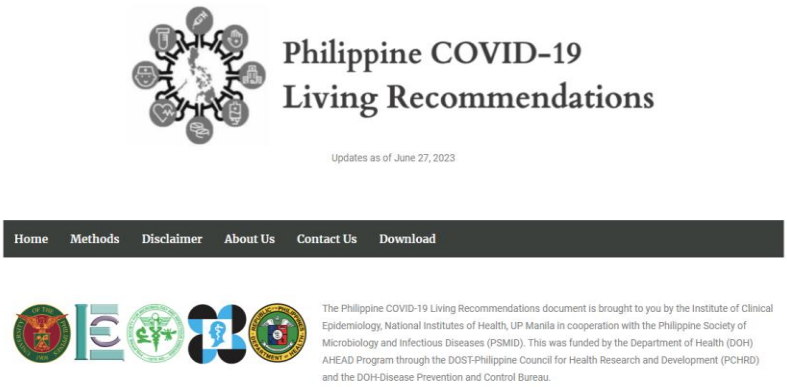
The Quick Guide contained the content in the PSMID website, including the introduction, CPG methodology, members of the living CPG task force, and the actual recommendation statements. The evidence summaries were not included in this document. This shorter format allowed for an easily accessible document 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. Latest PSMID Webpage for the Philippine COVID-19 LCPG.



Guideline Monitoring and Evaluation

Guideline implementation would be assessed through process and impact evaluation. Webage analytics were used at the initial project implementation. The Phase 2 manuscript was then externally reviewed and has been cleared by the DOH Clearing House for dissemination. 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.

External Review

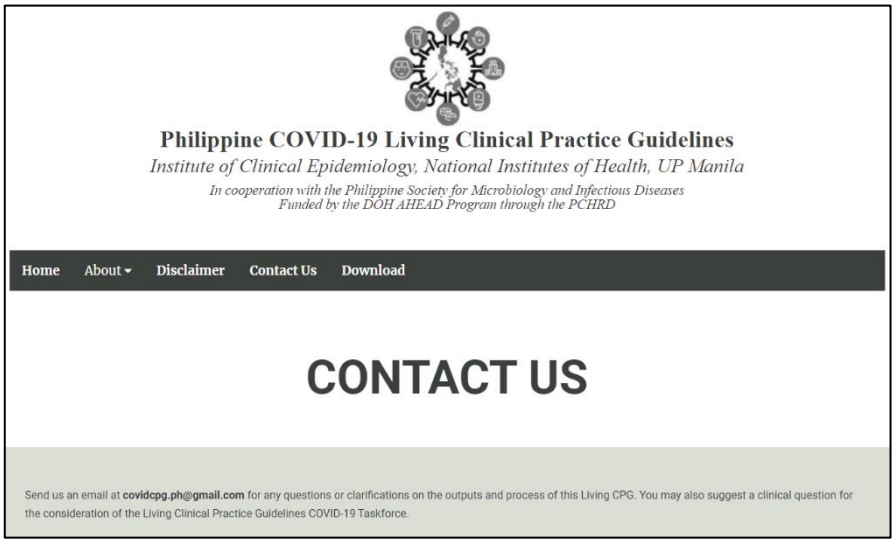
Eight external reviewers were assigned to review the evidence summaries of the three task forces. These reviewers were chosen by the chair of the Steering Committee for their expertise in the subject and their non-participation in this COVID-19 CPG development process. Each external reviewer was given a copy of the AGREE-REX Tool to be used in the assessment of CPG. Overall, the guideline recommendations has been assessed to be good for use in the appropriate context with scores ranging from 5-7 (7 being the highest) in all domains of the assessment tool.

Clarifications on the target population were addressed as some of the guideline questions have now included the pediatric population during this update. Some comments and recommendations included providing specific recommendations to overcome barriers (i.e. social and cultural differences) that may hinder acceptability of the guideline recommendations. Suggested inclusion in the scope of some guideline

questions mentioned will be considered and discussed by the Steering Committee if an update is needed.

The CPG webpage also served the dual purpose as a dissemination method and a way to collect the external reviews of the CPG processes, evidence summaries, and recommendations. This website (Figure 3) also allowed health professionals and key stakeholders to suggest additional clinical questions that could be included in the scope of this CPG.

Figure 3. Contact details in the Webpage for the Philippine COVID-19 Living CPG.



For Phase 3 of this living CPG, updates to previous reviews were highlighted on the website and indicated that these recommendations are updates as of the latest panel meeting.

Furthermore, the screening appraisal of the Department of Health-Disease Prevention and Control Bureau provided 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.

The DOH-Disease Prevention and Control Bureau has provided funding support to continue the surveillance search for the “living recommendations”.

Editorial Independence

FUNDING SOURCE

Phase 3 of the COVID-19 Living CPG project was funded by the Department of Health - Disease Prevention and Control Bureau under the National Practice Guidelines Development Program lodged under the University of the Philippines National Institutes of Health - Institute of Clinical Epidemiology. DOH participation was limited to the identification and suggested prioritization of key clinical questions. 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 Staff, and Consensus Panel, declared any potential conflicts of interest within the last 5 years, using a uniform Declaration of Conflict of Interest (DCOI) form as recommended in the DOH Manual [5]. These were reviewed by an independent COI Review Committee (COIRC) to screen and manage the COIs declared. The COI Review Committee is responsible for recommending the extent of participation that can be allowed. The decisions of the COI Review Committee are reported and published in the final manuscript of the Living CPG.

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

- **Allowable -** participation in the CPG development is allowed, with no constraints
- **Manageable with minor constraints** - there are identified COIs, and participation is allowed with minor constraints (e.g., COIs are declared aloud prior to panel discussions)
- **Manageable with major constraints** - there are identified COIs, and participation is allowed with major constraints (e.g. voting is disallowed but they can share their expertise with the group during panel discussions)
- **Disqualifying -** participation in the CPG development is disallowed. The scope or nature of COIs negate management and will sometimes outweigh the content expertise an individual may bring by serving as a full panelist, resulting in disqualification.

The restrictions may apply to the entire CPG or particular questions addressed by it. Specifics of the constraints will be detailed by the COI Review Committee for affected participants. For example, a participant with minor constraints may be allowed to discuss and vote on certain issues, with panel members constantly reminded about that person's conflicts. In contrast, a participant with major constraints might be allowed to discuss, but not allowed to vote.

Living Recommendations on Diagnosis and Screening of COVID-19

Q1. Among patients suspected to have COVID-19, should the 14-day symptom-based test be used in screening for COVID-19 infection?

As of 22 May 2023

RECOMMENDATION

We recommend the use of a 7-day symptom-based* test, instead of 14 days, to assess for possible COVID-19 infection among adults and children.**
(*Very low certainty of evidence; Strong recommendation)*

** Symptoms listed in the WHO Case Definition: acute onset of fever AND cough (ILI) OR acute onset of ANY THREE OR MORE of the following signs or symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, nausea/diarrhea/anorexia*

***Please refer to previous recommendation on testing using RTPCR and RAT*

Consensus Issues

The Panel considered feasibility, acceptability, cost-effectiveness, and practicality in determining the strength of this recommendation. While certainty of evidence is very low, the Panel decided a strong recommendation is warranted due to its beneficial impact to public health. Additionally, this recommendation was based focused on studies dealing with the Omicron variant. The Panel acknowledges that there may be a need to revisit recommendations when considering past and future COVID-19 variants.

KEY FINDINGS

- We found three observational studies, two of which included patients with and without COVID-19, presenting with and without the usual symptoms. Most of the symptoms showed a pooled sensitivity below 60%. Only cough had a sensitivity above 60%. The lowest sensitivities (10% and below) were seen with myalgia, shortness of breath, nausea/vomiting, diarrhea, and loss of smell or taste.
- Pooled specificity 60% and above was seen with fever, cough, fatigue, headache, myalgia, sore throat, runny nose/congestion, shortness of breath, nausea/vomiting, diarrhea and loss of smell or taste.
- Cough was the only symptom with both pooled sensitivity and pooled specificity above 60%.
- The third observational study compared the number of days spanned until resolution of symptoms in omicron-infected and delta-infected patients, and reported that the duration of acute symptoms was longer for delta (8.89 days; 95% CI 8.61-9.17) than omicron (6.87 days; 95%CI 6.58–7.16). This difference was statistically significant (MD 2.02 days lower with omicron, 95%CI 1.62 lower to 2.42 lower). This shorter period was even more marked in individuals who had received three doses of the vaccine.

WHAT'S NEW IN THIS VERSION

- This current update focuses on the use of the 14-day symptom-based test in the time of Omicron predominance, and includes evidence from studies 1) done in the time of Omicron predominance and 2) allowed the comparison with non-Omicron times.

Q2. Among patients suspected to have COVID-19, should rapid antigen tests be used for diagnosis of COVID-19?

As of 2 May 2023

RECOMMENDATION

Among adults and children suspected to have COVID-19 who are symptomatic, we suggest the use of RAT for the diagnosis of COVID-19 as an alternative to RT-PCR. *(Very low certainty of evidence; Weak recommendation)*

RECOMMENDATION

Among adults and children exposed to COVID-19 who are asymptomatic, we suggest against the use of RAT for the diagnosis of COVID-19 *(Very low certainty of evidence; Weak recommendation)*

Consensus Issues

The panel acknowledged that the previous recommendation was updated in the context of the Omicron variant last 2022. The panel emphasized that rapid antigen testing (RAT) is only an alternative to RT-PCR; furthermore, the panel reiterated that the use of RAT in asymptomatic individuals with known exposure to COVID-19 patients is discouraged because of its low sensitivity in this population.

KEY FINDINGS

- We found one systematic review and meta-analysis that included 18 studies done during the Omicron period. The study of Mohammadie et al. reported that overall, rapid antigen tests had a pooled sensitivity of 67% (95% CI 0.59–0.72) and pooled specificity of 100% (0.997–1.000). Subgroup analyses were done with respect to specimen, cycle threshold (CT) value, and symptomatology.
- Nasal swabs had a higher pooled sensitivity of 79% (95% CI 0.69–0.86) compared to nasopharyngeal swabs 67% (95% CI 0.62–0.72). The same finding was reported on the previous version of this review.
- The pooled sensitivity of samples with CT <25 and CT >25 was 90% (95% CI 0.82–0.95) and 11% (95% CI 0.05–0.23), respectively, in a subgroup analysis of seven articles.
- The sensitivity in symptomatic cases was 87% (95% CI 0.81–0.92) while that for asymptomatic cases was 61% (95% CI 0.39–0.79), based on three articles.

WHAT'S NEW IN THIS VERSION?

This updated review takes into consideration the predominant variant of concern, i.e., Omicron, and focuses on evidence regarding the diagnostic accuracy of rapid antigen tests in the time of Omicron variant predominance.

Q3. 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 1 February 2023

RECOMMENDATION

We recommend the use of self-administered rapid antigen test for the diagnosis of SARS-CoV-2 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 (Studies that challenge the robustness of a diagnostic kit under various conditions of stress); AND
4. Individuals present with symptoms for less than 7 days.

(Moderate certainty of evidence; Strong recommendation)

RECOMMENDATION

We recommend against the use of self-administered rapid antigen test for asymptomatic individuals. *(Moderate certainty of evidence; Strong recommendation)*

Consensus Issues

The previous recommendation on "routine screening" was removed since the evidence base presented are among asymptomatic individuals. To be consistent with the results of the evidence base, the Panel decided to vote on changing the recommendation to "recommend against diagnosis among asymptomatic individuals". Further review of evidence solely focused on routine screening should be done.

The Panel also noted that there is the are not enough evidence presented on the use of self-administered rapid antigen tests among special populations such as healthcare workers and immunocompromised individuals.

KEY FINDINGS

- Fifteen observational studies (eight new studies added to the seven studies previously reviewed) assessed the diagnostic accuracy of self-administered rapid antigen tests against RT-PCR as the reference standard. The studies included varied test brands (n=13), specimen types, and symptom status.
- The pooled sensitivity of self-administered rapid antigen test was 0.74 (95% CI 0.63-0.82) while the pooled specificity was high at 0.991 (95% CI 0.99-0.99). Heterogeneity among studies had an I^2 value of 54% (from I^2=97%) as the studies yielded more similar results.
- On subgroup analysis, self-administered rapid antigen test showed the following sensitivity results when used in the following conditions:

- Symptomatic individuals (Sn 0.78, 95% CI 0.70-0.85; n=5,761) with a heterogeneity of I^2 =0.48 across studies;
- Asymptomatic individuals (Sn 0.57, 95% CI 0.27-0.83; n=9,639) with a heterogeneity of I^2 =0.24 across studies;
- Specimens of symptomatic individuals taken from exhaled breath condensate (Sn 0.92, 95% CI 0.64-1.00; n=105), nasal mid-turbinate (Sn 0.86, 95% CI 0.80-0.91; n=696), or anterior nares (Sn 0.76, 95% CI 0.75-0.78; n=7,915);
- Specimens of asymptomatic individuals taken from nasal mid-turbinate (Sn 0.75, 95% CI 0.35-0.97; n=157), anterior nares (Sn 0.26, 95% CI 0.23-0.31; n=3,978), or combined oropharyngeal and nasopharyngeal areas (Sn 0.40, 95% CI 0.28-0.52; n=5,504)
- Specimens of symptomatic individuals with high viral loads at RT-PCR cycle threshold <25 (Sn 0.95, 95% CI 0.89-0.98; n=140);
  Specimens of asymptomatic individuals with high viral loads at RT-PCR cycle threshold <25 (Sn 0.76, 95% CI 0.64-0.76; n=187);
- Specific brands of rapid antigen test, namely LumiraxDx (Sn 0.97, 95% CI 0.92-0.99; n=5,535), Inflammacheck device (Sn 0.92, 95% CI 0.64-1.0; n=105), COVID-VIRO ALL IN (Sn 0.91, 95% CI 0.83-0.96; n=593), Drager antigen test (Sn 0.89, 95% CI 0.79-0.95; n=379), and Abbott Panbio (Sn 0.84, 95% CI 0.71-0.94; n=290);
- Seven studies with high methodological quality or low risk of bias on symptomatic individuals (Sn 0.75, 95% CI 0.73-0.77; n=5,061); and
- Two studies with high methodological quality or low risk of bias on asymptomatic individuals (Sn 0.26, 95% CI 0.22-0.30; n=3,872).

- The overall certainty of evidence for test sensitivity was tagged as moderate for both symptomatic and asymptomatic individuals due the presence of risk of bias issues (patient selection, conduct of index test, and reference standard) despite having similar results across studies.

WHAT'S NEW IN THIS VERSION?

This update contains eight additional observational studies that assessed the diagnostic accuracy of self-administered rapid antigen tests. Five among these were published in 2022, three of which specifically involved the Omicron SARS-CoV-2 variant, the most prevalent variant in our country based on the latest COVID-19 biosurveillance report [1]. The studies included varied test brands, specimen types, and symptom status.

Relative to the previous review, pooled sensitivity obtained from a total of 15 studies is 0.74 (95% CI 0.63-0.82) from 0.77 (95% CI 0.62-0.87). A pooled specificity of 0.991 (95% CI 0.99-0.99) also does not deviate from the previously obtained 0.996 (95% CI 0.99-1.00). Heterogeneity among studies had an I^2 value of 54% (from I^2=97%) as the studies yielded more similar results. Three studies which included children and adolescents as test subjects provided a sensitivity of 0.66 (95% CI 0.64-0.68). This version also discussed updates on the guidelines set by other groups.

Q4. Among patients suspected to have COVID-19, should breath tests be used to diagnose COVID-19 infection?

As of 2 March 2023

RECOMMENDATION

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

Consensus Issues

The Panel considers that it is too premature to make a recommendation on Breath Testing as the technology is not available in the Philippines and the information on its use in other countries is not extensive.

KEY FINDINGS

- This review has a total of 11 cross-sectional studies on the use of breath tests in the diagnosis of COVID-19 infection.
- The overall accuracy of breath tests was high, with pooled sensitivity of 95% (95% CI 0.90-0.97) and pooled specificity of 93% (95% CI 0.86-0.97). However, the overall certainty of evidence was low due to issues of risk of bias and significant heterogeneity. This heterogeneity may be attributed to the different mechanisms of the devices despite using the same idea of breath testing. Further evidence is recommended.
- Currently, there are no available forms of breath testing sold locally and information about cost and resource requirements are limited.

WHAT'S NEW IN THIS VERSION?

Five new cross-sectional studies were added. Additional breath tests include the use of spectroscopy which could also detect semi- and non-volatile organic compounds, aside from VOCs (Volatile Organic Compounds) detected from spectrometry, rapid antigen, and olfactory technology.

Q5. Among patients suspected to have COVID-19, should antibody tests be used to diagnose COVID-19 among vaccinated adults and children?

As of 2 May 2023

RECOMMENDATION

There is no evidence to recommend for or against antibody testing to diagnose COVID-19 disease among vaccinated patients.

RECOMMENDATION

We suggest against the routine measurement of SARS-CoV-2 antibody titers after vaccination. In the rare situations where we need to determine prior COVID-19 disease or infection, we suggest the use of nucleocapsid antibody testing among vaccinated individuals, along with infectious disease specialist consultation. (*Very low certainty of evidence, Weak recommendation)*

Consensus Issues

The panel noted that there are no available studies on the use of antibody tests for the diagnosis of COVID-19. The panel also brought up issues of cost and goals in antibody testing, noting that useful clinical applications of antibody testing are limited such as in MIS-C cases and vaccination in immunocompromised individuals, hence the emphasis for expert consultation in the use of these tests.

KEY FINDINGS

- We included six (6) seroprevalence studies (n=24,070 samples) that investigated the diagnostic accuracy of antibody tests in the detection of past exposure to COVID-19 using reverse transcription polymerase chain reaction (RT-PCR) as the reference standard.
- The overall certainty of evidence is very low due to serious risk of bias, very serious inconsistency and very serious indirectness.
- The pooled sensitivity of antibody tests was 99% (95% CI 96.7–99.7; I^2=73.2%; very low certainty) while pooled specificity was 11.9% (95% CI 2.5-41.4; I^2=73.2%; very low certainty). Heterogeneity across the studies was substantial (I^2=0-99%).
- Sensitivity was high across all subgroups ranging from 95%-100%, while specificity was noted to be high only in a subgroup measuring Nucleocapsid antibodies (90% specificity; 90% CI 89%- 91%; very low certainty).
- No studies evaluating the accuracy of antibody tests compared to RT-PCR in determining COVID-19 disease were found.
- No direct studies evaluating the accuracy of antibody tests compared to RT-PCR in determining past COVID-19 exposure were found. Only seroprevalence studies with subgroups of interest that allow the construction of a 2x2 table for diagnostic accuracy were included.

