Pediatric Infectious Disease Society of the Philippines Journal
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CLINICAL PRACTICE GUIDELINES

PHILIPPINE PEDIATRIC COVID-19 LIVING CLINICAL PRACTICE GUIDELINES as of March 2022

Philippine Pediatric COVID-19 Living Clinical Practice Guidelines Task Force[1]

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

EXECUTIVE SUMMARY

The Coronavirus disease 2019 (COVID-19) pandemic has triggered a global crisis and has affected millions of people worldwide. With the evolution of the different variants of concern, the incidence of COVID-19 in the pediatric population has risen. The Surveillance and Analysis of COVID-19 in Children Nationwide (SALVACION) Registry, developed by the Pediatric Infectious Disease Society of the Philippines (PIDSP) and the Philippine Pediatric Society (PPS), has reported 3,221 cases as of March 31, 2022, with 90.4% requiring hospitalization and 36.2% with moderate to critical disease severity. Given the magnitude of the impact of COVID-19, with most of the clinical recommendations available designed towards adult patients, there was an urgent need for clinicians, public health officials and the government to also prioritize evidence-based clinical practice guidelines for the pediatric population. Hence, the development of the Philippine Pediatric COVID-19 Living Clinical Practice Guidelines was conceptualized. This independent project, funded and supported by the PPS and PIDSP, aimed to formulate up-to-date, evidence-based recommendations on the treatment, diagnosis, infection prevention and control of COVID-19 in children.

Following the standard CPG development process outlined in the DOH Manual for CPG Development and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology, 15 evidence summaries and 24 recommendations were generated by 12 consensus panelists representing their specific health organizations and institutions.

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CONFLICT OF INTEREST DECLARATION

- **Jeriel R. de Silos -** Consultant, COVID-19 Response to NCR, World Health Organization Philippine Country Office (2020); Evidence Review Expert, Philippine COVID-19 Living Clinical Practice Guidelines (Cloth mask vs. medical mask use)
- **Norielyn Villela M. Evangelista -** Medical Officer IV, Department of Health - Disease Prevention and Control Bureau
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- **Daisy M. Medina -** Peer reviewer and section editor, The Filipino Family Physician Journal
- **Maria Theresa T. Policarpio -** Editor in chief, PAPP Interim Guideline on the Pulmonary Care in Pediatric COVID-19; Chair, PAPP COVID Task Force
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SUMMARY OF RECOMMENDATIONS

	Recommendation	Strength of Recommendation	Certainty of Evidence
1	As an alternative specimen to nasopharyngeal swab, we recommend the use of saliva specimen for RT-PCR* among non-hospitalized children suspected of COVID-19 infection. **The use of three specific saliva RT-PCR assays is recommended: Allplex 2019-nCOV assay, Cobas 6800, QuantStudio 7 system.*	Strong	Moderate
2	As an alternate specimen to nasopharyngeal swab, we suggest the use of mid-turbinate swab for RT-PCR* among non-hospitalized children suspected of COVID-19 infection. **The use of two specific mid-turbinate RT-PCR assays is recommended: RealStar SARS-CoV-2 RT-PCR kit or Aptima SAR-CoV-2 Assay.*	Weak	Moderate
3	We suggest against the use of nasopharyngeal aspirate as an alternative clinical specimen among non-hospitalized children suspected of COVID-19 infection.	Weak	Moderate
4	We suggest the against routine use of intravenous immunoglobulin for children with COVID-19 infection.	Weak	Very low
5	We suggest the use of systemic corticosteroids (dexamethasone) among children with severe and critical COVID-19 infection.	Weak	Very low
6	We suggest the addition of tocilizumab to systemic steroids in patients with moderate to severe COVID-19 infection, particularly where there is evidence of systemic inflammation.	Weak	Very low
7	We suggest the use of remdesivir in hospitalized children with severe COVID-19 infection.	Weak	Very low
8	We suggest the use of remdesivir in non-hospitalized children with COVID-19 infection with at least one (1) risk factor* for disease progression. **The risk factors for disease progression are hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity, immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer or sickle cell disease.*	Weak	Low
9	We suggest against the routine use of anticoagulation in children with COVID-19 infection or MIS-C.	Weak	Very low
10	There is insufficient evidence to recommend the use of casirivimab plus imdevimab as treatment of non-hospitalized children with COVID-19 infection with ≥1 risk factor* for severe COVID-19. **The risk factors are 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.*	--	Low

	Recommendation	Strength of Recommendation	Certainty of Evidence
11	There is insufficient evidence to recommend the use of casirivimab plus imdevimab as treatment of hospitalized children with COVID-19 infection with ≥1 risk factor* for severe COVID-19. **The risk factors are 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
12	There is insufficient evidence to recommend the use of bamlanivimab plus etesevimab as treatment of non-hospitalized children with COVID-19 infection with ≥1 risk factor* for severe COVID-19. **The risk factors are 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.*	--	Low
13	There is insufficient evidence to recommend the use of sotrovimab as treatment of non-hospitalized children with COVID-19 infection.	--	Low
14	We suggest against the use of sotrovimab as treatment of hospitalized children with COVID-19 infection.	Weak	Low
15	We suggest against the use of amubarvimab plus romlusevimab as treatment of children with COVID-19 infection.	Weak	Low
16	We suggest against the use of regdanvimab as treatment of children with COVID-19 infection.	Weak	Low
17	We suggest against the routine use of vitamin D for the prevention of COVID-19 infection in children.	Weak	Very low
18	We suggest against the routine use of vitamin C for the prevention of COVID-19 infection in children.	Weak	Very low
19	We suggest against the routine use of zinc for the prevention of COVID-19 infection in children.	Weak	Low
20	We suggest against the use of vitamin D as adjunctive treatment for COVID-19 infection in children.	Weak	Very low
21	We suggest against the use of vitamin C as adjunctive treatment for COVID-19 infection in children.	Weak	Very low
22	We suggest against the use of zinc as adjunctive treatment for COVID-19 in children.	Weak	Low
23	We recommend the implementation of supportive strategies* to optimize mental health among children and adolescents during the COVID-19 pandemic. **Supportive strategies for mental health during the COVID-19 pandemic include psychological counseling, physical and leisure activities (outdoor and online exercise platforms, art and dance), mindfulness meditation training, personal and spiritual coping, strengthening social support and connecting online with*	Strong	Low