Q6. Among asymptomatic individuals scheduled for non-urgent, non-emergent surgery, should RT-PCR and clinical risk assessment vs clinical risk assessment alone be done to screen for COVID-19?

As of 27 June 2023

RECOMMENDATION

Among asymptomatic individuals scheduled for non-emergent/non-urgent surgery, we suggest using clinical risk assessment alone to screen for COVID-19.
(*Very low certainty of evidence, Weak recommendation)*

RECOMMENDATION

Among asymptomatic individuals scheduled for non-emergent/non-urgent surgery who have been diagnosed to have COVID-19 within the last 90 days, we suggest against the use of SARS-CoV-2 RT-PCR.
(*Very low certainty of evidence, Weak recommendation)*

Consensus Issues

The panel emphasized that clinical risk assessment should include asking about history of COVID-19 symptoms and a possible history of exposure to SARS-CoV-2. There are certain important qualifiers and potential confounders that the review did not find evidence for and hence were not discussed, including the vaccination status of the patient, associated comorbidities, immunocompromised status, and the length and type of operative procedure, among others. The panel acknowledged the low sensitivity of clinical risk assessment alone in screening for COVID-19 cases for asymptomatic individuals but the panel pointed out the delays and costs incurred when requiring RT-PCR testing prior to non-emergent/non-urgent surgery. The panel also pointed out that this recommendation is subject to change if there should be a significant increase of COVID-19 infections among the population.

KEY FINDINGS

- This updated review contains four observational studies as indirect evidence sources for diagnostic accuracy and postoperative outcomes. Three new observational studies were included, in addition to one study mentioned from the previous review. We excluded two studies from the earlier version due to very serious indirectness issues.
- Based on three observational studies, clinical risk assessment had low sensitivity ranging from 0.38-0.50, compared to RT-PCR test as the gold standard for detecting COVID-19 infection. Four cross-sectional studies revealed that clinical risk assessment or symptom screening questionnaires have variable specificity range of 0.62-1.00 [113-116]. In terms of postoperative outcomes, two observational studies showed that patients who tested positive for COVID-19 had significantly increased risk of postoperative all-cause mortality compared to those who were COVID-19 negative preoperatively.
- The overall certainty of evidence regarding the sensitivity and specificity of risk assessment questionnaires and all-cause mortality outcome was deemed to be very low. Serious risk of bias was noted from the a) subjective interpretation of the index test (risk assessment or symptom questionnaire) and b) study methodology

(observational), where the clinical outcomes were concerned. Moreover, the small sample size and event rates in one outcome contributed to serious imprecision issues.

- Lastly, issues of indirectness were also noted since patients for semi-urgent procedures were recruited in two studies, and outcomes on unscreened patients were uninvestigated in all four studies [113-116].

Q7. Among individuals previously infected with COVID-19, what criteria should be used to end isolation?

As of 27 June 2023

RECOMMENDATION

For **asymptomatic fully vaccinated adults**, or **symptomatic fully vaccinated adults with mild COVID-19**, we suggest the use of the criterion for ending isolation: At least 5 days have passed since the first positive COVID-19 RT-PCR test (*Low certainty of evidence, Weak recommendation)*

RECOMMENDATION

For **asymptomatic not fully vaccinated adults**, or **symptomatic not fully vaccinated adults with mild COVID-19**, we suggest the use of the criterion for ending isolation: At least 7 days have passed since the first positive COVID-19 RT-PCR test (L*ow certainty of evidence, Weak recommendation)*

RECOMMENDATION

For **symptomatic adults with moderate COVID-19** diagnosis and **any vaccination status**, we suggest the use of the following symptom-based criteria for ending isolation:

- At least 10 days have passed since the onset of symptoms AND
- No fever during the previous 72 hours without the use of antipyretic medications AND

There has been substantial improvement in respiratory or other symptoms of the acute illness, as applicable. (L*ow certainty of evidence, Weak recommendation)*

RECOMMENDATION

For **symptomatic fully vaccinated adults with severe-to-critical COVID-19** , we suggest the use of the following symptom-based criteria for ending isolation:

- At least 20 days have passed since the onset of symptoms AND
- No fever during the previous 72 hours AND without the use of antipyretic medications AND
- There has been substantial improvement in respiratory or other symptoms of the acute illness, as applicable.

(*Low certainty of evidence, Weak recommendation)*

RECOMMENDATION

For **symptomatic not fully vaccinated adults with severe-to-critical COVID-19**, we suggest the use of the following symptom-based criteria for ending isolation:

- Minimum of 20 days have passed since the onset of symptoms AND
- No fever during the previous 72 hours without the use of antipyretic medications AND
- There has been substantial improvement in respiratory or other symptoms of the acute illness AND

With multi-disciplinary consultation among relevant subspecialists (L*ow certainty of evidence, Weak recommendation)*

Consensus Issues

The Panel discussed the basis for the evidence behind the latest World Health Organization recommendations released in January 2023, and how it is different from the evidence being presented in the Evidence Summary. The WHO conditional recommendations were based on a rapid review of a modeling study that is still yet to be published (pre-print). The Panel also decided to change the semantics for the third condition to apply as “respiratory and other symptoms, as necessary” to make it more applicable to atypical COVID-19 presentations. However, they acknowledged that the transmission of COVID-19 is mostly through the respiratory route, hence placing ”respiratory” as an important qualifier. Most of the studies in this evidence summary are based on respiratory symptoms.

KEY FINDINGS

Eighteen observational studies were included in this version to investigate how the vaccination status and various outcomes related to infectivity are connected. From this data, the review provides additional recommendations related to duration of isolation based on the aforementioned conditions for end of isolation.

a. **Duration of infectivity:**

- **Based on disease severity**
  One study showed that among asymptomatic patients viral culture is positive only until the 5th day from first positive culture. In the same study, among symptomatic patients with mild disease the peak viral RNA isolation were observed at 3-6th day from onset and not detectable by the 10th [140]. Another study showed that among moderately symptomatic samples the peak viral isolation was noted on the first week and not detectable by the 12th day [147]. One study also showed that those with severe disease mostly remain infectious for at least 20 days.
- **Based on vaccination status**
  One study found no significant difference (p=0.16) in the proportion of culture-positive results between fully vaccinated and not fully vaccinated individuals at 5th day of illness. (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) [137]. In contrast, another study showed that among fully vaccinated individuals viral culture positivity is lower at 4 days compared to 8-

10 days. Negative conversion of viral culture is fast er in fully vaccinated with a median of 1.75 days compared to partially/unvaccinated individuals with a median of 4.38 days [144]. This is supported by another study which showed that vaccinated individuals had faster viral clearance by 2 days (5.5 days [95% credible intervals 4.6-6.5] vs. 7.5 days for unvaccinated [95% CI 6.8-8.2 days]) and shorter infection duration by 2.3 days (8.7 days, [95% CI 7.6-9.9] vs 11.0 days [95% CI 10.3-11.8] for unvaccinated) [129]. Overall, the pooled result showed that fully vaccinated individuals have a significant faster viral clearance rate compared to partially and unvaccinated individuals (P<0.00001)

b. **Secondary attack rate:** Based on three observational studies, the secondary attack rate was significantly lower by 40.85% (95% CI -48.47% to -33.24%) for fully vaccinated compared to not fully vaccinated individuals [135,138,144]. (P<0.00001)

c. **Immunocompromised individuals**: Compared to immunocompetent individuals, time to PCR clearance was not significantly different both for severely (hazards ratio 1.375) and moderately immunocompromised patients (hazard ratio 1.25). 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). Compared to immunocompetent individuals, time to PCR clearance was similar for severely (aHR 0.98, 95% CI 0.84-1.15) and moderately immunocompromised patients (aHR 0.86, 95% CI 0.71-1.05) [139]. This is supported as well by one study using viral culture, wherein virus was noted to be still culturable among mild-moderately affected samples at 16th day of onset among immunocompromised vs 9th day among immunocompetent. The difference was not statistically significant (p 0.161). Though in one case report that used viral culture as well on a patient who has B cell suppressed disease, viral culture was still positive up to 72nd day indicating need of test based strategy for clearance of patients with said disease [145].

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

Living Recommendations on Non-Pharmacologic Interventions for Prevention

Q8. In the community, in what settings should mask wearing be required?

As of 2 May 2023

RECOMMENDATION

In the community setting, we recommend the use of a face mask for preventing COVID-19 in crowded, enclosed, and poorly ventilated spaces (L*ow certainty of evidence; Strong recommendation)*

Consensus Issues

The panel upgraded the strength of recommendation to strong, acknowledging that masking in community settings is a form of public health intervention with benefits not limited to COVID-19 prevention, especially in crowded and poorly-ventilated spaces.

KEY FINDINGS

- There were two non-randomized studies that compared the incidence of COVID-19 in the community setting (school) in the post-vaccination era. Both studies found that the lifting of mask mandates was associated with an increased incidence of COVID-19 cases [178,179].

Q9. In the community, what ventilation and air filtration measures should be recommended to prevent COVID-19 transmission?

As of 22 May 2023

RECOMMENDATION

We recommend the use of natural ventilation* in indoor spaces to prevent COVID-19 transmission, if possible and safe to do so. *(Good practice statement)*

** Includes opening doors and windows and electric fans*

RECOMMENDATION

We recommend the use of mechanical ventilation systems with appropriate filtration systems** in indoor spaces to prevent COVID-19 transmission if *natural ventilation is not feasible or adequate*. (*Very low certainty of evidence, Strong recommendation)*

*** Includes HVAC systems and portable air cleaners*

Consensus Issues

The Panel opted to issue this good practice statement, despite being based on indirect evidence, due to its perceived net benefits to public health. For both

recommendations, the Panel also considered existing recommendations from other regulating authorities in order to be consistent with existing public health practices.

KEY FINDINGS

- Two observational studies compared mechanically ventilation and naturally ventilated areas in schools and hospitals. We also found one randomized crossover trial investigating the effect of HEPA filters in households of individuals with COVID-19 [191-193].
- Classrooms with mechanical ventilation had lower incidence of COVID-19 compared to those with natural ventilation. There was no significant difference in SARS-CoV-2 detection in bioaerosols between mechanically ventilated and naturally ventilated hospital spaces [191].
- The addition of HEPA filters in portable air cleaners did not result in a significant difference in SARS-CoV-2 RNA detection in household air samples [193].
- The overall certainty of evidence is very low due to risk of bias (randomization and allocation concealment issues, inadequate adjustment for confounders) and imprecision.

Q10. In the community, should carbon dioxide (CO2) monitors be used to reduce transmission of COVID-19?

As of 1 February 2023

RECOMMENDATION

We suggest the use of carbon dioxide (CO2) monitors in enclosed spaces to guide actions to improve ventilation and reduce the risk of transmission of SARS-CoV-2. (*Low certainty of evidence, Weak recommendation)*

Consensus Issues

Panel members clarified the appropriateness and completeness of the evidence question “Should Carbon Dioxide monitors be used to reduce the transmission of COVID-19?”. It was clarified that the question precludes an intermediary outcome that is not explicitly stated (for example, using CO2 monitors to improve ventilation). The Steering Committee clarified that the more important outcome is clinical in nature, that is: reducing transmission of COVID-19, of which the results were based on mostly indirect evidence.

KEY FINDINGS

- In this update, we found no studies that directly answered the research question; hence, the studies presented constitute indirect evidence.
- Mathematical modelling described that the air renewal rate has a significant role for event durations >0.5hr and that transmission probability decreased with opened windows [222].
- The estimated transmission risk (Hr) for COVID-19 ranged from intermediate (with surgical masks) to high (no masks, teacher infected). Controlled mechanical ventilation systems and wearing well-fitting FFP2–N95 masks indoors contributed

to the decrease transmission risk of COVID-19 (AR 35%/50%, without masks for Alpha and Omicron BA.1 to 20%/30% with mask) [226].

- The fraction of rebreathed air can be inferred from the ratio of CO2 concentration in the room and the estimate of the fraction of infected air is translated into a likelihood of infection rate [207].
- The higher the number of visitors in an area, the higher the predicted CO2 concentration [223].
- In a clinical cardiology clinic setting, aerosol concentration increased with increasing CO2 levels and in a well-ventilated room, the aerosol concentration and CO2 levels declined after the stress test stopped [225].
- An RCT revealed that the median time per day with CO2 concentration >800 ppm was 110 minutes prior to the use of CO2 monitors, 82min in the sham control (CO2 monitors face down) and 78min in the intervention (with CO2 monitor readings shown) [230].
- Perceived actions to reduce CO2 levels include opening windows and doors, taking periodic breaks where occupants can leave the room, reducing occupancy and avoiding high intensity activities, increasing fresh air supply, keeping ventilation fans running during occupied periods, and installing local exhaust systems.

WHAT'S NEW IN THIS VERSION?

- Eight new studies were added to the initial 6 studies in the previous evidence summary.
- New evidence is comprised of 2 observational studies, 1 cross-sectional study, 2 data modelling, 1 RCT, and 2 case studies. Three observational studies described ventilation as a function of CO2 concentration (Vernez et. al, Huessler et al, and Somsen et. al).
- One study (Burridge et. al) used mathematical modelling to estimate the baseline probability of airborne infection using CO2 level as variable.
- One cross-sectional study (Rodriguez et al), used CO2 levels in estimating COVID-19 infection risk while another study (Costanzo et. al) integrated the estimation of risk levels in a mobile application.
- One randomized controlled trial measured the length of time that carbon dioxide levels exceeded 800ppm, 1000ppm, and 1400ppm before, during, and after the use of carbon dioxide monitors.
- Two studies demonstrated possible limitations and harm in using CO2 monitors in estimating COVID-19 risk of infection.
- Lastly, one case study discussed that provision of theoretical basis and guidance resulted in better understanding of ventilation system and airborne transmission risk using CO2 monitors.
- Additional recommendation from the Welsh government on the use of CO2 monitors.

Living Recommendations on Prophylactic Interventions for COVID-19

Q11. Among close contacts of COVID-19 patients, should casirivimab-imdevimab be used as post-exposure prophylaxis?

As of 2 December 2022

RECOMMENDATION

We suggest against the use of casirivimab-imdevimab as post-exposure prophylaxis against COVID-19. (L*ow certainty of evidence, Weak recommendation)*

Consensus Issues

The panel decided that more evidence should be available in order to recommend the intervention due to in vitro evidence showing decreased activity of Casirivimab+Imdevimab against newer and more predominant SARS-CoV-2 variants (e.g., Omicron and its subvariant), There are still issues with equity especially on its wide availability in the local market and its large cost (₱70,000). As of this writing, the Philippine FDA has only granted Emergency Use Approval.

KEY FINDINGS

- Findings from one (1) randomized controlled trial investigating casirivimab + imdevimab cocktail as post-exposure prophylaxis for RT-PCR SARS-CoV-2 negative close contacts of COVID-19 patients showed a significant decrease in symptomatic and asymptomatic COVID-19 infection, and a decrease in duration of infection among those who developed COVID-19 [251].
- No significant difference was found in terms of serious adverse events between those given casirivimab + imdevimab and placebo [251].
- The overall certainty of evidence was rated low due to indirectness of the study population and imprecision in one critical outcome.

WHAT'S NEW IN THIS VERSION?

This version includes new recommendations from other groups. No new clinical trial data have emerged after the previously reported clinical trial [251].

Q12. Among close contacts of COVID-19 patients, should AZD7422 (Tixagevimab-Cilgavimab) be used as prophylaxis for COVID-19 infection?

As 2 March 2023

RECOMMENDATION

Pre-exposure Prophylaxis
We suggest against the use of AZD7442 (tixagevimab-cilgavimab) as pre-exposure prophylaxis against COVID-19. (*Very low certainty of evidence, Weak recommendation)*

RECOMMENDATION

Post-exposure Prophylaxis
We suggest against the use of AZD7442 (tixagevimab-cilgavimab) as post-exposure prophylaxis against COVID-19. (*Very low certainty of evidence, Weak recommendation)*

Consensus Issues
Following the presentation on the latest findings on post-exposure prophylaxis using AZD7442 (tixagevimab-cilgavimab), the panel notes that there are not enough high-quality studies that support the effectiveness against prevailing variants. The study presented was conducted prior to the emergence of the omicron variant.

KEY FINDINGS

- Two randomized controlled trials investigated the efficacy and safety of tixagevimab-cilgavimab (AZD7442) as prophylaxis for COVID-19 infection: one as pre-exposure prophylaxis, and the other as post-exposure prophylaxis.
- **As pre-exposure prophylaxis.** Those given AZD7442 showed significant reduction in the development of symptomatic COVID-19 infection and severe/critical COVID-19 infection in all participants as well as in individuals with increased risk of inadequate response to COVID-19 vaccine, individuals with high risk of exposure, individuals with comorbidities and individuals with high risk of severe COVID, compared to those given placebo. There was no significant difference in adverse events and serious adverse events between the AZD7442 (tixagevimab-cilgavimab) group and the placebo group. The overall quality of evidence was rated very low due to serious risk of bias (downgraded for attrition bias, indirectness, and imprecision in two critical outcomes, namely, mortality and emergency department visit) [272]. However, recently US FDA withdraw its emergency use authorization (EUA) for AZD7442 as pre-exposure prophylaxis since the predominant and emerging omicron subvariants are not susceptible to AZD7442.
- **As post-exposure prophylaxis.** Results showed inconclusive results for the following outcomes: RT-PCR positive symptomatic COVID-19 infection, severe or critical COVID-19 infection, and emergency department visit. The subset of participants with negative or missing SARS-CoV-2 RT-PCR result at baseline who were given AZD7442 showed statistically significant reduction in the development of RT-PCR positive symptomatic COVID-19 infection. Individuals given AZD7442 showed statistically significant reduction in the development of adverse events, but no significant difference in serious adverse events when compared to placebo [273]. The overall quality of evidence was rated very low due to serious risk of bias (downgraded for attrition bias, indirectness, and imprecision for four critical outcomes, namely, RT-PCR positive symptomatic COVID-19 infection, severe or critical COVID-19 infection, emergency department visit and serious adverse events).

Living Recommendations on the Treatment of COVID-19

Q1. Among COVID-19 patients, should favipiravir be used for treatment?

As of 03 April 2023

RECOMMENDATION

We recommend against the use of favipiravir among patients with COVID-19 (*Moderate certainty of evidence; Strong recommendation*)

Consensus Issues

The consensus panel strongly recommended against the use of favipiravir among patients with COVID-19, based on a moderate certainty evidence that it has no benefit in any of the critical outcomes (i.e. all-cause mortality, clinical improvement, clinical deterioration or need for hospitalization). Furthermore, the panelists also recognize another important outcome, where patients who received favipiravir had significantly higher risk of adverse events, such as hyperuricemia, hematologic effects, hepatobiliary disorders, gastrointestinal effects including diarrhea and nausea, skin disorders like rashes, and cardiac effects like bradycardia and chest pain. As of writing, there are 20 ongoing clinical trials among adults, the results of which may further elucidate on the use of favipiravir in COVID-19 treatment.

KEY FINDINGS

- A total of twenty-two (22) randomized controlled trials (RCTs) were found on the use of favipiravir among patients with COVID-19 [1-4, 6-13, 15, 17-23].
- Favipiravir has no significant benefit on all-cause mortality, clinical improvement, symptom progression, time to recovery, nor hospitalization.
- Pooled results show favipiravir had a significant benefit in viral negative conversion by day 7.
- Favipiravir has significantly more reported adverse events, especially in the inpatient subset, while no significant difference was seen for serious adverse events [1-7, 21].
- The overall certainty of evidence was rated moderate due to serious risk of bias in some critical outcomes.

WHAT'S NEW IN THIS VERSION?

This version includes data from sixteen (16) additional randomized controlled trials. The previously included randomized controlled clinical Phase 3 trial by Dabbous et al. on the efficacy of favipiravir compared to a hydroxychloroquine-based therapy as standard of care was retracted due to questionable reliability of data, hence excluded in this review.

Q2. Among COVID-19 patients, should remdesivir be used for treatment?

As of 05 December 2022

RECOMMENDATION

We suggest the use of remdesivir among hospitalized adult patients with mild to moderate COVID-19 infection with at least 1 risk factor* for progression to severe disease. (L*ow certainty of evidence, Weak recommendation)*

**60 years old or older, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity (a body-mass index [BMI; the weight in kilograms divided by the square of the height in meters] of ≥30), immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer, or sickle cell disease*

RECOMMENDATION

We recommend the use of remdesivir among non-hospitalized adult patients with mild to moderate COVID-19 infection with at least 1 risk factor* for progression to severe disease. (Moderate *certainty of evidence; Strong recommendation)*

**60 years old or older, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity (a body-mass index [BMI; the weight in kilograms divided by the square of the height in meters] of ≥30), immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer, or sickle cell disease*

RECOMMENDATION

We suggest the use of remdesivir in children (hospitalized or ambulatory) with mild to moderate COVID-19 infection with at least 1 risk factor for disease progression. (Very l*ow certainty of evidence; Weak recommendation)*

RECOMMENDATION

We suggest the addition of remdesivir to dexamethasone in adult patients with COVID-19 infection requiring oxygen supplementation but do not require mechanical ventilation*. (L*ow certainty of evidence; Weak recommendation)*

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

RECOMMENDATION

We suggest the addition of remdesivir to dexamethasone in children with COVID-19 infection requiring oxygen supplementation but do not require mechanical ventilation. (*Very low certainty of evidence, Weak recommendation)*

RECOMMENDATION

We suggest against the use of remdesivir among adult patients with COVID-19 infection who are already on non-invasive or invasive mechanical ventilation. (L*ow certainty of evidence, Weak recommendation)*

RECOMMENDATION

We suggest against the use of remdesivir among children with COVID-19 infection who are already on non-invasive or invasive mechanical ventilation.
(*Very low certainty of evidence, Weak recommendation)*

Consensus Issues

The panel issued separate recommendations for hospitalized and non-hospitalized adult patients with mild to moderate COVID-19, mainly due to different treatment duration (3 days for non-hospitalized vs 5 days for hospitalized) and critical outcomes measured (need for hospitalization or ER visit for non-hospitalized; need for mechanical ventilation and clinical deterioration for hospitalized). Like other antivirals, benefit of remdesivir is expected to be greater if given early in the disease course. Outpatients are more likely to receive remdesivir early in their disease course, hence are more likely to benefit from the drug's antiviral activity. This is in contrast to hospitalized patients who are more likely to receive remdesivir during the latter phase of their disease course. However, the panel also considered the high resource requirements in giving remdesivir to outpatients with mild to moderate COVID-19. The three-day regimen will require intravenous home infusions or multiple visits to the emergency room for the infusion.

With the introduction of vaccines against COVID-19, patients are more likely to have mild to moderate COVID-19, not requiring admission unless with risk factors for disease progression. The panel recognized that there are instances wherein adult patients are admitted due to other condition(s) and incidentally have mild-moderate COVID-19 infection as well. The panel believed that since there is evidence supporting use of remdesivir in hospitalized patients with mild to moderate COVID-19, this treatment option ought to be made available to this subgroup of patients, albeit low certainty of evidence. Only 1 of the 10 RCTs excluded vaccinated patients (outpatient study) while the rest did not mention the participants' vaccination status, since most RCTs on hospitalized COVID-19 patients were done early in the COVID-19 pandemic and prior to vaccine rollout. Hence, the panel did not include vaccination status as one of the qualifiers in the current recommendations.

The panel did not specify age in the recommendations for children, because randomized controlled trials (RCTs) specific to the pediatric population are still lacking. There was only 1 RCT on outpatients which explicitly reported inclusion of 8 adolescents (12-18 years old). Hence, the recommendations for children were extrapolated from adult studies and certainty of evidence was further downgraded due to indirectness. Recommendations from other groups vary, depending on the country's regulatory approval. US NIH recommends remdesivir for children 12 to 17 years of age, while Australian COVID-10 guidelines states that remdesivir may be given to children at least 28 days old and weighing at least 3kg.

KEY FINDINGS

- A total of 10 RCTs on the use of remdesivir in treatment of COVID-19 were included in this review [24-35].
- Remdesivir showed significant benefit for outpatients with mild to moderate disease with at least one risk factor for disease progression in terms of COVID 19-related and all-cause hospitalizations, and need for medically-attended visits [33].

- For hospitalized patients, remdesivir had a slight benefit in reducing all-cause mortality at day 28.
- Subgroup analysis by disease severity showed a trend towards reduction in mortality among those with severe disease, with no effect on those with critical disease and inconclusive effect for those with mild-moderate disease.
- Subgroup analysis by oxygen requirement showed trend towards mortality reduction for patients on low and high flow oxygen, and a trend towards increased mortality for those on mechanical ventilation [26-28, 30-32, 34].
- There was inconclusive effect on those without oxygen support.
- Remdesivir showed benefit in decreasing clinical deterioration, improving recovery rate, and reducing the need for mechanical ventilation.
- There was inconclusive effect on the need for ICU admission [31].
- No increased risk of adverse events, including serious adverse events, was seen [25, 27-28, 30, 32-35].
- The overall certainty of evidence was low due to serious risk of bias AND inconsistency or imprecision in several critical outcomes.

WHAT'S NEW IN THIS VERSION?

This update contains the final results of the WHO solidarity trial and the DisCoVeRy trial [26, 28, 35].

Q3. Among COVID-19 patients, should molnupiravir be used for treatment?

As of 25 January 2023

RECOMMENDATION

We suggest the use of molnupiravir within 5 days of symptom onset in adult patients with COVID-19 infection who are non-oxygen requiring and with at least one risk factor* for progression. (*Very 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

RECOMMENDATION

We suggest against the use of molnupiravir among children with COVID-19.
(*Very low certainty of evidence, Weak recommendation)*

Consensus Issues

Molnupiravir showed no significant benefit on critical outcomes (all-cause mortality, clinical improvement, need for hospitalization, and serious adverse events). Although there is evidence of benefit on the subgroup analysis of the need for hospitalization on unvaccinated participants, the panel took into consideration that the study on vaccination may not be reflective of the vaccination status in our country since 90% of the participants in the study are vaccinated with three doses. Another consideration is the duration of the last dose of vaccination since immunity may wane depending on the time it was given. The panel also noted that there is benefit on subgroup analysis on all-cause mortality among the mild to moderate non-hospitalized patients. However, because of the current definition of moderate COVID-19 in our guideline, the panel emphasized that the studies only included the non-oxygen requiring participants, hence specifying it as part of the recommendation to avoid confusion.

Children are a vulnerable population since there is no evidence for the use of molnupiravir and there is still no FDA recommendation for the use of molnupiravir in children with COVID-19, suggesting against the use of molnupiravir will be beneficial for children.

KEY FINDINGS

- Eleven (11) randomized controlled trials (RCTs) studied the effect of molnupiravir on the treatment of COVID-19 compared to standard of care and/or placebo.
- Molnupiravir did not significantly decrease the all-cause mortality 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. Subgroup analysis on mortality based on vaccination did not show significant benefit across subgroups.
- Molnupiravir did not show significant reduction in the need for hospitalization at day 29 compared to standard of care and/or placebo. Subgroup analysis based on vaccination status in need for hospitalization show significant benefit on unvaccinated subgroup but did not show significant benefit on vaccinated subgroup.

- Molnupiravir did not show significant benefit on clinical improvement and need for mechanical ventilation compared to standard of care and/or placebo.
- Molnupiravir did not show increase in clinical improvement based on WHO progression scale of 1 or less at day 15 and day 29.
- There was no significant benefit of the use of molnupiravir in viral negative conversion at day 7 and emergency room visit/acute care visit at day 29 compared to standard of care and placebo.
- Adverse events and serious adverse events were similar between molnupiravir and standard of care and/or placebo.
- The over-all risk of bias was downgraded to very low due to serious risk of bias, serious inconsistency, and serious imprecision.

WHAT'S NEW IN THIS VERSION?

Six (6) new RCTs (Butler 2022, Johnson 2022, Khoo 2022, Kumarasamy 2022, Tippabhotla 2022 and Zou 2022) are included in this update. One of the studies is a preprint (Tippabhotla 2022).

Q4. Among COVID-19 patients, should paxlovid or nirmatrelvir+ritonavir be used for treatment?

As of 05 December 2022

RECOMMENDATION

We recommend the use of nirmatrelvir+ritonavir within 5 days of symptom onset among unvaccinated symptomatic adult patients with high risk* for progression to severe disease. (*Moderate certainty of evidence, Strong recommendation)*

*Risk factors include any of the following: ≥60 years of age; BMI >25kg/m^2; cigarette smoking; immunosuppressive disease (including HIV infection with CD4 cell count <200mm^3 and viral load <400 copies/mL) or prolonged iatrogenic immunosuppression; chronic lung, cardiovascular, kidney, or sickle cell disease; hypertension; diabetes; cancer; neurodevelopmental disorders or other medically complex conditions; or medical-related technological dependence

RECOMMENDATION

We suggest the use of nirmatrelvir+ritonavir among unvaccinated, symptomatic pediatric patients 12 years of age and older weighing at least 40kg with high risk for progression to severe disease. (L*ow certainty of evidence, Weak recommendation)*

Consensus Issues

Since ritonavir is a strong cytochrome P450 (CYP) 3A4 inhibitor, it poses the risk of having drug to drug interaction, increasing the blood concentration of certain drugs. It is important to consider other medication/s being taken by the patient before giving the drug. Here is a link of some of the drugs contraindicated with nirmatrelvir+ritonavir: https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/.

Another issue raised during the panel meeting is the research gap that should be addressed. For one, the studies only included unvaccinated patients, so this must also be taken into consideration, such that the recommendation is made only among unvaccinated patients. Another is that one of the issues raised with the drug is COVID-19 reinfection, yet the study included did not include as an outcome those who developed re-infection. These research gaps must also be taken into consideration prior to the use of the drug.

For the use of the drug among children, one panelist abstained from voting for or against use of paxlovid in children citing that direct evidence on benefit and harm in this population was still lacking.

KEY FINDINGS

- There is one multinational randomized control trial (n=2,246) with moderate certainty of evidence included in this review [48].
- Nirmatrelvir+ritonavir decreases the risk of all-cause mortality and COVID-19 related hospitalization.
- Nirmatrelvir+ritonavir also decreased the risk of any serious adverse events.

- There was no significant difference in the risk of adverse events; however, there is an increased risk in adverse events considered related to the drug among those given nirmatrelvir+ritonavir.
- Common adverse events reported include dysgeusia, diarrhea, headache, nausea, and vomiting. No available studies are available for children and adolescents.

Q5. Among COVID-19 patients, should baricitinib be used for treatment?

As of 25 January 2023

RECOMMENDATION

We recommend the use of baricitinib in addition to corticosteroids among critical COVID-19 patients on high-flow nasal cannula oxygenation, noninvasive ventilation, or invasive mechanical ventilation. (Moderate *certainty of evidence, Strong recommendation)*

RECOMMENDATION

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

Consensus Issues

Generally, there were no panel issues on the use of baricitinib. The present recommendation is now based on seven clinical trials with evidence on its benefit for patients with critical COVID-19.

KEY FINDINGS

- A total of seven studies reported critical outcomes on the use of baricitinib for COVID-19 [49-55].
- The overall certainty of evidence was moderate because of serious inconsistency in some of the outcomes reported.
- Baricitinib appears to have benefit in terms of decreasing 28-day mortality and need for respiratory support compared to standard of care, majority of which were given corticosteroids.
- There were no excess risk of serious adverse events, venous thrombosis, or complications of infection associated with baricitinib in the studies reviewed.
- The mortality benefit appears to be limited to unvaccinated patients and to those requiring noninvasive and invasive mechanical ventilation at baseline.
- The benefits and risks of using baricitinib in patients aged 2 to 17 is still unclear [53].

WHAT'S NEW IN THIS VERSION?

Five new randomized controlled trials were included [51-55]. Use of baricitinib among vaccinated and pediatric patients were reviewed.

Q6. Among COVID-19 patients, should tofacitinib be used for treatment?

As of 16 January 2023

RECOMMENDATION

We suggest against use of tofacitinib among adult patients with COVID-19.
(L*ow certainty of evidence, Weak recommendation)*

RECOMMENDATION

We suggest against use of tofacitinib among children with COVID-19.
(*Very low certainty of evidence, Weak recommendation)*

Consensus Issues

The consensus panel maintained its recommendation against the use of tofacitinib in the treatment of adults with COVID-19, due to its lack of benefit in all critical outcomes, except for the composite outcome of death or respiratory failure and the harm due to adverse events. On further analysis by the panel, the perceived benefit was disproportionately driven by respiratory failure, rather than death. Based on current evidence, tofacitinib may be able to prevent respiratory failure but not death, mainly because there are other factors that contribute to COVID-19 deaths. Evidence from adult studies were extrapolated and used by the panel in coming up with a recommendation against the use of tofacitinib in children with COVID-19, hence the certainty of evidence was further downgraded to very low due to indirectness.

KEY FINDINGS

- There are three (3) randomized controlled trials (RCTs) that investigated the effect of tofacitinib compared to placebo or standard of care as treatment for patients with COVID-19 [56-58].
- Patients treated with tofacitinib had a significant reduction in the composite outcome of 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, two studies showed that there were 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 [56, 58].
- The very serious imprecision due to the limited number of events contributed to the downgrading of evidence to a low certainty of evidence.

WHAT'S NEW IN THIS VERSION?

Two new published RCTs [57-58] are included in this update.

Q7. Among COVID-19 patients, should ivermectin be used for treatment?

As of 16 January 2023

RECOMMENDATION

We recommend against the use of ivermectin in the treatment of children and adults with COVID-19 regardless disease severity.
(*Very low certainty of evidence, Strong recommendation)*

Consensus Issues

The panel unanimously recommended against the use of ivermectin in the treatment of children and adults with COVID-19 based on the most recent evidence which included a total of 27 randomized controlled trials (RCTs). The addition of twelve (12) new RCTs brought the total number of participants to 8,700, compared with 1,700 participants from the previous review, and further confirmed that ivermectin has no benefit in all the critical outcomes, including all-cause mortality, clinical improvement, need for hospitalization, clinical deterioration, and need for ICU admission or mechanical ventilation. The panel acknowledged that the extent of misuse and abuse of ivermectin in COVID-19 treatment has markedly subsided probably because the public is now more knowledgeable and informed, and that more effective treatment options are locally available. The panel also emphasized that although ivermectin is not expensive per se, spending for the drug may still be considered costly, as it would incur unnecessary expense.

KEY FINDINGS

- Twenty-seven (27) randomized controlled trials investigated the effect of ivermectin compared to placebo or standard of care as treatment for patients with COVID-19 [59-84].
- Evidence showed that although ivermectin did not cause significant harm compared with placebo or standard of care, there remains lack of conclusive benefit in any of the critical and important outcomes.
- Ivermectin did not show significant benefit on all-cause mortality, regardless of severity, hospitalization status, or dose of ivermectin used.
- Ivermectin did not show significant benefit in other critical or important outcomes, including clinical deterioration, need for mechanical ventilation, ICU admission, clinical improvement, time to symptom resolution, hospitalization and duration of hospitalization and virologic clearance.
- Adverse events and serious adverse events did not significantly differ between ivermectin and control groups.
- 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.
- Evidence on the use of ivermectin in children is lacking, hence the recommendation for pediatric patients were extrapolated from adult studies.

WHAT'S NEW IN THIS VERSION?

This version includes 27 randomized controlled trials (RCTs) with twelve (12) new trials comparing ivermectin and standard of care or placebo (Abbas 2022, Bramante 2022, Buonfrate 2022, Chahla 2022, Dela Rocha 2022, Lim 2022, Manomaipiboon 2022, Mirahmadizadeh 2022, Naggie 2022, Reis 2022, Rezai 2022A, Rezai 2022B). One RCT is a preprint (Bukhari 2021). Two RCTs were excluded in this update due to their retraction (Pott-Junior 2021, Elgazzar 2020).

Q8. Among COVID-19 patients, should colchicine be used for treatment?