	peers, and health-promoting activities.		
	Recommendation	**Strength of Recommendation**	**Certainty of Evidence**
24	We recommend a multi-layer approach using multiple non-pharmacologic interventions* in school settings to limit transmission of COVID-19 in schools. **The non-pharmacologic interventions are wearing of masks of students, physical distancing, engineering controls (ventilation, personal hygiene and handwashing, disinfection of surfaces), administrative controls (blended learning, phased reopening, no/reduced mixing of classes, restriction of class size, minimized or staggered breaks, symptom monitoring, self-quarantine, contact tracing, and early testing).*	Strong	Very low

The Philippine Pediatric COVID-19 Living CPG used the following definitions for the spectrum of severity of COVID-19 based on the Interim Guidelines on the Screening, Classification and Management of Pediatric Patients with Suspected or Confirmed COVID-19 of PIDSP (as of January 8, 2022):

Mild COVID-19 – no pneumonia or hypoxia/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 clinical signs of non-severe pneumonia (cough or difficulty of breathing + fast breathing and/or chest indrawing) and no signs of severe pneumonia, including $SpO_2 \geq 95\%$ on room air; while the diagnosis can be made on clinical grounds, chest imaging may assist in diagnosis and identify or exclude pulmonary complications

Severe COVID-19 – with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following:

- Central cyanosis or SpO_2 <95%; severe respiratory distress (e.g. fast breathing, grunting, very severe chest indrawing); general danger signs: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions
- Tachypnea (in breaths/min):
    - 3 months old to 12 months old: ≥50 breaths per minute
    - 1 year old to 5 years old: ≥40 breaths per minute
    - 5 to 12 years old: ≥30 breaths per minute
    - ≥12 years old: ≥20 breaths per minute

Critical COVID-19 – with any one of the following:

- Acute respiratory distress syndrome (ARDS)
- Sepsis
- Septic shock
- Acute thrombosis
- MIS-C

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CHAPTER 1: INTRODUCTION

Coronavirus disease 2019 (COVID-19) has grown into a pandemic and global crisis affecting multiple sectors of society. As of December 27, 2021, over 279 million confirmed COVID-19 cases have been reported globally. In the Philippines, as of December 15, 2021, the number of cases in the Philippines has reached more than 2.8 million with 50,449 COVID-19 related deaths. The national strategy towards the new normal is prevention, detection, isolation, treatment, and reintegration (PDITR). The PDITR strategy has been expanded to include vaccination, with the arrival of COVID-19 vaccines from donor countries and international organizations. Since the launch of the national vaccination campaign against COVID-19 in March 2021, the Philippines had 47 million fully vaccinated individuals as of December 26, 2021. Notwithstanding these strategies, none of the epidemiologic projections on COVID-19 in the Philippines point to a foreseeable end of the pandemic, especially with the rise of variants with increased transmissibility.

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

Objectives

The Philippine Pediatric 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 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 in children
2. Summarized available literature on each priority question related to COVID-19 management, infection prevention and control in children
3. Formulated recommendations on COVID-19 management, infection prevention and control in children based on the evidence summaries presented

Target Population

This CPG was intended to apply primarily for Filipino children aged 0 to 18 years old 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, pediatricians, 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

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CHAPTER 2: GUIDELINE DEVELOPMENT METHODOLOGY

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

2.1 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, pediatrics, infectious diseases, pulmonology, infection control, and public health. All members have technical knowledge and expertise on clinical management and policy development related to COVID-19 in children.

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 was also a representative 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 children who were infected themselves, acted also as patient advocates to reflect patients' and public's views and preferences.

Key Clinical Issues and Questions

The Philippine Pediatric COVID-19 Living CPG tackled five central themes in COVID-19: Screening and Diagnosis, Treatment, Prophylactic Interventions, Adjunct Interventions, and Non-Pharmacologic Interventions.

Table 1 below summarizes the topics covered. 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 Pediatric COVID-19 Living CPG.

Screening and Diagnosis	Treatment
• Alternative clinical specimens to nasopharyngeal swab for RT-PCR	• Intravenous immunoglobulin (IVIG) • Corticosteroids • Tocilizumab • Remdesivir • Anticoagulation • Monoclonal antibodies
Prophylactic Interventions	**Adjunct Interventions**
• Vitamin D • Vitamin C • Zinc	• Vitamin D • Vitamin C • Zinc
Non-Pharmacologic Interventions	
• Supportive strategies to optimize mental health • Preventive interventions used in school settings to reduce transmission	

2.2 Evidence Synthesis

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

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

Search Methods

Primary studies and systematic reviews were searched from inception until February 2022, 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)

Detailed search strategies for each clinical question were presented in the respective full-text evidence summaries.

Inclusion and Exclusion Criteria

As a rule, questions on clinical efficacy and safety of interventions were answered using randomized controlled trials (RCT). 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 pediatric patients with COVID-19 or healthy children. 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 [9] 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 [6]. 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.

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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				

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.

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

However, there were three reasons if the Consensus Panel was unable to make a recommendation [7]:

1. Confidence in effect estimates is so low that the panel feels 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.

For these evidence reviews where the panel was unable to make a recommendation, the recommendation was stated as "There is insufficient evidence to recommend the use of…"

The implications of strong and conditional recommendations are enumerated in Table 4 [7].