As of 15 March 2023

RECOMMENDATION

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

Consensus Issues

The consensus panel recommends against the use of colchicine in the treatment of COVID-19 patients despite the certainty of evidence. This is mainly due to its potential harm without benefit in any of the critical outcomes, especially with the background of the local availability of other effective drugs for COVID-19. Most recent evidence showed that colchicine significantly increased risk of adverse events, without benefit in all-cause mortality, need for mechanical ventilation, hospital discharge within 28 days, need for hospitalization, need for ICU admission, need for hemodialysis or hemofiltration, clinical deterioration, and length of hospitalization. Although there were no studies among children, the panel opted to issue a blanket recommendation for adults and children against use of colchicine in COVID-19. Following the principle of "first do no harm," an intervention should not be prescribed without any evidence supporting its use. Although the effect of colchicine on the different variants could not be extracted, the studies were performed from 2020-2022, covering a wide span of time period, during which different variants were predominant.

KEY FINDINGS

- Nineteen (19) randomized controlled trials (RCTs) investigated the effect of colchicine compared to standard of care as treatment for patients with COVID-19 [85-103].
- Colchicine showed net potential harm (significant increase in adverse events) with no significant benefit in all-cause mortality, need for mechanical ventilation, hospital discharge within 28 days, need for hospitalization, need for ICU admission, need for hemodialysis or hemofiltration, clinical deterioration, and length of hospitalization.
- Several 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.

WHAT'S NEW IN THIS VERSION?

This version includes an additional 16 randomized controlled trials – 14 new studies and 2 studies which were previously included as preprint studies that have published versions available.

Q9. Among COVID-19 patients, should fluvoxamine be used for the treatment?

As of 05 December 2022

RECOMMENDATION

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

RECOMMENDATION

We suggest against the use of fluvoxamine among children and adolescent patients with mild to moderate COVID-19 infection. (*Very low certainty of evidence, Weak recommendation)*

Consensus Issues

Current evidence showed that fluvoxamine had some benefit only on one critical outcome (need for hospitalization) and was inconclusive in terms of all-cause mortality and clinical deterioration. Although adverse events and serious adverse events were not significantly increased in the fluvoxamine group, there were reports of exacerbation of COVID-19 and respiratory failure. Hence, the panel unanimously agreed given the available evidence, the risk of harm, especially the serious adverse events outweighs the marginal benefit of reduction in the need for hospitalization.

KEY FINDINGS

- Five (5) published randomized controlled trials (RCTs) (n=3,353) investigated the effectiveness of fluvoxamine compared to placebo among confirmed symptomatic non-hospitalized COVID-19 patients [104-108].
- There was a significant reduction in emergency room visits and the need for hospitalization among patients taking fluvoxamine [104, 106-107], however, there were inconclusive evidence in terms of other critical outcomes such as all-cause mortality [106-107], clinical deterioration [104-105, 108], healthcare utilization [105-107], and serious adverse events.
- The preliminary result of a Phase 2 published trial had issues on performance and detection bias [108]. The serious risk of bias, serious inconsistency and serious imprecision led to the downgrading of evidence to very low certainty.

WHAT'S NEW IN THIS VERSION?

Three new published RCTs [105, 106, 108] are included in this update.

Q10. Among COVID-19 patients, should bamlanivimab in combination with etesevimab be used for treatment?

As of 16 January 2023

RECOMMENDATION

We suggest against the use of bamlanivimab and etesevimab combination therapy as treatment COVID-19 patients (L*ow certainty of evidence, Weak recommendation)*

Consensus Issues

Although available evidence showed net benefit in terms of all-cause mortality, COVID-19-related hospitalizations and emergency department visits, and need for oxygen supplementation with the use of bamlanivimab and etesevimab combination therapy, there were concerns on its activity against the omicron variant, which is the predominant circulating variant at the time this recommendation was made. Studies showed that omicron variant can be resistant to this combination therapy; hence, the panel decided to reverse the previous recommendation regarding its use.

KEY FINDINGS

- The evidence on the use of bamlanivimab + etesevimab combination therapy was based on four randomized controlled trials (RCT) among non-hospitalized patients with COVID-19 [109-112].
- The combination of bamlanivimab and etesevimab compared to placebo showed significant benefit in primary composite outcome of need for hospitalization, emergency room visit, and death [109-111]. It also showed significant reduction in the all-cause mortality [110-111], need for hospitalization [109-110, 112], duration of hospitalization [110, 112], need for oxygenation [112], symptom resolution at day 15 [109], and mean reduction in viral load compared to placebo [109].
- There was no significant difference in need for mechanical ventilation [112], intensive care unit (ICU) admission [109, 112], symptom resolution at day 7, symptom resolution at day 11, and viral clearance [109-111].
- There was no significant difference in adverse events and serious adverse events between the two groups [109-111].

WHAT'S NEW IN THIS VERSION?

This version includes two new published randomized controlled trials.

Q11. Among COVID-19 patients, should casirivimab-imdevimab be used for treatment?

As of 15 March 2023

RECOMMENDATION

We suggest the use of casirivimab-imdevimab as an alternative to anitivirals* among symptomatic, non-hospitalized COVID-19 adult patients with risk factor for severe disease,** only when the predominant circulating variant is not Omicron SARS-CoV-2. (*Very low certainty of evidence, Weak recommendation)*

**When other drugs (i.e. molnupiravir and paxlovid [nirmatrelvir-ritonavir]) are contraindicated*
***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 the use of casirivimab-imdevimab as treatment for hospitalized COVID-19 patients. (*Very low certainty of evidence, Strong recommendation)*

RECOMMENDATION

We recommend against the use of casirivimab-imdevimab as treatment for asymptomatic, non-hospitalized patients. (*Very low certainty of evidence, Strong recommendation)*

RECOMMENDATION

We recommend against the use of casirivimab-imdevimab as treatment for in children with COVID-19. (*Very low certainty of evidence, Strong recommendation)*

Consensus Issues

The consensus panel suggested the use of casirivimab-imdevimab as an alternative to antivirals (e.g. molnupiravir and paxlovid [nirmatrelvir-ritonavir]) only among symptomatic, non-hospitalized adults with at least one risk factor for severe disease, based on very low certainty of evidence. This is based on the evidence that it had a significant benefit in terms of need for hospitalization and duration of COVID-19 symptoms. The panel however recognizes that all the randomized controlled trials (RCTs) used in the evidence were done at a time before the Omicron SARS-CoV-2 became predominant. Indirect evidence from in-vitro studies showed that casirivimab-imdevimab is ineffective against the Omicron variant, hence the additional caveat about the predominant circulating variant.

The panel also considers that casirivimab-imdevimab is costly and will entail additional costs for its intravenous administration. Additional expenses include emergency room fees and doctor's fees, which may vary across different hospitals. Hence, casirivimab-imdevimab should be reserved for patients in whom more cost-effective drugs are contraindicated due to allergy or adverse effects, and only when the predominant circulating variant is not Omicron SARS-CoV-2.

On the other hand, the panel strongly recommended against the use of casirivimab-imdevimab among non-hospitalized adults with asymptomatic COVID-19 and hospitalized adults with moderate to severe COVID-19. Current evidence showed that in these subgroup of patients, casirivimab-imdevimab had no benefit in any of the critical outcomes. The panel also considered its ineffectiveness against the Omicron variant, availability of more cost-effective drugs against COVID-19 and its prohibitive cost.

Lastly, the panel strongly recommended against the use of casirivimab-imdevimab in children with COVID-19 due to insufficient evidence that it has benefit in the pediatric population. There was only one RCT including 26 patients with asymptomatic COVID-19 and result was inconclusive in terms of development of COVID-19 symptoms. No other outcomes were reported, including harm.

KEY FINDINGS

- Seven (7) RCTs evaluated the efficacy of casirivimab-imdevimab as treatment for patients with COVID-19 [113-119].
- Casirivimab-imdevimab did not improve all cause-mortality nor the need for mechanical ventilation [114-118].
- Casirivimab-imdevimab significantly reduced viral load clearance, but only among those infected with delta variant, with slower clearance rate for those infected by Omicron variant [119].
- Among hospitalized patients given casirivimab-imdevimab, there was no significant difference in clinical improvement and/or discharge at day 28.
- Casirivimab-imdevimab showed significant benefit in terms of decreasing the risk of hospitalization, COVID-19 related medically attended visit (MAVs), and duration of symptoms among symptomatic outpatients, but not among asymptomatic outpatients.
- Among seronegative asymptomatic outpatient children, there was likewise no significant benefit when given casirivimab-imdevimab [116].
- Casirivimab-imdevimab had significantly less reported adverse and serious adverse events compared to those who received placebo/standard of care.
- The overall certainty of evidence was rated very low because of serious risk of bias, indirectness, inconsistency, and imprecision of results.

WHAT'S NEW IN THIS VERSION?

This version includes data from one (1) new pre-print randomized clinical trial and 5 of the previous pre-prints have been published.

Q12. Among COVID-19 patients, should tixagevimab-cilgavimab be used for treatment?

As of 12 December 2022

RECOMMENDATION

We suggest the use of tixagevimab-cilgavimab as treatment for unvaccinated non-hospitalized patients with mild to moderate COVID-19 with at least 1 risk factor* for progression to severe disease. (*Very low certainty of evidence, Weak recommendation)*

**Risk factors for severe COVID-19: age ≥65 years, body-mass index ≥35kg/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*

RECOMMENDATION

We suggest the use of tixagevimab-cilgavimab as treatment for unvaccinated hospitalized COVID-19 patients in addition to standard of care. (*Low certainty of evidence, Weak recommendation)*

RECOMMENDATION

We suggest against the use of tixagevimab-cilgavimab among children with COVID-19. (*Very low certainty of evidence, Weak recommendation)*

Consensus Issues

The consensus panel gave a weak recommendation supporting the use of tixagevimab-cilgavimab among unvaccinated, non-hospitalized and hospitalized adult patients with COVID-19 due to low certainty of evidence, applicability issues, and the drug's prohibitive cost. The panel emphasized that both trials on tixagevimab-cilgavimab were done at a time when Delta was the predominant variant, hence the results may have limited applicability because Omicron is now the predominant variant locally. The panel also highlighted the fact that the benefits are among the unvaccinated patients, while most of the patients in our country are already vaccinated. The cost of a full treatment course consisting of one (1) intravenous dose of tixagevimab-cilgavimab was estimated at around ₱28,000 based on an international report. The panel saw that there are more cost-effective treatment options presently available in the local market. Clinicians are advised to ensure due diligence in discussing with their patients the drug's perceived benefits in light of the low certainty of evidence and the trials' applicability issues.

Since there are no available studies of use of tixagevimab cilgavimab among children, and no FDA approval has been granted, suggesting against the use of the drug among children will be more beneficial.

KEY FINDINGS

- There were two randomized controlled trials that compared tixagevimab-cilgavimab against placebo as treatment for COVID-19 infection [120-121].

- Tixagevimab-cilgavimab significantly reduced death (all-cause mortality) at day 28 (RR of 0.65, 95% CI 0.46-0.93) and day 90 (RR of 0.72, 95% CI 0.53-0.97) compared to those given placebo.
- There was no significant difference in the risk of adverse events (RR 0.91, 95% CI 0.74-1.11) and serious adverse events among those given tixagevimab-cilgavimab compared to the placebo group (RR 0.72, 95% CI 0.50-1.04) [120-121].
- The overall certainty of evidence was rated very low due to serious risk of bias downgraded for indirectness, attrition bias, inconsistency, and imprecision in one critical outcomes (all-cause mortality) among non-hospitalized patients.
- No available studies are available for children and adolescents.

Q13. Among COVID-19 patients, should sotrovimab be used for treatment?

As of 16 January 2023

RECOMMENDATION

We suggest against the use of sotrovimab among children and adult patients with COVID-19. (*Very low certainty of evidence, Weak recommendation*)

Consensus Issues

The consensus panel unanimously voted against the use of sotrovimab in the treatment of both children and adults with COVID-19, based on the drug's ineffectiveness against Omicron variants and the drug's prohibitive cost. Although current evidence showed that sotrovimab had benefit on the composite outcome of death or hospitalization and all-cause hospitalization among non-hospitalized unvaccinated adults at risk for disease progression, recent in-vitro studies demonstrated that similar with other monoclonal antibodies, sotrovimab is ineffective against Omicron variants, particularly BA.2, BA.4 and BA.5. Given that Omicron remains to be the predominant variant locally, this was well considered by the panel, hence the recommendation. Since the drug has not been granted emergency use authorization (EUA) in the Philippines, it is not yet available locally. A full treatment course was estimated to cost US$2,100 (₱115,000), which the panel deemed more costly than other effective and locally available drugs against COVID-19.

KEY FINDINGS

- Two (2) RCTs investigated the effect of sotrovimab as treatment for COVID-19 compared to standard of care or placebo [122-123].
- There was no significant benefit in all-cause mortality, composite outcome of disease progression or mortality, need for mechanical ventilation, clinical improvement, nor virologic clearance with sotrovimab for COVID-19.
- Sotrovimab was shown to have significant effect in the reduction in the composite outcome of hospitalization or all-cause mortality among non-hospitalized COVID-19 patients at risk for progression when administered within 5 days of symptom onset [122].
- Sotrovimab was also shown to have benefit for all-cause hospitalization among non-hospitalized patients [122].
- Sotrovimab had no significant difference for adverse and serious adverse events compared to placebo [122-123].
- The overall certainty of evidence was rated very low because of imprecision, heterogeneity, and indirectness.

Q14. Among COVID-19 patients, should Lianhua be used as treatment?

As of 03 April 2023

RECOMMENDATION

We suggest the use of Lianhua in the symptomatic relief of adult patients with non-severe COVID-19. (Very l*ow certainty of evidence, Weak recommendation)*

RECOMMENDATION

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

Consensus Issues

This recommendation agrees with the FDA's approval for use of Lianhua only for symptomatic relief but not for COVID-19 treatment. The consensus panel suggests the use of Lianhua for the symptomatic relief among adults with non-severe COVID-19, based on a very low certainty evidence that it has benefit in time to symptom recovery and reduction in clinical deterioration. Current evidence in terms of harm remains inconclusive, based on both direct evidence (randomized controlled trials among patients with COVID-19) and indirect evidence (meta-analysis on use of Lianhua on selected non-COVID-19 disease like influenza, Mycoplasma pneumonia and hand-foot-mouth disease). The panel also recognized that the Dangerous Drug Board Committee on Reclassification issued provisional removal of Lianhua Qingwen capsules from the list of dangerous drugs, due to its minimal Ephedra content (9.14mg Ephedra per capsule), posing low or negligible risk of abuse. The dose used in the RCTs were similar to the manufacturer's dose recommendation of 4 capsules 3x/day, however the duration varied across studies, ranging from 7 to 14 days.

On the other hand, the panel unanimously suggested against the use of Lianhua among children with COVID-19 due to lack of good-quality evidence, with only one retrospective non-randomized controlled study available as of writing. The panel also emphasized the potential harm of Lianhua, due to risk of hemolysis among patients with G6PD deficiency and cardiac toxicity due to its Ephedra content, amount of which may not be negligible particularly in young children.

KEY FINDINGS

- Seven (7) randomized controlled trials investigated the effect of Lianhua compared to standard of care as treatment for patients with COVID-19 [124-131].
- Lianhua showed significant benefit in preventing clinical deterioration or progression to severe disease among patients with non-severe COVID-19 [124-128, 131].
- There was no significant benefit in mortality, and day-14 improvement in fever, cough and fatigue [126-129].
- There was no significant difference in adverse events or serious adverse events between the Lianhua and control group [124-125, 127, 129, 131].
- The overall certainty of evidence was rated very low due to very serious risk of bias and serious imprecision in some critical outcomes.
- One retrospective non-randomized controlled study involving children aged 2 months to 13 years with suspected COVID-19 showed that Lianhua increased the

disappearance rates of fever, cough, and expectoration. No significant difference in the disappearance rates of shortness of breath, digestive tract symptoms, nasal obstruction, runny nose was observed [130].

Q15. Among COVID-19 patients, should metformin be used for treatment?

As of 19 March 2023

RECOMMENDATION

We suggest against the use of metformin as treatment for COVID-19.
(L*ow certainty of evidence, Weak recommendation)*

Consensus Issues

No benefit on the critical outcomes of mortality and hospitalization were seen on the use of Metformin for COVID-19 hence the panel suggested against its use for treatment.

KEY FINDINGS

- Metformin did not improve mortality or hospitalization rates of patients with COVID-19 based on two randomized trials [132-133].
- A lower proportion of patients diagnosed with long COVID were seen among patients who were previously treated with metformin for acute COVID-19 [134].
- The rates of serious adverse events were no different between patients receiving metformin and those on placebo [133].
- Overall certainty of evidence was low due to ascertainment of outcome of interest (for long COVID), inconsistency, and imprecision across different outcomes.

Living Recommendations on the Critical Care Management of COVID-19

Q1. Among COVID-19 patients, should intravenous corticosteroids be used in treatment?

As of 25 January 2023

RECOMMENDATION

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

RECOMMENDATION

We suggest the use of methylprednisolone 1-2mg/kg/day for 5 to 10 days as an alternative to dexamethasone among adult patients with severe and critical COVID-19. (*Very low certainty of evidence, Weak recommendation)*

RECOMMENDATION

We suggest the use of dexamethasone at 0.15mg/kg/day or a maximum dose of 6mg per day for up to 10 days among pediatric patients with severe and critical COVID-19. (*Very low certainty of evidence, Weak recommendation)*

RECOMMENDATION

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

RECOMMENDATION

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

Consensus Issues

The available evidence still supports the recommendation of using standard dose dexamethasone for up to 10 days for adult patients with severe and critical COVID-19. In the pediatric population, there is very limited data on the use and its adverse events in COVID-19. This present recommendation was also cross referenced with the existing local guidelines from the Pediatric Infectious Disease Society of the Philippines (PIDSP).

KEY FINDINGS

- The use of intravenous methylprednisolone when compared with intravenous dexamethasone demonstrated significant reduction in mortality, marginal clinical improvement measured using the WHO Ordinal Scale for Clinical Improvement, and reduction in inflammatory markers [1, 2-13]. However, other clinical outcomes such as need for mechanical ventilation, oxygen support escalation, and need for intensive care unit admission were all inconclusive. Overall certainty of evidence was very low.
- The use high-dose dexamethasone (>12mg per day) when compared with the standard (6-12mg per day) dosing regimen did not show benefits in terms of all-cause mortality at 28, 60, and 90 days, need for mechanical ventilation, ventilator-free days, and incidence of serious adverse events which include secondary bacterial and fungal infection, hyperglycemia, and thrombotic events [18-23]. Overall certainty of evidence was moderate.
- In terms of the timing of corticosteroid initiation, pooled data showed a trend towards reduction in mortality for early (within 24 hours of admission) initiation of corticosteroids. Incidence of mechanical ventilation was likewise reduced when corticosteroids are initiated early on admission [24-31]. Overall certainty of evidence was very low.
- Safety and effectiveness of corticosteroids for COVID-19 have not been adequately evaluated in clinical trials with pediatric patients. Multivariable regression analysis in one multinational prospective cohort study in pediatric critical COVID-19 patients without multisystem inflammatory syndrome showed that the effect of dexamethasone or methylprednisolone on mortality was inconclusive [32]. Overall certainty of evidence was very low.