Table 4. Implications of the Strength of Recommendation to Patients, Clinicians, and Policymakers [7].

	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.

Patient Views and Preferences

Patient views and preferences were represented by a nurse 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 were still considered in the rating of the outcomes and formulation of recommendations.

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:

Table 5. Outcome Ratings by the Consensus Panel

	Critical Outcomes	Important but not critical outcomes
Screening and Diagnosis	• Sensitivity and specificity • Positive and negative predictive values • Likelihood ratio	• Adverse events
Treatment	• Mortality • Recovery • Hospitalization • Adverse events • Clinical improvement • Duration of ICU stay • Need for mechanical ventilation • Duration of hospital stay	• Negative viral conversion
Treatment – Anticoagulation	• Mortality • Thrombosis • Bleeding events	
Prophylactic Interventions	• Forward transmission • Adverse events • Incidence of COVID-19 • Viral load	
Non-Pharmacologic Interventions – School Setting	• Transmission rates • Number of outbreaks • Attack rate • Incidence rate • Prevalence rate • Number of cases	
Non-Pharmacologic Interventions – Mental Health	• Depression • Perception of overall well-being • Anxiety • Resilience	• Life satisfaction • Mindfulness

Consensus Process

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

There was one recommendation that required a modified Delphi activity. This was the recommendation regarding the preventive interventions to prevent transmission of COVID-19 in the school setting. Although the panel agreed on the recommendation, the panel voted separately for the individual non-pharmacologic interventions (NPIs) to

be included in the recommendation. Only those NPIs that reached a minimum of 75% vote were included. This was settled on March 29, 2022.

2.4. External Review

The CPG webpage served the dual purpose of a dissemination method and a way to collect the external reviews of the CPG processes, evidence summaries, and recommendations. The manuscripts were also distributed to individual PPS members for their inputs and feedback. This website (https://www.psmid.org/philippine-covid-19-living-recommendations-3/) also allowed health professionals and key stakeholders to suggest additional clinical questions that could be included in the scope of this CPG. This was simultaneously linked to the PPS website (https://pps.org.ph/philippine-pediatric-covid-19-living-clinical-practice-guidelines/).

Over the weeks and months, we will gather feedback from users and members of the Living CPG Taskforce to improve the readability of the webpage, such as toggling of topics, recommendations, and evidence summaries, changing from topics to questions in the listing, rearranging various sections into headers (such as CPG methodology, task force members, contact details, etc.), and other formatting changes.

2.5. Guideline Dissemination

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

The recommendation statements and evidence summaries of the Philippine Pediatric COVID-19 Living CPG were uploaded in the online webpage of the Philippine COVID-19 Living CPG hosted on the PSMID website on **April 4, 2022**, in order to maintain a single repository of all local clinical recommendations on COVID-19, for both the adult and pediatric populations. It has undergone improvements from the feedback of CPG users and members of the Living CPG task force.

The short *Living Recommendations document* 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, PPS 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 Panel 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 PPS and PSMID websites.

2.6 Guideline Monitoring and Evaluation

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

Impact evaluation for the Philippine Pediatric COVID-19 Living CPG would include bi-annual surveys of the following (1) clinicians managing pediatric 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 pediatric COVID-19 patients can be assessed by measuring adherence of healthcare providers and institutions to the recommendations of the Philippine Pediatric COVID-19 Living CPG. Strong

recommendations would be included in a quality-of-care checklist on COVID-19 care for children, while weak recommendations would be relevant if the identified conditions are satisfied.

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

2.7. Updating of Guidelines

Due to the rapidly evolving science of COVID-19 treatment and diagnosis, the Philippine Pediatric COVID-19 Living CPG was updated continuously. The Living CPG Development Process is summarized in Figure 1.

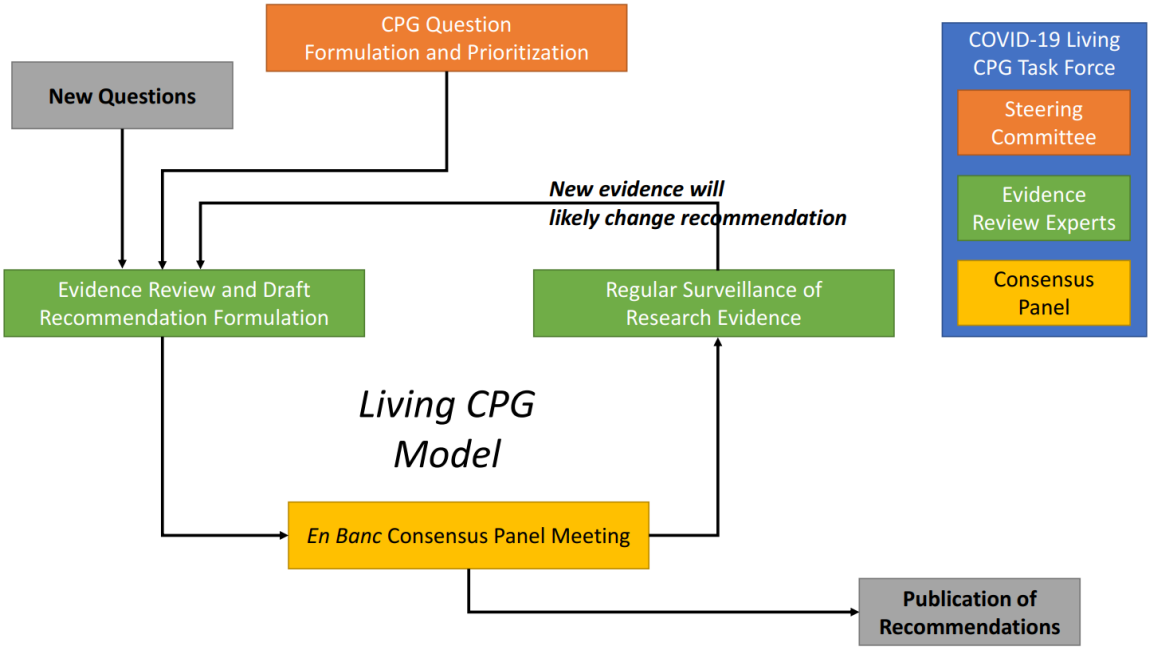

Figure 1. Philippine Pediatric COVID-19 Living CPG Development Process.

After the initial PPS-PIDSP funding for six months, the DOH Disease Prevention and Control Bureau has provided funding support for another six months to continue the surveillance search for the "living recommendations". Further funding will be sought from professional societies and other government agencies to ensure the sustainability of the living CPG throughout the COVID-19 pandemic.

2.8 Editorial Independence

Funding Source

This CPG project was funded by the PPS and PIDSP. Though both organizations were part of the Steering Committee and the Consensus Panel, their influence on the guideline content was limited to the identification of key clinical questions and the discussion of the recommendations. The funding agencies 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 CPG, including the Steering Committee, Technical Working Group, and Consensus Panel, declared any potential conflicts of interest within the last 4 years, using a uniform Declaration of Conflict of Interest (DCOI) form as recommended in the DOH Manual [5]. These were reviewed by an independent

Oversight Committee (OC) and the Steering Committee, to screen and manage the COIs declared. The Oversight Committee was responsible for recommending the extent of participation that can be allowed.

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

a. **Acceptable** – if there are no intellectual nor financial conflicts of interest
b. **Manageable A** – if there are intellectual conflicts of interest only. They can vote but they need to declare their intellectual conflicts (e.g., affiliation with institutions, positions in an organization, authorship in paper or CPG)
c. **Manageable B** – if there are some intellectual and financial conflicts of interest. They cannot vote but they can share their expertise with the group. Examples include panelists from government agencies directly involved in the implementation of the program and panelists from the agency funding the guidelines. The specific terms of management shall be set forth by the OC and shall relate to specific clinical questions.

The declared COIs and decision of the Oversight Committee of members of the Consensus Panel are listed in the beginning of this article. The other members of the Consensus Panel and Evidence Review Experts did not have any conflicts of interest.

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CHAPTER 3:
RECOMMENDATIONS and KEY FINDINGS of the EVIDENCE SUMMARIES

3.1 Screening and Diagnosis of COVID-19 in Children

Which clinical specimen can be used as an alternative to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 infection in children?

	RECOMMENDATIONS	CONSENSUS ISSUES
1	**As an alternative specimen to nasopharyngeal swab, we recommend the use of saliva specimen for RT-PCR* among non-hospitalized children suspected of COVID-19 infection. (Moderate certainty of evidence; Strong recommendation)** **Nasopharyngeal swab is the specimen of choice for RT-PCR for the diagnosis of COVID-19 infection in children. The use of three specific saliva RT-PCR assays is recommended: Allplex 2019-nCOV assay, Cobas 6800, or QuantStudio 7 system.*	There were no consensus issues noted.
2	**As an alternative specimen to nasopharyngeal swab, we suggest the use of mid-turbinate swab for RT-PCR* for among non-hospitalized children suspected of COVID-19 infection. (Moderate certainty of evidence; Strong recommendation)** **Nasopharyngeal swab is the specimen of choice for RT-PCR for the diagnosis of COVID-19 infection in children. The use of two specific mid-turbinate RT-PCR assays is recommended: RealStar SARS-CoV-2 RT-PCR kit or Aptima SAR-CoV-2 Assay.*	There were no consensus issues noted.
3	**We suggest against the use of nasopharyngeal aspirate as an alternative clinical specimen among non-hospitalized children suspected of COVID-19 infection. (Low certainty of evidence; Weak recommendation)**	This recommendation was based on one study performed in children however, due to the low certainty of evidence and issues on availability of the test, the panel voted against the use of nasopharyngeal aspirate in children.

Seven cross-sectional studies on the use of saliva specimen were retrieved however, only three studies were appraised to have no serious risks of bias. Pooled analysis was done for the three studies to check for diagnostic accuracy. Saliva RT-PCR had a sensitivity: 0.87 (95% CI 0.81, 0.91) and specificity: 0.98 (95% CI 0.97, 0.99). Predictive values (PV) ranged from 91.7% - 96.8% and likelihood ratios (LR) for positive result was 45 and 0.13 for a negative result. These accuracy estimates had moderate certainty of evidence. The following assays were used: 1) Allplex 2019-nCoV assay, 2) Cobas 6800, and 3) QuantStudio 7 system.

One study each on using mid-turbinate swab and nasopharyngeal aspirate (NPA) both showed moderate sensitivity but wide confidence interval and high specificity. Other PV and LR accuracy estimates were interpreted moderate to high among non-hospitalized and hospitalized children suspected of COVID-19, respectively. However, while mid-turbinate swab evidence was moderate in certainty of evidence, NPA RT-PCR was based on a study with low certainty of evidence.

No studies in children were seen using the following specimens: oropharyngeal swab, pharyngeal swab, nasal swab, and sputum for RT-PCR.

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3.2 Treatment of COVID-19 in Children

3.2.1. Should intravenous immunoglobulin be used in the treatment of children with COVID-19 infection?

RECOMMENDATION

We suggest against the routine use of intravenous immunoglobulin for children with COVID-19 infection. (Very low certainty of evidence; Weak recommendation)

Consensus Issues
The recommendation was based on the evidence from one retrospective cohort study in children and seven randomized controlled trials in hospitalized adults with moderate to severe COVID-19. Although the evidence in adults showed a significant benefit in reducing clinical deterioration, duration of hospital stay and ICU admission, the evidence was rated as very low due to serious risks of bias, indirectness and imprecision. On the other hand, the evidence in pediatric patients was inconclusive. Coupled with the high cost of the treatment, the panel decided to vote against the routine use of the drug. However, the panel agreed that IVIG may be considered especially when no other treatment option is available. In special circumstances such as MIS-C, expert opinion should be sought.