WHAT'S NEW IN THIS VERSION?

This review includes evidence updates on the use of intravenous methylprednisolone versus dexamethasone (4 new randomized controlled trials) [14-17], standard-dose at 6-12mg per day versus high-dose dexamethasone at >12mg per day (6 new randomized controlled trials) [18-23], and early (or within 24 hours of admission) versus non-early (more than 24 hours of admission) initiation of corticosteroids [24-31] (1 new retrospective cohort study) [27] in adult patients with severe and critical COVID-19.

Additionally, new evidence base on corticosteroid, particularly dexamethasone and methylprednisolone, use in pediatric critical COVID-19 patients without multisystem inflammatory syndrome (1 new prospective cohort study) [32].

Q2. Among COVID-19 patients, should anticoagulation be used for treatment?

As of 20 February 2023

RECOMMENDATION

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

RECOMMENDATION

We suggest the use of standard dose prophylactic anticoagulation over intermediate dose prophylactic anticoagulation among hospitalized adults with moderate, severe, or critical COVID-19 disease unless there are any contraindications. (*Low certainty of evidence, Weak recommendation)*

RECOMMENDATION

We suggest against the routine use of any anticoagulation among adults with mild COVID-19 in the outpatient setting unless there is a pre-existing non-COVID indication. (*Low certainty of evidence, Weak recommendation)*

RECOMMENDATION

We suggest the use of oral anticoagulation after hospital discharge among adults admitted for moderate, severe, or critical COVID-19 and who are suspected to have a high risk for VTE at-or-near hospital discharge. (*Low certainty of evidence, Weak recommendation)*

RECOMMENDATION

We suggest the use of prophylactic dose anticoagulation among hospitalized pregnant patients with moderate, severe, or critical COVID-19 disease unless there are any contraindications. (*Very low certainty of evidence, Weak recommendation)*

RECOMMENDATION

We suggest prophylactic dose anticoagulation among hospitalized pediatric patients more than 12 years of age with moderate, severe, or critical COVID-19 or MIS-C unless there are any contraindications. (*Very low certainty of evidence, Weak recommendation)*

Consensus Issues

The presence of moderate, severe, or critical COVID-19 infection increases the risk of microvascular thrombosis in patients hence the use of anticoagulation is suggested. In patients with no evidence of a pre-existing thrombotic event, a prophylactic standard dose is favored as the panel put heavier premium and emphasis on the potential for harm.

In the outpatient setting, mild COVID will carry a lower thrombotic risk compared to hospitalized patients, therefore in the absence of a known thrombotic event,

anticoagulation must be considered only if there are indications since there is potential for serious adverse effects, limited monitoring, and added cost. Indications for its use may include but not limited to: left ventricular thrombus, atrial fibrillation, venous thromboembolism, or CVD infarct.

Only one trial with a low certainty of evidence was available for the use of oral anticoagulation post discharge. The study used Rivaroxaban 20mg tab once a day for 35 days given based on a VTE risk scoring system and D-dimer level prior to discharge.

The panel weakly suggests the use of prophylactic anticoagulation in children as the risk of thrombotic events seems higher for children more than 12 years old and this age group may benefit from the intervention.

KEY FINDINGS

- This updated review on the use of anticoagulants (AC) among patients with COVID-19 made use of evidence from twenty randomized control trials (RCTs), 12 of which are new studies not included in the previous recommendation [33-44].
- Overall, the certainty of evidence was low due to issues in blinding, allocation, imprecision, and significant heterogeneity especially in some of the critical outcomes.
- In the comparison of those receiving full dose (or therapeutic dose AC) versus prophylactic dose (standard low dose to intermediate dose AC), efficacy endpoints show no significant difference in terms of all-cause mortality, organ support-free days, and need for invasive mechanical ventilation while there was evidence to support therapeutic dose AC for incidence of any thrombotic events.
- Safety outcomes on the other hand show that prophylactic dose AC led to significantly less incidence of major bleeding episodes especially among those with severe COVID-19 disease.
- There was no significant difference for other bleeding events not considered major bleeding and heparin-induced thrombocytopenia.
- For those receiving intermediate dose versus standard dose AC, efficacy outcomes showed no significant difference in all-cause mortality and need for invasive mechanical ventilation.
- In preventing the incidence of any thrombotic events, overall, there was no difference between the two groups however in the subgroup of moderate disease, intermediate dose led to less incidence but this effect was highly influenced by one study.
- Safety outcomes showed no significant difference for major bleeding and any bleeding not considered major as well as for heparin-induced thrombocytopenia.
- For patients with mild disease in the outpatient setting, there was no significant difference in terms of efficacy (all-cause hospitalization, all-cause mortality, and any thrombotic events) for those that received AC and those that did not.
- Any bleeding episodes showed no significant difference but those receiving AC at best can receive minimal benefit but at worst can have increased risk of bleeding.
- One study showed that those who received AC while being admitted will benefit with receiving oral AC post discharge as it decreases pooled incidence of mortality and venous thrombotic events (VTE) with no occurrence of bleeding.

- For special populations, no direct evidence was seen among pregnant patients with COVID-19 however data from observational studies showed the same trend of increased risk for VTE for pregnant patients with COVID-19 compared to pregnant patients without the disease. Recommendations are thus based on the general population.
- For the pediatric population, a phase-2 non-randomized single-arm clinical trial showed the safety of enoxaparin use among pediatric patients with moderate to severe COVID-19 and MIS-C. Incidence of VTE and mortality among those receiving anticoagulation were lower in the pediatric population as compared to the adult population.

WHAT'S NEW IN THIS VERSION?

Twelve new RCTs were added to the previous 8 to come up with the evidence presented in this review [33-44].Aside from the comparisons of therapeutic versus prophylactic dose anticoagulation, and intermediate dose and standard dose AC for hospitalized patients with moderate to severe COVID-19, we also present evidence for COVID-19 patients with mild disease in the outpatient setting and patients post-discharge.Similar recommendations are put forward in this review for the first two comparisons as with the previous review while evidence for non-benefit for outpatients and benefit for post-discharge are presented.Recommendation among pregnant women and pediatric populations are included in this review as well.

Q3. Among severe to critical COVID-19 patients, should side lying position be used? Among non-intubated severe COVID-19 patients, should self-proning be used?

As of 22 March 2023

RECOMMENDATION

We suggest awake prone positioning or self-proning in non-intubated adult patients with severe and critical COVID-19. (*Very Low certainty of evidence, Weak recommendation)*

RECOMMENDATION

We suggest prone positioning among intubated adult patients with critical COVID-19 in ARDS. (*Very low certainty of evidence, Weak recommendation)*

RECOMMENDATION

We suggest the use of side lying in non-intubated adult patients with severe and critical COVID-19 who cannot tolerate proning. (*Very low certainty of evidence, Weak recommendation)*

Consensus Issues

A weak recommendation was given on the use of awake prone positioning among non-mechanically ventilated adult patients with severe and critical COVID-19 on the basis of observed benefit in the reduction for the need of mechanical ventilation and absence of serious adverse events (harms of proning), low cost and resources required for the intervention, and equity. The panel further highlighted to consider the contraindications to prone positioning which include: pregnancy, patients with fractures, hemodynamic instability, patients who are unable to perform proning (e.g., obesity, recent abdominal/thoracic surgery), among others. Across the studies reviewed, the duration of the intervention varied from two hours to as long as tolerated with regular monitoring.

Similarly, among mechanically ventilated patients, prone positioning should be done as indicated (in ARDS patients which was reflective of the population in the reviewed studies) and in hemodynamically stable patients. Proper technique, however, should be performed and personnel training should likewise be considered.

The panel also weakly recommended implementing side lying or lateral positioning for patients who cannot tolerate prone positing (evidence was based on only one study who performed side lying after prone positioning). No study was available on side lying alone.

KEY FINDINGS

- Among non-intubated severe patients with COVID-19, pooled results of nine randomized controlled trials showed a statistically significant difference favoring proning in terms of need for intubation [45-53]. There is also a trend towards benefit

for proning in terms of mortality, need for intensive care, length of hospital stay in days, and length of ICU stay in days. Pooled estimates from six RCTs which reported data on adverse events (IV-line dislodgement, pain or discomfort, nausea/vomiting, pressure ulcers, coughing, dizziness, and shortness of breath) and serious adverse events (cardiac arrest, hypotension, desaturation, aspiration pneumonia, and venous thromboembolism) during proning only showed a trend towards harm.

- Two small observational studies of 20 subjects combined with COVID-19 patients associated acute respiratory distress syndrome under mechanical ventilation showed that side lying provided a statistically significant benefit by decreasing the incidence of overdistension and lung collapse, increase in lung compliance, a decrease in driving pressure and transpulmonary driving pressure, and improvement in oxygenation [59-60]. One prospective cohort study of 52 subject with severe, non-intubated COVID-19 patients showed that positioning intervention (prone or lateral) did not show significant statistical difference in terms of rate of intubation and length of hospitalization. The same study showed a statistically significant increase comparing P/F ratio and ROX index before and after doing positional intervention (prone or lateral). [61]
- Proning for critical, mechanically-ventilated COVID-19 patients showed a statistically significant benefit in in-hospital mortality based on one retrospective cohort study with 261 subjects [54]. The same study showed significant statistical improvement comparing oxygenation-saturation index (OSI), oxygenation-index (OI) and arterial oxygen partial pressure to fractional inspired oxygen (PaO_2: FiO_2) before and after doing proning intervention. Four observational single arm studies among critical, mechanically-ventilated COVID-19 patients also showed a significant statistical improvement in P/F ratios before and after doing proning interventions [55-58]. There were no adverse events reported.
- The certainty of evidence for both side lying and proning are very low due to serious risk of bias, substantial heterogeneity, and imprecision.

WHAT'S NEW IN THIS VERSION?

As of November 10, 2022, five new randomized controlled trials (RCTs) [49-53] for proning in awake, non-intubated COVID-19 patients and one retrospective cohort study [54] and 4 single arm observational studies [55-58] for proning in critical, mechanically-ventilated COVID-19 were identified. One prospective observational cohort study and one prospective single arm observational study for side-lying in COVID-19 patients were likewise included in this review to evaluate the effects of proning and side-lying in COVID-19 patients [60-61].

Q4. Among COVID-19 and acute respiratory failure patients, should high flow nasal oxygen therapy be used?

As of 15 March 2023

RECOMMENDATION

We suggest the use of high flow nasal oxygen therapy 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)*

RECOMMENDATION

We suggest the use of either high flow nasal oxygenation therapy or non-invasive positive pressure ventilation in patients with severe to critical COVID-19 who do not respond to conventional oxygen therapy in the absence of any indication for emergent invasive mechanical ventilation. (*Very low certainty of evidence, Weak recommendation)*

RECOMMENDATION

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

Consensus Issues

The panel weakly suggests the use of high flow oxygen therapy after nil or suboptimal response to conventional oxygen therapy (low flow nasal cannula/face mask) which reflects the available evidence where most studies employed sequential oxygen supplementation. It should be noted however that a subset of patients may benefit from immediate intubation and contraindications to high flow nasal oxygen therapy such as facial deformities, uncooperative/combative patients, etc. should likewise be considered. The choice between high flow nasal oxygen therapy and non-invasive positive pressure ventilation will be influenced by the clinical indication (i.e., oxygenation vs. ventilation) and patient acceptability.

KEY FINDINGS

- Eight randomized controlled clinical trials were evaluated which investigated the efficacy of high-flow nasal oxygen therapy (HFNOT) among hospitalized COVID-19 patients with acute respiratory failure [62-69]. HFNOT was compared to conventional oxygen therapy (COT) (face mask, venturi face mask, non-rebreather face mask) and non-invasive ventilation (NIV) (CPAP, Helmet).
- For HFNOT vs COT, pooled results showed benefit with regards to improvement of PaO_2/FiO_2 ratio and changes in respiratory rate among patients who received HFNOT compared to those receiving COT. In addition, a trend towards benefit can be seen in terms of 28-day mortality, need for intubation, length of hospital stay, and length of ICU stay to those in the HFNOT group compared to those in the COT. With regards to changes in heart rate, clinical recovery, and ventilator-free days, no significant difference was found between the two groups. The certainty of evidence is low due to serious risk of bias and imprecision.

- For the comparison between HFNOT and NIV, a trend towards benefit can be observed in patients in the HFNOT group in terms of 28-day mortality. However, with regards to the need for mechanical ventilation, results shows that there is less need for mechanical ventilation in those who were in the NIV treatment group. No significant difference is observed in hospital length of stay and ventilator free days between the two groups. The certainty of evidence is very low due to serious risk of bias, inconsistency, and imprecision.

WHAT'S NEW IN THIS VERSION?

Four new randomized controlled trials were added for this review to evaluate the use of high-flow nasal oxygen therapy (HFNOT) therapy in COVID-19 patients. The previous recommendation was extrapolated from 3 published randomized controlled trials (RCT) and one pre-print RCT. Also, in this review, the studies comparing HFNC to Conventional Oxygen Therapy (COT) and Non-invasive ventilation (NIV) were appraised and examined together [70].

Q5. Among COVID-19-associated acute respiratory distress syndrome patients, should lung protective ventilation, high PEEP, and driving pressure-limited strategies be used?

As of 02 May 2023

RECOMMENDATION

We recommend the use of a lung protective ventilation strategy (tidal volume 4-6mL/kg ideal body weight, plateau pressure less than 30cmH_2O, and an appropriate PEEP) among mechanically ventilated adult patients with COVID-19-associated ARDS. (*Very low certainty of evidence, Strong recommendation)*

RECOMMENDATION

We suggest against the routine use of high PEEP strategy among mechanically ventilated adult patients with COVID-19-associated ARDS. We further suggest to individualize PEEP or employ a PEEP strategy based on respiratory mechanics (i.e., compliance) in patients with COVID-19 infection. (*Very low certainty of evidence, Weak recommendation)*

RECOMMENDATION

We suggest to maintain the driving pressure less than 15cmH_2O among mechanically ventilated adult patients with COVID-19-associated ARDS. (*Very low certainty of evidence, Weak recommendation)*

Consensus Issues

The difficulty of doing high quality studies or randomized controlled trials on critical patients is recognized hence, despite the certainty of evidence in this review, a strong recommendation was given for the use of lung protective ventilation in mechanically ventilated adult patients with COVID-19-associated ARDS. This strategy has been followed and utilized pre-COVID in patients with ARDS.

The immediate use of high PEEP was previously employed and advocated in mechanically ventilated patients to increase oxygenation in patients. However, in recent years, due to the identified harm of barotrauma and lung damage, the strategy has shifted to individualizing the use of PEEP based on the patient's clinical status, respiratory mechanics, and presentation. This is also suggested in the management of COVID-19-associated ARDS based on this review and consensus decision.

Based on the study by Ottolina [18], patients were grouped to higher PEEP strategy when median FiO_2 of 80% (IQR 70-100%) and a median PEEP of 14.7cmH_2O (IQR 13.7-16.7) was used. This follows the operational definition of higher and lower PEEP strategies according to The Acute Respiratory Distress Syndrome Clinical Network (ARDSNet) table.

KEY FINDINGS

- In this evidence review update, we synthesized current evidence on lung protective ventilation, use of higher versus lower positive end-expiratory pressure (PEEP), and driving-pressure limited strategy [71-85].
- For lung protective ventilation, one multicenter retrospective study (PRoVENT COVID) showed that the use of higher tidal volume was associated with similar to higher risk for mortality when compared with lower tidal volume [73]. Certainty of evidence was very low due to non-randomized designs and small sample size.
- Data from two retrospective studies which examined the association of higher PEEP versus lower PEEP levels with mortality among adult patients with COVID-19-related acute respiratory distress syndrome (COVID-19 ARDS) on invasive mechanical ventilation [77-78]. Pooled analysis of two studies showed that the use of higher PEEP when compared to lower PEEP showed no association with all-cause mortality. Subgroup analysis on adult patients with COVID-19 ARDS and acute kidney injury on mechanical ventilation demonstrated that higher PEEP levels was associated with all-cause mortality. Overall certainty of evidence was very low due to risk of bias and imprecision.
- A multicenter observational study demonstrated the association of higher dynamic driving pressure (>14cmH_2O vs 12cmH_2O) during the initial four days of IMV with mortality [85]. Certainty of evidence was very low due to non-randomized designs and small sample sizes.

Q6. Among COVID-19-associated acute respiratory distress syndrome patients, should extracorporeal membrane oxygenation be used?

As of 19 May 2023

RECOMMENDATION

We suggest to offer the use of extracorporeal membrane oxygenation for judiciously selected adult COVID-19 patients with acute respiratory distress syndrome refractory to optimal mechanical ventilation based on the ELSO or NHS England criteria. (*Very low certainty of evidence, Weak recommendation)*

**after careful consideration of cost, resources, expertise available*

RECOMMENDATION

We suggest to offer the use of extracorporeal membrane oxygenation for judiciously selected pediatric COVID-19 patients with acute respiratory distress syndrome refractory to optimal mechanical ventilation based on the ELSO criteria. (*Very low certainty of evidence, Weak recommendation)*

**after careful consideration of cost, resources, expertise available*

Consensus Issues

A suggestion to offer ECMO is given after consideration of the perceived benefits from the available evidence and limitations posed by the intervention. The panel recognizes the cost, resources, and expertise needed to place a patient on ECMO. Sustainability or capacity to maintain on ECMO is likewise important since once ECMO is initiated, it would be difficult to simply withdraw treatment when resources or financial capability is depleted.