There were no randomized controlled trials (RCT) found on the use of intravenous immunoglobulin (IVIG) in the treatment of COVID-19 infection in children during the search. However, there was one retrospective cohort study which compared the use of IVIG+CS with CS alone among pediatric patients with Multisystem Inflammatory Syndrome in Children (MIS-C). This showed that addition of IVIG demonstrated tendency towards harm for the composite outcome (use of inotropic support or mechanical ventilation on or after day 2 or death) and inconclusive findings for the other outcomes. When IVIG alone was compared with CS alone (IVIG vs CS) among patients with MIS-C, results were inconclusive for the same composite outcome and for the other outcomes.

Since data in children is limited, indirect evidence was also used through extrapolation of results from the studies included in the Philippine COVID 19 Adult Living Clinical Practice Guideline Phase II as well as from the new adult RCTs found in the search. Pooled results of the seven (7) RCTs on adults showed that the use of IVIG resulted in significant benefit on clinical deterioration, shorter duration of hospital stay and of ICU admission but no significant difference for the rest of the outcomes and adverse events.

The overall certainty of evidence was very low. Thus, there is still insufficient evidence on the use of IVIG for the treatment of COVID-19 in children.

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3.2.2. Should corticosteroids be used in the treatment of children with COVID-19 infection?

RECOMMENDATION

We suggest the use of systemic corticosteroids (dexamethasone) among children with severe and critical COVID-19 infection. (Very low certainty of evidence; Weak recommendation)

Consensus Issues
The recommendation was based on the findings from 20 randomized controlled trials done in hospitalized adult patients with COVID-19. Despite the very low certainty of evidence, the panel agreed that the benefit of significantly reducing all-cause mortality in COVID-19 patients as well as the availability and low cost of dexamethasone is enough to justify its use among pediatric patients with severe and critical COVID-19.

There were no direct studies that enrolled pediatric patients with COVID-19, which compared the use of corticosteroids (CS) with standard care or placebo. Twenty randomized controlled trials (RCTs) on the use of systemic CS as treatment for COVID-19 were included in this review, and all of them included adult COVID-19 patients. These studies used any of the following agents in their experimental arm: Dexamethasone (DEX), Hydrocortisone (HCT), Methylprednisolone (MP), or Prednisolone (PRDL). One study compared inhaled plus intranasal Ciclesonide (CIC) with standard care or placebo.

Pooled estimates for all-cause mortality showed that it was significantly reduced in the systemic CS group; subgroup analysis showed DEX to be the only CS showing significant benefit over standard care or placebo. The results were inconclusive for COVID-19-related mortality. One study showed a significant increase in length of intensive care unit (ICU) stay; another study showed more ventilator-free days in the systemic CS group. However, the studies which used DEX had very low overall certainty of evidence which is partly due to the indirectness caused by the predominantly adult population included.

Comparing MP with DEX, there was a significant decrease in World Health Organization Ordinal Scale (WHO OS) scores and length of hospital stay for the MP group. Mortality and need for mechanical ventilation (MV) were similar for both drugs. For the different doses of DEX, there were conflicting results on mortality rates, length of ICU stay, adverse events (AEs) and other outcomes.

Comparing the systemic CS group and the control group, the results were inconclusive for clinical improvement at 28 days, length of hospital stay, ICU admission rate, intubation rate, extracorporeal membrane oxygenation (ECMO) rate, life support-free days, Sequential Organ Failure Assessment (SOFA) score, and AEs.

Inhaled plus intranasal CIC did not show significantly different results for respiratory symptom resolution, overall symptom resolution, hospital admission rate, mortality, or AEs.

The included RCTs had very low to moderate certainty due to issues with blinding, selective reporting, indirectness, imprecision, and heterogeneity. One cost-effectiveness study showed that the use of 6 mg DEX per day was more cost-effective than standard care for COVID-19.

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3.2.3. Should tocilizumab be used in the treatment of children with COVID-19 infection?

RECOMMENDATION

We suggest the addition of tocilizumab to systemic steroids in patients with moderate to severe COVID-19 infection, particularly where there is evidence of systemic inflammation. (Very low certainty of evidence; Weak recommendation)

Consensus Issues
Although the evidence was based on 17 randomized controlled trials done in hospitalized adult patients with moderate to severe COVID-19, the panel voted for the use of tocilizumab as treatment for COVID-19 in children due to the significant benefit in all-cause mortality and need for mechanical ventilation.

There were no observational or randomized controlled trial (RCT) data on the effectiveness of tocilizumab for the treatment of acute COVID-19 infection in pediatric patients. Taking this into consideration, the review considered the effect of tocilizumab on adults with Covid-19 as indirect evidence for our chosen population basing it primarily on the recently updated Philippine Adult LCPG Phase II.

Pooled results of 17 RCTs (n=9,649) which investigated the efficacy of tocilizumab among hospitalized adult patients with moderate to severe COVID-19 infection comparing to placebo and/or standard of care showed significant benefit in all-cause mortality and need for mechanical ventilation with no significant increase in the risk for adverse events and serious adverse events among those who received tociluzumab. Adverse events reported were neutropenia, leukopenia, anxiety, arrhythmia, insomnia, stroke, constipation, pneumothorax, intracranial bleeding, and pulmonary embolism among others. In addition, co-administration with steroids demonstrated benefit with significant reduction in mortality.

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3.2.4. Should remdesivir be used in the treatment of children with COVID-19 infection?