KEY FINDINGS

- We reviewed 10 cohort studies which determined the effects of extracorporeal membrane oxygenation (ECMO) among adult patients with COVID-19-associated acute respiratory distress syndrome [86-95]. Overall, the use of ECMO significantly reduced all-cause mortality when compared with optimal ventilator strategy. In propensity-matched analysis, greater association between ECMO and reduction in mortality was observed. However, the use of ECMO was associated with longer duration of mechanical ventilation, duration of intensive care unit stay, and overall length of hospitalization. In terms of adverse events, the use of ECMO was associated with significant coagulopathy, gastrointestinal bleeding, intracranial hemorrhage, pneumothorax, and pulmonary embolism. Six out of 10 cohort studies were assessed to have high risk of bias due to issues of comparability of intervention and control groups while four out of 10 cohort studies were assessed to have low risk of bias. Overall certainty of evidence downgraded to very low due to risk of bias and inconsistency. All outcomes included in this review were in-hospital outcome measures.

- We reviewed 13 observational studies which described the effects of ECMO among children with COVID-19 ARDS [96-109]. Overall, the mortality among children with COVID-19 ARDS who received ECMO was 23.08% by summation. However, the association was not statistically significant. Serious adverse events observed with the use of ECMO were acute kidney injury, cerebral hemorrhage, cerebral infarction, circuit thrombi, pneumothorax, pulmonary hemorrhage, gastrointestinal bleeding, pulmonary embolism, right atrial thrombosis, and seizures. Overall certainty of evidence was very low due to risk of bias and imprecision.

Q7. Among long COVID-19 patients with residual pulmonary symptoms, should pulmonary rehabilitation be done to improve pulmonary function and quality of life?

As of 03 April 2023

RECOMMENDATION

We suggest individualized pulmonary rehabilitation with pre-intervention medical clearance for patients with long COVID syndrome who show residual pulmonary symptoms to improve pulmonary function and quality of life. (*Low certainty of evidence, Weak recommendation)*

Consensus Issues

Pulmonary rehabilitation is a multi-component and a multi-disciplinary process which aims to improve functionality and quality of life. This non-pharmacologic intervention, however, may not be available in all centers especially in smaller institutions. Despite this, and although the included studies had small sample sizes and there was high heterogeneity in intervention strategies, the documented harms are very low and the balance of effects favors the perceived benefits (both in respiratory and non-respiratory outcomes).

KEY FINDINGS

- A total of five randomized controlled clinical trials were evaluated which investigated the effect of pulmonary rehabilitation on the pulmonary function and quality of life among long COVID patients with residual pulmonary symptoms [110-114].
- Pooled results showed significant benefit on pulmonary function test (FEV, FVC, and FEV1/FVC) as well as an increase in exercise capacity and physical fitness score after PR as shown by a higher 6MWT and VO_2max in those who underwent pulmonary rehabilitation (PR).
- Other than this, participants in the PR group showed significant improvement in health-related QoL scores across all domains after the intervention and a significantly lower post-intervention self-rated anxiety score compared to the control group.
- Lastly, with regards to safety outcomes, the most common symptoms experienced ranged from chest tightness, cough, and weakness with chest tightness occurring more in the PR group.
- Certainty of evidence was very low because of serious risk of bias and imprecision in most of the critical outcomes

Q8. Among multisystem inflammatory syndrome in children (MIS-C) patients, should intravenous immunoglobulin (IVIg) and steroids be used?

As of 19 May 2023

RECOMMENDATION

We suggest the use of steroids (methylprednisolone) among children diagnosed with multisystem inflammatory syndrome in children. (*Very low certainty of evidence, Weak recommendation)*

RECOMMENDATION

We suggest to offer the use of IVIg in combination with steroids among children diagnosed with multisystem inflammatory syndrome associated with significant organ involvement*. *(Very low certainty of evidence; Weak recommendation)*

**Based on six cohort studies, patients with MIS-C who received combination of steroids and IVIg had more severe initial presentation, with more frequent initial acute left ventricular dysfunction, ICU care upon admission, and requirement of hemodynamic support upon admission [16]; higher troponin levels, and higher need for inotropes upon admission [10]; high proportion of patients with abnormal inflammatory mediators on admission [14]; lower mean ejection fraction at baseline, lower platelet counts, and higher CRP and ferritin [15]; significantly more extensive organ involvement (higher frequency of respiratory, ocular and cardiovascular involvement) [20]; and higher cases of severe MIS-C, lower platelet and lymphocyte count, and higher CRP [19]*

Consensus Panel Issues

It is recognized that MISC and Kawasaki Disease in children have similarities hence the use of steroids and IVIg was postulated to improve outcomes for MISC. However, the available evidence shows benefit only for steroids with inconclusive results for the use of IVIg. Combination therapy may be offered in MISC with significant organ involvement but it is important to note that this is based only on six cohort studies (very low certainty of evidence) and only with a trend towards benefit on non-critical outcomes. The presence of concomitant Kawasaki Disease should be ascertained and identified as this would entail the use of IVIg which is considered standard of care.

KEY FINDINGS

- One randomized controlled trial (RCT) [116] compared the use of steroid versus IVIg in the treatment of MIS-C. A significant decrease in need for respiratory support, a critical outcome, was noted in patients given steroids alone. Moreover, there is no significant difference between steroids and IVIg in terms of presence of serious adverse events, length of hospital stay, need for intensive care unit (ICU) admission, and duration of respiratory support. Quality of evidence was very low due to presence of serious risk of bias due to lack of blinding in the patients, caregivers, and outcome assessors, low sample size, and use of a single small study.
- Seven retrospective cohort studies [115, 117-122] explored the effect of IVIg plus steroid versus IVIG alone in the treatment of children diagnosed with MIS-C. IVIg plus steroids showed significantly less persistent fever and reduced need for adjunctive therapy, which were both important outcomes. Meanwhile, the

combined therapy did not show significant difference in reducing mortality, need for mechanical ventilation, hospital length of stay, need for ICU admission, and the need for vasopressor versus IVIg alone. Evidence has serious risk of bias, due to the study design, imprecision, and inconsistency of the outcomes hence the quality is very low.

- Four retrospective cohort studies [117-118, 121, 123] compared the use of steroid alone versus the combined IVIg plus steroid in the treatment of MIS-C. There was no noted significant difference between the two groups in any the critical and important outcomes: mortality, need for mechanical ventilation, hospital length of stay, need for ICU admission, need for vasopressors, persistence of fever and need for adjunctive therapy. However, there was a trend towards benefit with the combined IVIg plus steroid in the need for ICU admission and trend towards benefit with steroids alone in terms of persistence of fever. Quality of evidence was very low due to the serious risk of bias due to the study design, imprecision, and inconsistency of the outcomes.
- Pertinent in the population used for the combined IVIg plus steroid group in six cohort studies (Parts 2 and 3), was the significant organ involvement and a more severe disease presentation upon admission.

Living Recommendations on Vaccines

Q1. Among persons of high-risk, what is the clinical and immunologic efficacy, effectiveness, and safety of a first booster (third) dose?

As of 23 March 2023

RECOMMENDATION

Among the **immunocompromised**, we suggest the use of the following COVID-19 vaccines as **homologous** booster at least two months after the primary series.

a. monovalent BNT162b2 (Pfizer-BioNTech) (*Very low certainty of evidence, Weak recommendation)*
b. monovalent mRNA-1273 (Moderna) (L*ow certainty of evidence, Weak recommendation)*

RECOMMENDATION

Among the **elderly**, we suggest the use of the following COVID-19 vaccines as **homologous** booster at least two months after the primary series:

a. monovalent BNT162b2 (Pfizer-BioNTech) (*Very low certainty of evidence, Weak recommendation)*
b. AdCOV2.S (Janssen)/ AdCOV2.S (Janssen) (*Very low certainty of evidence, Weak recommendation)*

RECOMMENDATION

Among **immunocompromised population** we suggest the following heterologous booster vaccination regimen:

a. mRNA-based / mRNA-based (*Very low certainty of evidence, Weak recommendation)*
b. mRNA-based / ChAdOx1 **(AstraZeneca) booster** (*Very low certainty of evidence, Weak recommendation)*
c. BNT162b2 (Pfizer-BioNTech) / **monovalent mRNA-1273 (Moderna) booster** (*Very low certainty of evidence, Weak recommendation)*
d. mRNA-based / Ad26.CoV2.S (**J&J) booster** (*Very low certainty of evidence, Weak recommendation)*
e. AstraZeneca first dose, CoronaVac second dose / **monovalent Moderna or Pfizer booster** (*Very low certainty of evidence, Weak recommendation)*
f. **AstraZeneca / monovalent Moderna or Pfizer booster** (*Very low certainty of evidence, Weak recommendation)*
g. CoronaVac / **monovalent Pfizer booster** (*Very low certainty of evidence, Weak recommendation)*

RECOMMENDATION

Among the **immunocompromised population, there is insufficient evidence to recommend** the following heterologous booster vaccination regimen due to insufficient evidence:

a. Janssen / **monovalent Moderna or Pfizer booster** (*Very low certainty of evidence, Weak recommendation)*
b. CoronaVac primary ***/*** **monovalent *Moderna*** (*Very low certainty of evidence, Weak recommendation)*

RECOMMENDATION

Among the **elderly population**, we suggest the following heterologous COVID-19 booster vaccination regimen:

a. ChAdOX (AstraZeneca) Primary / **mRNA-based** (*Very low certainty of evidence, Weak recommendation)*
b. BNT162b2 (Pfizer BioNTech) or mRNA1273 (Moderna) or ChAdOx1Oxford-AstraZeneca or Ad26CoV2 (J&J) / **mRNA-based** (L*ow certainty of evidence, Weak recommendation)*
c. mRNA-based vaccine / **mRNA-based booster**(*Very low certainty of evidence, Weak recommendation)*
d. CoronaVac Primary / **monovalent BNT162b2 (Pfizer-BioNTech)** (*Very low certainty of evidence, Weak recommendation)*
e. CoronaVac Primary / **ChAdOX (AstraZeneca)** (*Very low certainty of evidence, Weak recommendation)*

Consensus Issues

The Panel only considered the monovalent version of the Pfizer vaccine in this updated recommendation. This was due to the limited evidence available for bivalent Pfizer vaccine as a first booster (third dose).

KEY FINDINGS

Homologous vaccine booster in the immunocompromised

- In immunocompromised adults, there were 34 observational studies (five from the previous update) on the effectiveness, immunogenicity, and safety of homologous **monovalent BNT162b2 (Pfizer-BioNTech)** vaccine as booster [2-36]. It showed reduced incidence of confirmed symptomatic COVID-19, COVID-19-related hospitalization, severe COVID-19, and COVID-19-related mortality compared with those not given a booster. Humoral response, but not cellular response, was observed to increase after a booster dose. Reported serious adverse events (SAEs) were not increased after a booster dose.
- For homologous **monovalent mRNA-1273 (Moderna**) booster in immunocompromised adults, there was one RCT [37] and four observational studies [5, 10, 25, 38] that investigated its efficacy or effectiveness, immunogenicity, and safety. It resulted in reduced incidence of severe or critical COVID-19, COVID-19 infection, and increased immunogenicity compared with no booster. It also showed increased risk of local, mild adverse events (pain and swelling) with no interference in daily activities.

- Immunocompromising conditions included hematologic, oncologic and breast malignancies, liver cirrhosis, chronic kidney disease requiring dialysis, HIV and organ transplant.
- Overall certainty of evidence was very low for monovalent BNT162b2 (Pfizer-BioNTech) due to serious risk of bias from confounding and outcome measurement biases, indirectness, inconsistency in immunogenicity outcomes across studies, and imprecision. For mRNA-1273 (Moderna), overall certainty of evidence was low due to imprecision and indirectness.

Homologous vaccine booster in the elderly

- There were five (2 cohort and 3 before-after studies) on **monovalent BNT162b2 (Pfizer-BioNTech**) as first booster in the elderly population [39-43], some with underlying chronic medical conditions and living in nursing homes. It showed reduced incidence of COVID-19 infection, severe COVID-19, COVID-19-associated hospitalization and COVID-19-related mortality compared to no booster. It also showed increased humoral and cellular responses, except in COVID-19-recovered elderly. There were no SAEs nor adverse events reported. Overall certainty of evidence was very low due to risk of bias, inconsistency, indirectness, and imprecision.
- One RCT (ENSEMBLE2) on **Ad26.COV2.S (Janssen)** as a booster [44] included adults and elderly, Data were not available for subgroup analysis of the elderly and immunocompromised. It showed no difference in incidence of moderate to severe-critical COVID-19, and severe to critical COVID-19 compared to no booster. It also showed increased antibody response and reduced risk of hypersensitivity reaction and unsolicited vaccine-related adverse events compared to no booster but no differences in SAEs, hemorrhagic, embolic and thromboembolic adverse events compared to no booster. Overall certainty of evidence was low due to attrition bias, indirectness, and imprecision.

Heterologous vaccine booster in the immunocompromised

- All studies found on the **mRNA-based vaccine** for this population used the monovalent vaccine [45-68]. It was used as heterologous booster to the following:
  - **ChAdOx1 (AstraZeneca) or CoronaVac as primary series** did not show any difference in the risk for COVID-19 mortality and COVID-19-related pneumonia compared to no booster. It reduced the risk of COVID-19-related hospitalization but increased the risk of requiring mechanical ventilation during COVID-19 infection. It enhanced humoral immune response, with increased anti-Receptor Binding Domain (anti-RBD) IgG titer and SARS-CoV2 Spike-1 IgG response as well as the cellular immune response. The risk for adverse events increased compared to no booster. Pain and tenderness on the injection site, myalgia and fatigue were the most common adverse events.
  - **ChAdOx1 (AstraZeneca) as primary vaccine** had no reported COVID-19-related deaths but with mild COVID-19 infection in observational studies. It increased immunogenicity responses and increased incidence of adverse events compared to no booster.

  - **CoronaVac as a primary series**, based on an observational study had no reported cases of COVID-19 infection.
  - **Ad26.COV2.S (Janssen) primary series** had pain on injection site and fatigue as the most commonly reported adverse events.
  - **viral vector (ChADOx1 AstraZeneca or Ad26.COV2.S Janssen) primary series** had increased neutralizing antibodies based on a preprint cohort study.
- Monovalent mRNA1273 (Moderna) was heterologous booster to the following:
  - **BNT162b2 (Pfizer-BioNTech) primary series**, wherein there were cases of COVID-19 infection reported in an observational study. It increased humoral response: anti-RBD IgG titer, seroconversion, neutralizing antibody against COVID-19, and SARS-CoV2 Spike-1 antibody compared to no booster.
  - **Ad26.COV2.S (Janssen) or BNT162b2 (Pfizer-BioNTech) as primary series** and had no SAEs reported by an observational study.
- The monovalent BNT162b2 (Pfizer-BioNTech) was heterologous booster to the following:
  - **ChAdOx1 primary series**, wherein observational studies reported to have increased seroconversion from pre- to post-booster. The detection of neutralizing antibodies also increased specifically against the SARS-CoV2 Omicron variant compared to no booster.
  - **CoronaVac primary series** increased the neutralizing antibodies against SARS-CoV2 compared to no booster.
- Ad26.COV2.S (Janssen) was studied as heterologous booster to the following:
  - **BNT162b2 primary series**, had no reported COVID-19 infection in observational studies. It increased seroconversion and neutralizing antibodies against SARS-CoV2 but not the SARS-CoV2 Spike-1 antibody response compared to no booster.
  - **mRNA-based primary series** increased the anti-RBD IgG titer. It did not increase the risk for adverse events compared to no booster.
- ChAdOX1 recombinant (AstraZeneca) booster with mRNA-based primary vaccines increased humoral and cellular response compared to no booster.
- For the viral vector booster and mRNA-based vaccine combination, anti-RBD IgG titer increased as reported in an observational study [51].
- Studies included immunocompromised populations with varying conditions: autoimmune diseases on immunosuppressants, solid organ and oncohematological malignancies, chronic kidney disease with on-going dialysis, and those solid organ transplant (heart, lung, hepatic) recipients. There were several studies that described the presence of co-morbidities or underlying chronic illnesses such as diabetes, hypertension, cardiovascular disease, stroke, heart failure, renal disease or failure, respiratory illness, and liver disease. However, no subgroup analysis was done for the presence of these comorbidities.
- Overall certainty of evidence was very low to low due to serious risk of bias, indirectness, and imprecision. The sole RCT was rated to have moderate certainty of evidence.
- There was no evidence on the use of the following vaccines as first booster in high-risk population: bivalent mRNA-based vaccines, Sinopharm BBIBP, Bharat, Biotech BBV152 COVAXIN/BBV152, Cansino Biologics Ad5-nCoV-S

(recombinant), Novavax NVX-CoV2373, NVX-CoV2372 Nuvaxovid, and Sputnik V vaccine/Gamaleya/Gam-COVID-Vac as booster.

Heterologous vaccine booster in the elderly

- All studies found on the **mRNA-based vaccine** [BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna)] for the elderly population used the monovalent vaccine [1, 53, 64, 66]. It was used as heterologous booster for the following:
  - **ChAdOx1-S (AstraZeneca) primary series**, one cohort study showed reduced risk for COVID19-related mortality, severe COVID-19 infection and COVID19 infection of any degree. There were no immunogenicity and safety studies.
  - **BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) or ChAdOx1 (AstraZeneca) or Ad26.COV.2 (Janssen) as primary series**, one cohort study showed increased risk of COVID-19 infection, but reduced risk of COVID-related hospitalization and ICU-admission. The elderly population in this study all had chronic heart failure. There were no immunogenicity and safety studies.
- For mRNA-1273 (Moderna) booster following the first dose mRNA-1273 (Moderna) and second dose BNT162b2 (Pfizer-BioNTech) vaccine as primary. There was no reported SAE although systemic adverse events were described to occur in one-third of patients after a booster in one before-after study. There were no effectiveness and immunogenicity studies.
- With monovalent BNT162b2 (Pfizer-BioNTech) as the heterologous booster to CoronaVac primary vaccine, one before-after study showed rise in anti-RBD IgG titer and neutralizing antibodies.
- For ChAdOx-1 (AstraZeneca) as a booster following CoronaVac primary series, the anti-RBD IgG titer and neutralizing antibodies inhibiting SARS-CoV2 increased. No effectiveness and safety outcomes were available.
- The certainty of evidence was very low due to serious risk of bias, and indirectness except for one cohort study on mRNA-based booster with varying combinations of primary vaccine series rated as low.

Heterologous or Homologous mRNA-based booster

- For monovalent mRNA-based vaccine booster with unspecified mRNA-based primary, it demonstrated reduced likelihood of COVID-19 associated hospitalization compared to no booster (VISION study) [68].