	RECOMMENDATIONS	CONSENSUS ISSUES
1	**We suggest the use of remdesivir in hospitalized children with severe COVID-19 infection. (Very low certainty of evidence; Weak recommendation)**	Despite the very low certainty of evidence for hospitalized children, the panel voted for the use of remdesivir. This is due to the significant benefit in decreasing the risk for clinical deterioration (based on WHO progression scale) and the risk reduction in mechanical ventilation use, although this was not statistically significant. The panel also agreed that because there are very limited treatment options for pediatric patients with COVID-19, this would give better guidance to clinicians. The panel emphasized though that remdesivir should be used for pediatric patients with severe COVID-19 following the classification of PIDSP and PSMID (on low flow oxygen support).
2	**We suggest the use of remdesivir in non-hospitalized children with COVID-19 infection with at least one (1) risk factor for disease progression. (Low certainty of evidence; Weak recommendation)** **The risk factors for disease progression are hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity, immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer or sickle cell disease.*	The panel voted for the use of remdesivir in non-hospitalized children with COVID-19 infection based on the evidence from one double-blind, placebo controlled randomized controlled trial done among patients aged 12 years old and above. This study showed significant benefit in preventing COVID-19 related hospitalization or all-cause mortality. Remdesivir was given to the patients 7 days from symptom onset and to those with at least one of the following risk factors: hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity, immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer or sick cell disease.

There are no randomized controlled trials (RCTs) to evaluate the use of remdesivir in the treatment of COVID-19 in the pediatric population. One observational study (n=77) among pediatric patients described the compassionate use of Remdesivir for all 77 patients. It showed 83% of cases recovered after 28 days of follow-up. On subgroup analysis, those on invasive ventilation took a significantly longer time to recover and time to discharge than those without, with 32% of patients presenting at least 1 adverse event. Pooled results of ten RCTs evaluating the use of remdesivir in adults outpatients with mild to moderate COVID-19 with risk factors has shown significant benefit in terms of reducing risk for hospitalizations and death. For hospitalized/in-patients, remdesivir decreased the risk only for clinical deterioration as measured by the WHO progression scale but did not show benefit in other outcomes: all-cause mortality, need for mechanical ventilation and time to clinical improvement. No increased risk of adverse events and serious adverse events

were noted. Overall certainty of evidence was rated low to very low due to serious risk of bias, inconsistency, indirectness and imprecision.

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3.2.5. Should anticoagulation be used in the treatment of children with COVID-19 infection?

RECOMMENDATION

We suggest against the routine use of anticoagulation in children with COVID-19 infection or MIS-C. (Very low certainty of evidence; Weak recommendation)

Consensus Issues
The recommendation was based on the findings from two cohort studies done on pediatric patients with COVID-19 infection and MIS-C. There were no significant benefits noted in both studies. However for those with high risk of thrombotic events, the panel suggested to seek expert opinion.

There was no significant benefit for prophylactic anticoagulation over no anticoagulation in preventing thrombotic events for hospitalized children with COVID-19 or MIS-C in two cohort studies. Risk of bleeding while on prophylactic anticoagulation was inconclusive. In the second study, no deaths and thrombotic events were reported. Overall certainty of evidence was downgraded to very low due to high risk of bias, very small sample size, low event rate and wide confidence intervals.

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3.2.6. Should monoclonal antibodies be used in the treatment of children with COVID-19 infection?

	RECOMMENDATIONS	CONSENSUS ISSUES
1	**There is insufficient evidence to recommend the use of casirivimab plus imdevimab as treatment of non-hospitalized children with COVID-19 infection with ≥1 risk factor* for severe COVID-19. (Low certainty of evidence)**	The recommendation is based on two pre-print studies done on hospitalized patients aged 12 years and above. Although there was a significant decrease in the risk for mechanical ventilation use or death for patients given the intervention, most of these studies were conducted on adults and prior to the emergence of the Omicron variant as the dominant variant of concern.
2	**There is insufficient evidence to recommend the use of casirivimab plus imdevimab as treatment of hospitalized children with COVID-19 infection with ≥1 risk factor* for severe COVID-19. (Very low certainty of evidence)**	The recommendation is based on two pre-print studies and a published one on non-hospitalized patients aged 12 years and above who were both symptomatic and asymptomatic for COVID-19. Although there was a significant decrease in the risk for COVID-19 related hospitalization, ER visit or death and ICU admission, most of these studies were conducted on adults and prior to the emergence of the Omicron variant as the dominant variant of concern.
3	**There is insufficient evidence to recommend the use of bamlanivimab plus etesevimab as treatment of non-hospitalized children with COVID-19 infection with ≥1 risk factor* for severe COVID-19. (Low certainty of evidence)**	The recommendation is based on two published studies done on non-hospitalized patients aged 12 years and above. Although there was a significant decrease in the risk for COVID-19 related hospitalization and death, most of these studies were conducted on adults and prior to the emergence of the Omicron variant as the dominant variant of concern.
4	**There is insufficient evidence to recommend the use of sotrovimab as treatment of non-hospitalized children with COVID-19 infection. (Low certainty of evidence)**	The recommendation is based on one published study done on non-hospitalized patients. Although there was a significant decrease in the risk for COVID-19 related hospitalization and use of supplemental oxygen, the study was conducted on adults and prior to the emergence of the Omicron variant as the dominant variant of concern.
5	**We suggest against the use of sotrovimab as treatment of hospitalized children with COVID-19 infection. (Low certainty of evidence; Weak recommendation)**	The recommendation is based on one published study done on hospitalized adult patients that showed inconclusive results in terms of reducing risk for use of supplemental oxygen, mechanical ventilation and all-cause mortality. The low certainty of evidence with the inconclusive results were the reasons why the panel voted against the use of this drug.
6	**We suggest against the use of amubarvimab plus romlusevimab as treatment of children with COVID-19 infection. (Low certainty of evidence; Weak recommendation)**	The recommendation is based on one published study done on hospitalized adult patients that showed inconclusive results in terms of reducing risk for use of supplemental oxygen, mechanical ventilation and all-cause mortality. The low certainty of evidence with the inconclusive results were the reasons why the panel voted against the use of this drug.
7	**We suggest against the use of regdanvimab as treatment of children with COVID-19 infection. (Low certainty of evidence; Weak recommendation)**	The recommendation is based on one pre-print study done on hospitalized adult patients that showed inconclusive results in terms of reducing risk for use of supplemental oxygen and requirement for rescue therapy. The low certainty of evidence with the inconclusive results were the reasons why the panel voted against the use of this drug.

**The risk factors are 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.*

Ten randomized controlled trial (RCTs) evaluated the effect of monoclonal antibodies as treatment for patients with COVID-19. Five RCTs studied casirivimab-imdevimab (REGEN-CoV). Two RCTs studied bamlanivimab-etesevimab. Two RCTs studied sotrovimab, of which one RCT studied both sotrovimab and amubarvimab-romlusevimab. One RCT studied regdanvimab. In all of the RCTs, most of the population studied were adults. Three RCTs included children aged 12 years and above. The overall quality of evidence was very low because of indirectness and imprecision.

There was significantly decreased risk of COVID-19 related hospitalization, ER visit, mechanical ventilation, ICU admission or death for patients given intravenous casirivimab-imdevimab. There was significantly decreased risk of COVID-19 related hospitalization and death for non-hospitalized patients given bamlanivimab-etesevimab. There was significantly decreased risk of hospitalization and supplemental oxygen requirement for non-hospitalized COVID-19 patients given sotrovimab.

For the outcomes assessed, there was inconclusive evidence regarding the benefits of 1) subcutaneous casirivimab-imdevimab on asymptomatic COVID-19 patients, 2) sotrovimab on hospitalized COVID-19 patients, and 3) amubarvimab-romlusevimab and regdanvimab on COVID-19 patients.

Monoclonal antibody therapies were generally safe and well-tolerated by patients. However, the current evidence did not show specific results for children with COVID-19. Further studies are recommended to determine the efficacy of monoclonal antibodies as treatment for children with COVID-19.

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3.3 Prophylactic Interventions of COVID-19 in Children

3.3.1. Should vitamin D be used as a preventive measure for COVID-19 infection in children?

RECOMMENDATION

We suggest against the routine use of vitamin D for the prevention of COVID-19 infection in children. (Very low certainty of evidence, Weak recommendation)

Consensus Issues
Due to the uncertainty of the evidence as well as the cost and availability of the drug for the general population, the panel opted to vote against its use as an adjunctive treatment and preventive measure for COVID-19 in children. They also agreed that this recommendation is subject to change based on the availability of higher certainty of evidence. However, the panel strongly emphasized that vitamin D is necessary for those children with documented vitamin D deficiency.

Eight randomized controlled trials and one observational study, all done in the adult population, served as the evidence for treatment and prevention of COVID-19 in children, respectively. Indirect evidence from one observational study in adults suggests that vitamin D is not associated with reduced risk of SARS-CoV2 infection. Very low quality evidence from eight randomized controlled trials that compared vitamin D versus control in hospitalized adult patients with COVID-19 showed inconclusive results for the outcomes of mortality, ICU admission, need for mechanical ventilation, length of hospital stay, clinical improvement, and virologic clearance. The certainty of evidence was rated very low due to issues on risk of bias, indirectness, inconsistency and imprecision.

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3.3.2. Should vitamin C be used as a preventive measure for COVID-19 infection in children?

RECOMMENDATION

We suggest against the routine use of vitamin C for the prevention of COVID-19 infection in children. (Very low certainty of evidence, Weak recommendation)

Consensus Issues
This recommendation was made based on evidence from two adult observational studies. It revealed that vitamin C did not have significant benefit in preventing COVID-19 infection. Due to the uncertainty of the evidence, the panel opted to vote against the use of the drug specifically for the prevention of COVID-19. However, the panel agreed and strongly emphasized that when consumed within the proper dietary reference intake values, vitamin C is beneficial for the overall health of children. The panel also agreed that this recommendation is subject to change based on the availability of higher certainty of evidence.

We found no published studies done on the role of Vitamin C as preventive measure for COVID-19 in pediatric patients. Indirect evidence from two observational studies in adults showed no significant benefit in using Vitamin C for the prevention of COVID-19 infection. Overall certainty of evidence was very low.

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3.3.3. Should zinc be used as a preventive measure for COVID-19 infection in children?

RECOMMENDATION

We suggest against the routine use of zinc for the prevention of COVID-19 infection in children. (Low certainty of evidence, Weak recommendation)

Consensus Issues
This recommendation is based on the evidence from one randomized controlled trial in adults. The indirectness of the population and the intervention (zinc + vitamin C versus zinc alone) as well as the uncertainty of the evidence led the panel to vote against the use of zinc as a preventive measure for COVID-19 in children and the panel pointed out that this might change until higher certainty of evidence is available. The panel also agreed that the drug may be too costly for those from low- to mid-income families and availability may be an issue in far-flung areas. However, the panel concurred that zinc treatment is important for those with documented zinc deficiency.

We found no direct evidence on the use of zinc for the prevention of COVID-19 in pediatric patients. We found only one randomized controlled trial that enrolled adults, which revealed that compared to control, there was significant benefit of zinc for the outcomes of laboratory-confirmed SARS CoV2 infection (both seropositivity for antibody and positive RT-PCR at Day 42), acute respiratory symptoms, and symptoms of COVID-19. No hospitalization nor death was observed in all treatment arms.