WHAT'S NEW IN THIS VERSION?

Homologous booster

There were 38 new studies included in this review. Out of the 10 studies from the previous evidence summary (December 2021), three were excluded because they assessed immunogenicity studies earlier than two months after the primary series or participants were included in another study (duplication). There was one published conference abstract only on the efficacy and safety of Novavax COVID-19 vaccine as homologous booster (NVX-CoV2373) which could not be retrieved (Anez et al.)

In the immunocompromised, new studies on monovalent mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech) as a booster still showed reduced risk of COVID-19, and safety of the vaccines, with low and very low certainty of evidence, respectively.

In the elderly population, five studies on monovalent BNT162b2 (Pfizer-BioNTech) (two cohort and three before-after studies) showed reduced risk of COVID-19 mortality, hospitalization, severe COVID-19, increased immunogenicity, and without reported serious adverse events. One RCT (ENSEMBLE2) on Ad26.COV2.S (Janssen) showed increased immunogenicity with decreased risks of adverse events. There were no studies in the elderly in the previous update. Certainty of evidence for these studies were rated very low.

There are additional recommendations for the use of monovalent BNT162b2 (Pfizer-BioNTech) and Ad26.COV2.S (Janssen) as booster vaccines in the elderly population with and without underlying medical conditions.

Heterologous booster

There were 25 new studies included in this review, conducted from 2021 to 2022. Out of the six studies from the previous evidence summary, five were excluded because they were case series and one wherein the fourth dose was considered as the booster. The review now includes studies on the elderly population (n=4 studies). For the immunocompromised population, there are 22 studies. Previous evidence presented on immunocompromised population was on immunogenicity alone (1 RCT), whereas currently there are eight studies added on clinical efficacy and effectiveness with very low certainty of evidence. These studies presented evidence on (1) monovalent mRNA-based booster with ChAdOx1 or CoronaVac or Ad26.COV2.S (Janssen) primary vaccine; (2) monovalent mRNA-1273 booster with mRNA-1273 (first dose) BNT162b2 (second dose) as primary vaccine; (3) monovalent mRNA1273 booster with BNT162b2 as primary vaccine; and (4) Ad26.COV2.S or ChAdOx-1 recombinant booster with mRNA-based primary vaccine.

There are additional three recommendations on other primary and heterologous booster vaccination regimens for the immunocompromised population. These include mRNA-based heterologous booster to the following primary vaccines: (1) ChAdOx1 (AstraZeneca) first dose and CoronaVac second dose; (2) ChAdOx1 (AstraZeneca); (3) CoronaVac primary, Pfizer-BioNTech booster; and (4) mRNA-based primary with mRNA-based booster.

There are now recommendations on the elderly population based on new studies with effectiveness, safety, and immunogenicity outcomes.

Heterologous or Homologous mRNA-based booster

One new case-control study (VISION) with monovalent mRNA-based as a booster and mRNA-based vaccines as primary series provided data for effectiveness in the immunocompromised and elderly.

Q2. Among the general population, what is the clinical and immunologic efficacy, effectiveness, and safety of a second booster dose in the prevention of SARS-CoV-2 infection?

As of 02 February 2023

RECOMMENDATION

We suggest the preferential use of the following bivalent vaccines over monovalent mRNA vaccines as 2nd homologous booster among the general population:

a. BNT162b2 Bivalent (Pfizer-BioNTech)
b. mRNA-1273.214 (Moderna)

(*Very low certainty of evidence, Weak recommendation)*

RECOMMENDATION

We suggest the administration of the following second heterologous booster vaccination in the general population:

a. BNT162b2 (Pfizer monovalent)
b. mRNA-1273 (Moderna monovalent)
c. ChAdOx1 (AstraZeneca)

(*Very low certainty of evidence, Weak recommendation)*

RECOMMENDATION

There is no recommendation on the use of the following vaccines as a second homologous booster vaccination in the general population due to insufficient evidence:

a. CoronaVac (Sinovac) (*Very low certainty of evidence; No recommendation)*
b. NVX-CoV2373 (Novavax) (*Low certainty of evidence; No recommendation)*

Consensus Issues

The Panel considered the benefits of increased immunogenicity and seroconversion in voting on the recommendations for both homologous and heterologous booster vaccination regimens. However, the decision to withhold a recommendation on CoronaVac and NVX-CoV2373 as second homologous booster options was due to the limited evidence available.

For populations studied, quasi-experimental studies had a small sample size. In the case-control studies, thousands were involved. However, both types of studies had low certainty of evidence. The Delta and Omicron periods were studied over a 3-month follow-up period. The Panel gave value to use of immunogenicity and clinical outcomes. The recommendation for heterologous vaccines were chosen by the Panel based on waning immunity over time for breakthrough infections and the evidence presented an increase in immunogenicity and effect on seroconversion factor. Epidemiological-wise, there are more beneficial effects. There is a desire to increase immunogenicity.

KEY FINDINGS

- The systematic search done until February 16, 2023 yielded 12 studies on the COVID-19 vaccine second booster to the general healthy adult population. Seven studies on monovalent vaccine [70-65] and five studies on bivalent vaccines [77-81] were found.
- There were no studies on BBIBP-CorV (Sinopharm), Ad26-CoV2-S (Janssen/Johnson&Johnson) and Gam-COVID-Vac (Sputnik V) as second booster dose for the general healthy adult population.
- There was no significant difference in the odds of a COVID-19 associated hospitalization between receiving a second monovalent mRNA (heterologous and/or homologous) booster and not receiving a second booster. (Very Low overall certainty of evidence)
- A homologous second booster vaccination with monovalent BNT162b2 (Pfizer-BioNTech) showed a large 8.5-fold increase in humoral anti-spike protein IgG antibody response with modest cellular response against wild-type, beta, and delta variant in a quasi-experimental study. No serious adverse event related to vaccination were reported in that study. (Very Low overall certainty of evidence)
- One study showed that a homologous monovalent second booster with mRNA-1273 (Moderna) significantly reduced Omicron infection, but protection against hospitalization was not consistent across the Omicron subvariants tested. (Very Low overall certainty of evidence)
- An immunogenicity study showed that CoronaVac (Sinovac) showed a moderate 2.5-fold increase in neutralization antibody response but had low seroconversion against Omicron. (Very Low overall certainty of evidence)
- There was no clinical efficacy data available for NVX-CoV2373 (Novavax) as second booster. Safety outcomes showed no significant difference in the odds of having a local, systemic, and unsolicited adverse reactions between a second booster and a first booster of NVX-CoV2373 (Novavax). Increase in anti-rS IgG titers and neutralization titers were found after the first and second booster vaccination. However, there was not enough data available for a comparison on the immunogenicity outcome. (Low overall certainty of evidence)
- Real-world evidence data of heterologous monovalent second dose booster of either monovalent mRNA-1273 (Moderna), BNT162b2 (Pfizer-BioNTech), or ChAdOX1 (AstraZeneca) showed a significant risk reduction of COVID-19 infection among those who received a second booster vaccination compared to no second booster dose but with no significant benefit against progression to severe COVID-19. An immunogenicity study with monovalent mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech) as a heterologous second dose booster also showed a large-fold increase in anti-spike protein IgG antibody titers and cellular response against the wild-type strain. (Very Low overall certainty of evidence)
- For both bivalent BNT162b2 (Pfizer-BioNTech) and mRNA-1273.214 (Moderna) vaccines given as homologous second booster, one large real-world study showed that receiving a bivalent booster was significantly associated with a lower risk of COVID-19 infection and hospitalization among 18 to 64 years of age compared to no bivalent booster. (Very Low overall certainty of evidence)
- Both types of bivalent mRNA vaccine consistently showed a significantly larger increase in neutralization antibody titers against Omicron variants compared to the monovalent vaccine. (Very Low overall certainty of evidence)

- For the monovalent vaccines, no significant serious adverse events related to vaccination were reported across the studies on heterologous or homologous boosters, while for the bivalent vaccines, real-world safety data noted five reports of myocarditis and four reports of pericarditis. (Very low overall certainty of evidence)

Q3. Among healthcare workers, what is the efficacy and safety of a second COVID-19 vaccine booster dose in preventing COVID-19 infection?

As of 19 December 2022

RECOMMENDATION

We recommend the use of the homologous monovalent BNT162b2 (Pfizer-BioNTech) as second booster dose to prevent symptomatic COVID-19 infection in healthcare workers. (*Very low certainty of evidence; Strong recommendation)*

RECOMMENDATION

We recommend the use of the heterologous mRNA-1273 (Moderna) as a second booster dose to prevent COVID-19 infection in healthcare workers. (*Very low certainty of evidence; Strong recommendation)*

Consensus Issues

The Panel voted on these recommendations considering the significant benefits for this population which commonly encounters individual COVID-19 infection. In particular, evidence leans towards favoring a second booster dose to provide protection against waning immunity and increased protection against breakthrough infection. Additionally, they have positive economic implications, allowing for preservation of work productivity, due to decreased absences and availability of healthcare workers to render COVID-related and other medical services.

KEY FINDINGS

- Evidence as of November 2022 coming from one open-labeled, non-randomized clinical trial and two multicenter prospective cohort studies (two published [82, 84] and one preprint [83]) on the efficacy and safety of the COVID-19 vaccine second booster dose in healthcare workers (HCW) suggest that the monovalent BNT162b2 (Pfizer-BioNTech) homologous second booster significantly decreased the risk of symptomatic COVID-19 breakthrough infection but not for any breakthrough infection. Significant increases in anti-SARS-CoV-2 and neutralizing antibody titers were noted after administration of the second BNT162b2 booster dose.
- Very low-quality evidence from one study suggests that the heterologous monovalent mRNA-1273 (Moderna) second booster has no effect on the risk for any breakthrough infection or symptomatic breakthrough infection. Significant increases in anti-SARS-CoV-2 and neutralizing antibody titers were noted after administration of the mRNA-1273 booster dose compared to the control group. Most reported second booster adverse events were mild.
- There were no reported serious adverse events for both monovalent BNT162b2 (Pfizer-BioNTech) and monovalent mRNA-1273 (Moderna) as second boosters.
- There is no available evidence on the use of CoronaVac, ChAdOx1, BBV152, Ad26.CoV2.S and other vaccines as a second booster in health care workers.

Q4. Among persons of high-risk, what is the clinical and immunologic efficacy and safety of a third booster dose?

As of 23 March 2023

RECOMMENDATION

No recommendation can be made on the use of a third booster dose of COVID-19 vaccine (to complete 5 vaccine doses) for the high-risk population because there is no available evidence**.** *(No evidence; no recommendation)*

KEY FINDINGS

- The current evidence base, as of March 6, 2023, found no published studies on third booster doses in high-risk population as there are no completed studies with its full results including indirect evidence in the healthy population and health care workers.

Q5. Among adults with previous infection, what is the clinical and immunologic efficacy and effectiveness and safety of a booster?

As of 06 March 2023

RECOMMENDATION

Among adult individuals with previous COVID-19 infection who received standard doses of COVID-19 vaccine primary series, we suggest the use of a **homologous** first booster dose of monovalent mRNA vaccines. (*Very low certainty of evidence, Weak recommendation)*

RECOMMENDATION

Among adult individuals with previous COVID-19 infection who received standard doses of COVID-19 primary vaccine series, there is no recommendation for the use of a **heterologous** first booster dose of monovalent mRNA vaccines due to insufficient evidence. *(Very low certainty of evidence; No recommendation)*

Consensus Issues

The Panel opted to withhold a recommendation for heterologous vaccination due to the evidence having very low certainty. Indirect evidence was used when considering heterologous vaccination, with no studies looking into severe COVID-19 outcomes, actual adverse events, and other safety issues arising from boosters among those with previous COVID-19 infection.

KEY FINDINGS

- There were 4 observational studies [85-88] and 3 RCTs [89-91] that investigated the effect of monovalent mRNA booster dose among individuals with previous infection compared to those with 2 doses (primary series) and had not received a booster dose.
- A homologous booster dose of mRNA vaccine showed significant reduction in the odds of BA.1, BA.2 and any Omicron infection, regardless of variant. The odds of

severe, critical or fatal BA.1, BA.2 and any Omicron infection, were not significantly reduced.

- A heterologous booster of mRNA vaccine demonstrated significant harm for BA.1, BA.2 and any Omicron infection, regardless of variant.
- A booster dose of an mRNA vaccine with unspecified primary series combinations, did not show a significant difference in the odds of having Omicron BA.2 COVID-19 infection. One study showed that the odds of hospitalization due to Omicron infection were four-fold higher.
- Indirect evidence for the safety of a booster dose of an mRNA vaccine was evaluated from two RCTs on healthy individuals and one that included a few individuals with evidence of current or previous COVID-19 infection. A homologous booster dose of BNT162b2 did not show a significant reduction in the risk of all adverse events, serious adverse events and mortality. A heterologous booster dose of either BNT162b2 or mRNA-1273, showed no significant difference in the risk of serious adverse events but significantly increased risk of all adverse events which mostly mild (Grade 1).
- All studies had serious risk of bias due to selection, misclassification, unblinding and attrition. The risk of bias contributed to further downgrading of evidence to very low certainty due to inconsistency, indirectness and imprecision.

Q6. Among adolescents 12 to 17 years old, what is the efficacy, effectiveness and safety of COVID-19 vaccine in preventing COVID-19 infection?

As of 23 March 2023

RECOMMENDATION

We suggest the use of the BNT162b2 (Pfizer-BioNTech) vaccine, [given as 0.3mL (30ug) intramuscular injections, in 2 doses, 21 days apart] for healthy children 12 to 17 years old to prevent symptomatic SARS-CoV-2 infection. (L*ow certainty of evidence; Weak recommendation)*

RECOMMENDATION

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

RECOMMENDATION

There is insufficient evidence to recommend the use of the following for children 12 to 17 years old to prevent symptomatic SARS-CoV-2 infection:
a. ChAdOx1 (AstraZeneca) *(Very low certainty of evidence)*
b. CoronaVac (Sinovac) *(Low certainty of evidence)*
c. BBIBP-CorV (Sinopharm-Beijing) *(Low certainty of evidence)*
d. Recombinant Adenovirus *(Low certainty of evidence)*

RECOMMENDATION

There is insufficient evidence to recommend BNT162b2 in immunocompromised children 12 to 17 years to prevent symptomatic SARS-CoV-2 infection. (Very low certainty of evidence)

Consensus Issues

The Panel opted to specify age groups per vaccine recommendation to reflect the varying age ranges reflected in the available evidence presented for each vaccine. In this update, the Panel opted to change the certainty of evidence for the Pfizer vaccine to reflect the new evidence gathered in the literature search. Additionally, the Panel decided to update the CoronaVac vaccine recommendation wording to insufficient evidence considering the issues of vaccine hesitancy and potential implication of suggesting against vaccination.

KEY FINDINGS

- All retrieved studies were published, which included 4 meta-analyses/systemic reviews [92-95], 7 RCTs [96-102], and 15 effectiveness studies [103-117].
- Low certainty evidence showed that BNT162b2 (Pfizer-BioNTech) was effective, immunogenic and safe in healthy adolescents. There was no new trial on this vaccine in 12 to 17 years. However, there were 12 new effectiveness studies on BNT162b2 (Pfizer-BioNTech) in healthy adolescents. It was protective against infection with any of the variants, with higher protection against Delta than

Omicron. BNT162b2 is protective against hospitalization and emergency and urgent care (high certainty); and critical care and MIS-C (low). Very low certainty evidence from one study noted that BNT 162b2 was also immunogenic in 12 to 21 years old with rheumatic diseases while on immunomodulatory treatment but with possible increased exacerbation of illness.

- Low certainty evidence demonstrated that mRNA-1273 (Moderna) was effective, immunogenic and safe. There was no new trial in mRNA-1273 vaccine. There were two phase 2 trials on vector-based vaccines (ChAdOx1-19 and Ad5 vector COVID-19 vaccine). There were also two phase 1/2 RCTs on safety and immunogenicity of inactivated vaccines (CoronaVac and BBIBP CorV). The RCT on CoronaVac was reported in the previous review.

WHAT'S NEW IN THIS VERSION?

This updated review includes three additional RCTs on the use of COVID-19 vaccine in 12 to 17 years, of which two were vector-based and one inactivated vaccine. They were Phase 1 to 2 clinical trials and reported mostly the immunogenicity and safety of the vaccines. These bring to six the total number of efficacy trials, three of which were included in the original evidence.

There were also 13 effectiveness studies on the use of COVID-19 vaccines among 12 to 17 years, 12 on the healthy population and one on immunocompromised patients which were used as new evidence. Based on the new studies, certainty of evidence on the use of BNT162b2 in the healthy population was downgraded to low with weak recommendation. Evidence for COVID-19 vaccination of immunocompromised children 12 to 17 years old is presented but the evidence is still to recommend BNT162b2 in to prevent symptomatic SARS-CoV-2 infection.

Q7. Among children aged 6 months to 4 years old, what is the clinical and immunologic efficacy and effectiveness and safety of the primary series COVID-19 vaccine?

As of 02 February 2023

RECOMMENDATION

We suggest the use of monovalent **mRNA-1273 (Moderna)** vaccine in children 6 months to 4 years to prevent SARS-CoV-2 infection. (*Very low certainty of evidence, Weak recommendation)*

RECOMMENDATION

We suggest the use of **CoronaVac (Sinovac)** vaccine in children 3 to 5 years to prevent SARS-CoV-2 infection. (*Very low certainty of evidence, Weak recommendation)*

RECOMMENDATION

There is no recommendation on the use of the following vaccines in children 6 months to 2 years to prevent SARS-CoV-2 infection due to lack of evidence.

a. CoronaVac (Sinovac)
b. BBIBP-CorV (Sinopharm-Beijing)
c. WIBP-CorV (Sinopharm-Wuhan)

(*No certainty of evidence*)

RECOMMENDATION

There is no recommendation on the use of the following vaccines in children 3 to 5 years to prevent SARS-CoV-2 infection due to insufficient evidence.

a. BBIBP-CorV (Sinopharm-Beijing)
b. WIBP-CorV (Sinopharm-Wuhan)

(Low certainty of evidence)

RECOMMENDATION

There is no recommendation on the use of **BNT162b2 (Pfizer-BioNTech)** in children 6 months to 4 years to prevent SARS-CoV-2 infection due to insufficient evidence. *(Low certainty of evidence)*

Consensus Issues

The evidence on children 3 to 5 years old for each vaccine, BBIBP-CorV (Sinopharm-Beijing) & WIBP-CorV (Sinopharm-Wuhan) came from a single Phase 1-2 randomized controlled trial with small sample size only and the Consensus Panel decided this lowered the certainty of evidence from Moderate to Low Certainty.

KEY FINDINGS

- There were six published studies [118-123] on the primary series of COVID-19 vaccines in children 6 months to 4 years compared to placebo or non-vaccinated children or non-COVID vaccines. There was one study each on BNT162b2 (Pfizer-BioNTech), WIBP-CorV (Sinopharm-Wuhan) and two on CoronaVac (Sinovac). Data on mRNA-1273 (Moderna) & WIBP-CorV (Sinopharm-Wuhan) are from

published interim or preliminary results. The three studies on inactivated vaccines did not include younger children less than 2 years old. None of the studies used a bivalent vaccine.

- There were no studies on ChAdOx1 (AstraZeneca), Ad26-CoV2-S (Janssen/Johnson&Johnson), Gam-COVID-Vac (Sputnik V).
- A large randomized controlled trial (RCT) on mRNA-1273 (Moderna) vaccine showed significant decrease in risk for COVID-19 infection regardless of symptom for children 6 months to 5 years old. Immunogenicity results showed geometric mean ratios (GMRs) that are non-inferior to young adults. Solicited adverse reactions, mostly mild to moderate severity, were significantly higher in the vaccine group compared to placebo within seven days of vaccination. Risk of serious adverse events (SAE) related to vaccination between the two comparisons was not significantly different. There is one study withdrawal due to the vaccine. (Very Low certainty of evidence)
- A large population-based cohort study on CoronaVac (Sinovac) vaccine in children 3 to 5 years old showed protection against symptomatic laboratory-confirmed COVID-19 infection and hospitalization. A clinical trial (n=143) showed significantly higher immunogenicity response than placebo. Incidence of adverse reactions within 28 days after receiving the vaccine was comparable to placebo, with mild to moderate local and systemic adverse reactions. There was no reported SAE. (Very Low certainty of evidence)
- No study on clinical efficacy and immunogenicity of BNT162b2 (Pfizer-BioNTech) in children less than 5 years old is available. For safety, a large retrospective cohort study showed that off-label BNT162b2 vaccination has increased risk for local adverse reactions but decreased risk for systemic adverse reactions compared to on-label non-COVID-19 vaccination (i.e., influenza, MMR, etc.).
- No clinical efficacy data is available for BBIBP-CorV (Sinopharm-Beijing). A small study in children 3 to 5 years old showed significantly higher neutralizing antibody geometric mean titers (GMT) after the second BBIBP-CorV vaccine as compared to the control group. Incidence of adverse reaction (local and systemic) within 30 days after the second vaccination was not significantly different from placebo. All local and systemic adverse reactions were mild to moderate in severity. (Moderate certainty of evidence)
- A published interim analysis of a double blind RCT (n=336) on WIBP-CorV (Sinopharm-Wuhan) showed significant increase of 47- to 76-fold in GMT of neutralizing antibodies and 56- to 66-fold in specific IgG-binding antibodies after vaccination compared to placebo in children 3 to 5 years old. Only mild to moderate adverse events were observed and the incidence within 30 days after the primary series was not significantly different from placebo. (Moderate certainty of evidence)
- No study reported adverse events of myocarditis, pericarditis, MIS-C, and deaths although the studies had a short duration of follow-up.

Q8. Among children aged 5 to 17 years old who received the standard full doses of any COVID-19 vaccine, what is the clinical and immunologic efficacy, effectiveness, and safety of a booster dose?

As of 19 December 2023

RECOMMENDATION

We suggest the use of monovalent BNT1262b2 mRNA (Pfizer-BioNTech) vaccine as booster in healthy children 12 to 17 years old who received standard full doses of primary series to prevent SARS-CoV-2 infection*. (*Very low certainty of evidence, Weak recommendation)*

*After optimal coverage in the high-risk priority groups have been achieved.

RECOMMENDATION

There is no recommendation being made this time on booster administration in healthy children 5 to 11 years old who received standard full doses of primary series to prevent SARS-CoV-2 infection due to lack of evidence.

Consensus Issues

The decision of the Panel to withhold a recommendation for the 5 to 11 age group was due to lack of evidence, with indirect evidence being used to evaluate this specific group. While the indirect evidence showed beneficial results, these were observational studies having low validity and subject to confounding bias.

KEY FINDINGS

- The evidence, as of November 3, 2022, includes four (4) observational studies [124-127] on monovalent BNT162b2 mRNA vaccine as homologous first booster among healthy individuals 6 to 17 years of age compared to those who received standard doses of the primary series of COVID-19 vaccines.
- There were no studies found on children for bivalent mRNA vaccines, mRNA-1273 (Spike Vax), CoronaVac (Sinovac), BBIBP-CorV (Sinopharm), ChAdOx1 (AstraZeneca) and other vaccines as a booster.

12 TO 17 YEARS OLD

- A homologous booster dose of BNT162b2 mRNA vaccine given five months after the primary series demonstrated reduction in COVID-19 infection caused predominantly by Omicron and Delta variants, but no reduction in hospitalization. Myocarditis was not increased after a booster dose. There was no reported mortality. A moderate to large-fold increase in immunologic markers after a booster dose was noted. (Very low certainty due to inconsistency, imprecision, and serious risk of bias)

5 TO 11 YEARS OLD

- In the absence of studies in the 5 to 11 years old children, indirect evidence from the four studies in children aged 12 to 17 years on BNT162b2 mRNA vaccine as a booster dose was used. As shown above, benefit in preventing COVID-19 infection but not in hospitalization was demonstrated. There was a low incidence of serious adverse events. (Very low certainty)

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 to previous reviews.

For the third phase (December 2022 to June 2023), there were a total of 43 evidence summaries presented and 104 recommendations generated during 21 consensus panel meetings. Evidence summaries that were previously reviewed in the Pediatric COVID-19 Living CPG were already incorporated in this phase. 15 evidence summaries were new evidence reviews while 28 were updates to previous reviews. 2 topics (Pooled Testing and Lagundi) were deferred from panel presentation due to the identified need for further evidence review. Four topics (Return from Isolation, Tixagevimab-Cilgavimab prophylaxis,Molnupiravir and 2nd Boosters for the General Population) were re-visited during the duration of this phase due to the rapid change in the available evidence and the need for immediate review to update the existing recommendations. 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, if any.

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

Due to the WHO declaration of the end of COVID-19 as a public health emergency in May 2023, the panelists focused on the implementation of screening and diagnostic methods for COVID-19 for critical populations and instances such as RT-PCR testing for immunocompromised individuals and for surgery admissions. Population-based screening was deprioritized in favor of targeted testing according to symptomatology and the clinical need for a definitive COVID-19 diagnosis.

Limitations in the availability of treatment and critical care interventions, most especially those investigational drugs only being accessible through the public via FDA's emergency use authorization were discussed. Medical specialists, especially those from infectious diseases, pulmonary medicine, and critical care medicine, were important in effectively leading the use of these treatments for the management of COVID-19 patients. Moreover, the panelists highlighted observations that the majority of COVID-19 infections now are mild hence the use of these novel drugs should undergo individualized cost- and risk-benefit analyses for patients.

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 masks 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 general anti-vaccine movement.

RESOURCE IMPLICATIONS

As a low-middle-income country, our limited resources need 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 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 275,090 total clicks on the website. In 2023, there were 15,515 views with an average of 61 visits per day.

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 would be another first study to formally demonstrate the effects of CPG implementation in the country.

Conclusions and Recommendations

Phase 3 of the Philippine COVID-19 Living CPG identified 46 priority questions on COVID-19 management, infection prevention, and control, generated 44 evidence summaries, and came up with 102 recommendations. Thematic areas included in this

CPG were diagnosis, screening, and preventive interventions; treatment and critical care interventions; and vaccines. The CPG recommendations were used in the construction of testing and management algorithms for COVID-19.

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 and for future CPGs that would follow the living guideline methodology:

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. This ensures that panel members are aware of the previous issues discussed as well as mastery and efficiency of the process flow towards evidence to decision.
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 both 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. Set a protected day and time with the consensus panel members at least every 2 weeks to ensure their availability once there are guideline recommendations that need to be presented and updated.
5. 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.
6. The review and management of conflicts of interest of all project members, including consensus panelists, takes a considerable amount of time and is ideally done before the start of consensus panel meetings. Hence, this exercise of due diligence should be given consideration in the project timeline.
7. Involvement of stakeholders, including policy makers, especially in 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 Conflicts of Interest (COI) Review Committee – Review of Conflict of Interest

TREATMENT A CONSENSUS PANEL COI ASSESSMENTS

Name	Assessment	Remarks
Dr. Ma. Elinore A. Concha	Allowable	
Dr. Rowena Roselle P. Blanco-Santos	Allowable	
Dr. Maria Encarnita B. Limpin	Manageable with minor constraints	Declare non-financial interests as the author of articles on high-flow nasal cannula, rapid antigen, and RT-PCR testing for COVID-19
Dr. Mary Ann Bunyi	Manageable with major constraints	Declare financial interests in: 1. Sinovac COVID-19 vaccine 2. GSK for Sotrovimab in Children, and 3. Board Membership in Pfizer for PCV and Meningococcemia Vaccines Inhibit voting on the following topics: 1. Sotrovimab 2. Paxlovid 3. Tofacitinib 4. Inhaled Corticosteroids 5. Anticoagulation 6. Azithromycin 7. Other topics with potential COI as identified by Steering Committee
Dr. Sarah R. Makalinaw	Allowable	
Dr. Rommel Punongbayan	Allowable	
Dr. Karl Evans Henson	Manageable with major constraints	Declare financial interests in: 1. AstraZeneca for COVID-19 vaccine 2. Pfizer for Ceftazidime and Ceftazoline 3. BSV for Polymixin B 4. MSD for Ceftozolane Inhibit voting on the following topics: 1. Tixagevimab/cilgavimab 2. Paxlovid 3. Tofacitinib 4. Inhaled Corticosteroids 5. Anticoagulation 6. Azithromycin 7. Other topics with potential COI as identified by Steering Committee
Dr. Erwin R. De Mesa	Allowable	
Dr. Faith Joan C. Mesa-Gaerlan	Allowable	
Dr. Leila Ferrer	Allowable	

TREATMENT B CONSENSUS PANEL COI ASSESSMENTS

Name	Assessment	Remarks
Mr. Jeah Alvarez Sabillo	Allowable	
Dr. Pauline F. Convocar	Allowable	
Ms. Shirley P. Whisenhunt	Allowable	
Dr. Phorenice Francisco	Allowable	
Dr. Joseph Adrian Buensalido	Allowable	
Dr. Rowena Marie Samares	Allowable	
Dr. Joan Oliveros	Allowable	
Dr. Juliet-Sio Aguilar	Allowable	
Dr. Roberto Razo II	Allowable	
Dr. Jubert Benedicto	Manageable wth major constraints	Inhibit voting on melatonin

DIAGNOSIS, SCREENING, AND PROPHLYACTIC INTERVENTIONS CONSENSUS PANEL COI ASSESSMENTS

Name	Assessment	Remarks
Dr. John Andrew T. Camposano	Allowable	
Dr. Jane Eflyn Lardizabal-Bunyi	Allowable	
Dr. Virginia delos Reyes	Manageable with minor constraints	Declare financial interests in: 1. MSD and Vicore for Molnupiravir, Relebactam, and C21
Dr. Fatima Johanna T. Santos-Ocampo	Allowable	
Dr. Vernon Serafico	Allowable	
Dr. Mary Ann D. Lansang	Allowable	
Dr. Florido A. Atibagos	Allowable	
Ms. Dominga Gomez, RN	Allowable	
Ms. Victoria I. Ching, RN	Allowable	

VACCINES CONSENSUS PANEL COI ASSESSMENTS

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Dr. Ranali P. Mendoza	Allowable	
Dr. Julie Christie Visperas	Allowable	
Dr. Edmyr M. Macabulos	Allowable	
Dr. Sybil Lizanne Bravo	Allowable	
Dr. Maria Rhona Bergantin	Allowable	
Dr. Katrina Gomez	Allowable	
Dr. Frances Tan	Manageable with major constraints	Declare financial interests in: 1. DOST Mix and Match Vaccine Study 2. Pharmaceutical companies for antihistamines, emollients, and milk products Inhibit voting on all vaccine topics but may be part of discussion as technical expert
Dr. Elsie Locson	Allowable	

STEERING COMMITTEE COI ASSESSMENTS

Name	Assessment	Remarks
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Dr. Ivan N. Villespin	Allowable	
Dr. Arnel Gerald Q. Jiao	Allowable	
Dr. Evalyn A. Roxas	Allowable	
Dr. Donna Isabel S. Capili	Allowable	
Dr. Aileen R. Espina	Manageable with minor constraints	Declare non-financial interests in 1. Membership, Healthcare Professionals Alliance Against COVID-19 2. COVID-19 Public Statements by Invitation from Menarini 3. Technical Consultant - LabX Asia - Distributor of COVID-19 test kits
Dr. Rosemarie S. Arciaga	Allowable	

TECHNICAL STAFF COI ASSESSMENTS

Name	Role	Assessment	Remarks
Dr. Christopher G. Manalo	Technical Coordinator	Allowable	
Dr. Natasha Esteban-Ipac	Technical Coordinator	Allowable	
Dr. Maria Teresa S. Tolosa	Technical Coordinator	Allowable	
Dr. Ma. Lucila M. Perez	Technical Coordinator	Allowable	
Dr. Vaneza Leah A. Espino	Technical Assistant	Allowable	
Dr. April Padua Zamora	Technical Assistant	Allowable	
Dr. Michelle Cristine B Miranda	Technical Assistant	Allowable	

Dr. Julianne Keane M. Pascual	Technical Assistant	Allowable	
Dr. Diana R. Tamondong-Lachica	Facilitator	Allowable	
Dr. Bernadette Heizel Manapat-Reyes	Facilitator	Allowable	
Dr. Sandra T. Torres	Facilitator	Manageable with minor constraints	Declare past positions in Taketa and Abott during panel meetings.
Dr. Carol Stephanie Tan-Lim	Facilitator	Allowable	
Dr. Nathaniel C. Vicencio	Copy Editor	Allowable	
Dr. Maria Noreen Mendoza	Copy Editor	Allowable	
Dr. Jacqueline Ong	Copy Editor	Allowable	
Dr. Cynric S. Ang	Evidence Review Expert	Allowable	
Dr. Timothy Hudson David C. Carandang	Evidence Review Expert	Allowable	
Dr. Anton G. Elepaño	Evidence Review Expert	Allowable	
Dr. Frangelo Conrad P. Tampus	Evidence Review Expert	Allowable	
Dr. Liza Marie Bejemino	Evidence Review Expert	Allowable	
Dr. Jhon Ryan G. Enriquez	Evidence Review Expert	Allowable	
Dr. Maria Cristina H. Lozada	Evidence Review Expert	Allowable	
Dr. Faustine C. Ong	Evidence Review Expert	Allowable	
Dr. Patricia C. Orduña	Evidence Review Expert	Allowable	
Dr. Jofermarie O. Pineda	Evidence Review Expert	Manageable with minor constraints	To declare involvement in a trial of a COVID-19 vaccine and a trial on Tocilizumab
Dr. Katherine Ruth O. Relato	Evidence Review Expert	Allowable	
Dr. Leslie Del Barrio	Evidence Review Expert	Allowable	
Dr. Joanna Marie U. Tan	Evidence Review Expert	Allowable	
Dr. Andrea P. Reyes	Evidence Review Expert	Allowable	
Dr. Maria Florlean S. Quinoa.	Evidence Review Expert	Allowable	
Dr. Marie Gene D. Cruz	Evidence Review Expert	Manageable, with minor constraints	Declare financial and non-financial interests as a sub-investigator 2 for the Biokangtai COVID-19 Vaccine Trial by Shenzhen Kangtai Biological Products Co., Ltd

Dr. Cary Amiel G. Villanueva	Evidence Review Expert	Allowable	
Dr. Mark Jason DC Milan	Evidence Review Expert	Allowable	
Dr. Karen Joyce Cortez	Evidence Review Expert	Allowable	
Dr. Christine Caringal	Evidence Review Expert	Allowable	
Dr. Joan Roque Viado	Evidence Review Expert	Allowable	
Dr. Eva I. Bautista	Evidence Review Expert	Allowable	
Dr. Carolina Linda L. Tapia	Evidence Review Expert	Allowable	
Dr. Gloriosa C. Galindez	Evidence Review Expert	Allowable	
Dr. Marquis Von Angelo Syquio G. Joson	Evidence Review Expert	Allowable	
Dr. Giselle Anne Q. Adajar, MD	Evidence Review Expert	Allowable	
Dr. Angelo Martin B. Catacutan, MD	Evidence Review Expert	Allowable	
Dr. Christdianzen Grace P. Saroca	Evidence Review Expert	Allowable	
Dr. Julian Mikhael A. Buban	Evidence Review Expert	Allowable	
Dr. Lylah Reyes	Evidence Review Expert	Allowable	
Dr. Germana V. Gregorio	Evidence Review Expert	Allowable	

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	
Treatment, Critical Care, and Adjunct Interventions	December 05, 2022
	December 12, 2022
	January 16, 2023
	January 25, 2023
	February 20, 2023
	March 15, 2023
	March 22, 2023
	April 03, 2023
	April 24, 2023
	May 19, 2023
Diagnosis, Screening, and Preventive Interventions	December 02, 2022
	December 19, 2022
	February 01, 2023
	March 02, 2023
	March 16, 2023
	May 02, 2023
	May 22, 2023
Vaccines	December 19, 2022
	February 02, 2023
	March 06, 2023
	March 23, 2023

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
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	135-145
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	1
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)	7-8; 151
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	8-9
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)	9-14
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	10

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)	15
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	16
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
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	89
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	88
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)	89

	☒ 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	15
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; 146-149

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.


UNIVERSITY OF THE PHILIPPINES
1908
PHILIPPINE SOCIETY FOR MICROBIOLOGY AND INFECTIOUS DISEASES
1970 AD
REPUBLIC OF THE PHILIPPINES
DEPARTMENT OF HEALTH