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3.4 Adjunct Interventions for COVID-19 in Children

3.4.1. Should vitamin D be used as an adjunctive treatment for COVID-19 infection in children?

RECOMMENDATION

We suggest against the use of vitamin D as adjunctive treatment for COVID-19 infection in children. (Very low certainty of evidence, Weak recommendation)

Consensus Issues
Due to the uncertainty of the evidence as well as the cost and availability of the drug for the general population, the panel opted to vote against its use as an adjunctive treatment and preventive measure for COVID-19 in children. They also agreed that this recommendation is subject to change based on the availability of higher certainty of evidence. However, the panel strongly emphasized that vitamin D is necessary for those children with documented vitamin D deficiency.

Eight randomized controlled trials and one observational study, all done in the adult population, served as the evidence for treatment and prevention of COVID-19 in children, respectively. Indirect evidence from one observational study in adults suggests that vitamin D is not associated with reduced risk of SARS-CoV2 infection. Very low quality evidence from eight randomized controlled trials that compared vitamin D versus control in hospitalized adult patients with COVID-19 showed inconclusive results for the outcomes of mortality, ICU admission, need for mechanical ventilation, length of hospital stay, clinical improvement, and virologic clearance. The certainty of evidence was rated very low due to issues on risk of bias, indirectness, inconsistency and imprecision.

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3.4.2. Should vitamin C be used as an adjunctive treatment for COVID-19 infection in children?

RECOMMENDATION

We suggest against the use of vitamin C as adjunctive treatment for COVID-19 infection in children. (Very low certainty of evidence, Weak recommendation)

Consensus Issues
The recommendation was based on the evidence from eight (8) adult randomized controlled trials that showed no significant benefit and inconclusive results for length of hospital stay, length of ICU stay and need for mechanical ventilation. Although the panel deemed that the harm from the treatment was small, the benefits were uncertain when used as adjunctive treatment for COVID-19 infection. The uncertainty of the evidence coupled with the cost of the drug led the panel to vote against its use regardless of the route of administration. However, the panel agreed that vitamin C supplementation should still be given for those with low dietary vitamin C intake but not as a adjunctive treatment for COVID-19 infection. They also agreed that this recommendation is subject to change based on the availability of higher certainty of evidence.

We found no published studies on the role of Vitamin C as adjunct treatment in pediatric patients with COVID-19. Indirect evidence from eight (8) adult RCTs included in the Philippine COVID-19 Living Clinical Practice Guidelines [9] was reviewed. For the outcome of mortality, there was only a trend towards benefit with small negligible harm. There was no significant benefit and inconclusive results for length of hospital stay, length of ICU stay and need for mechanical ventilation. One study that used intravenous vitamin C reported no adverse events, while one that used oral preparation noted flushing, headache, vomiting and stomach pain. Overall certainty of evidence was very low because of indirectness, imprecision, and inconsistency.

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3.4.3. Should zinc be used as an adjunctive treatment for COVID-19 infection in children?

RECOMMENDATION

We suggest against the use of zinc as adjunctive treatment for COVID-19 infection in children.
(Low certainty of evidence, Weak recommendation)

Consensus Issues
The panel voted against the use of zinc as adjunctive treatment of COVID-19 in children based on the indirect evidence from six randomized controlled trials done in adults that showed inconclusive results in outcomes of in-hospital mortality, duration of recovery, length of hospital stay and hospitalization among ambulatory patients. The panel also agreed that there is a small to moderate potential for harm with moderate costs. However, the panel concurred that zinc treatment is important for those with documented zinc deficiency. They also agreed that this recommendation is subject to change until higher certainty of evidence is available.

Indirect evidence from 6 RCTs showed inconclusive results on the efficacy of zinc as adjunctive treatment, for the outcomes of in-hospital mortality, duration of recovery, length of hospital stay, and hospitalization among ambulatory patients. Adverse events were significantly higher in the group given zinc, and included local site irritation, metallic taste and GI intolerance.

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3.5 Non-Pharmacologic Interventions of COVID-19 in Children

3.5.1. What are the supportive strategies to optimize mental health among children during the COVID-19 pandemic?

RECOMMENDATION

We recommend the implementation of supportive strategies* to optimize mental health among children and adolescents during the COVID-19 pandemic. (Low certainty of evidence, Strong recommendation)

**Supportive strategies for mental health during the COVID-19 pandemic include psychological counseling, physical and leisure activities (outdoor and online exercise platforms, art and dance), mindfulness medication training, personal and spiritual coping, strengthening social support and connecting online with peers, and health-promoting activities.*

Consensus Issues
There were no consensus panel issues noted.

From the five randomized controlled trials (RCTs) included in this review, supportive strategies/interventions include psychological counseling, outdoor exercises, mindfulness meditation, utilization of online platforms for recreation, art and dance. There was a significantly lower mean level of anxiety in the intervention group across five studies. Two RCTs showed a significantly lower level of depression in the intervention group versus the comparator after instituting psychological counseling, outdoor exercise, and dance therapy. Psychological resilience and life satisfaction levels were shown to be higher in the intervention group after instituting psychological counseling and dance therapy. Mean levels of mindfulness were not significantly different between two types of art therapies (Mandala and emotion-based therapy) but levels were significantly higher post intervention. Overall well-being index is significantly higher in the intervention group after instituting aerobics exercises and mindfulness meditation.

Two qualitative studies elucidated possible effective coping strategies utilized in two countries, namely connecting online, engaging in leisure and health promoting activities, personal and spiritual coping and having social support from family, religious community and school personnel.

The over-all certainty of evidence was low. There was a decrease in anxiety and depression and increase in psychological resilience, life satisfaction, positive emotion score and overall well-being. No net harm was noted in the included RCTs based on the mean levels of measured outcomes after instituting the above interventions.

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3.5.2. What preventive interventions should be used in school settings to reduce transmission of COVID-19?

RECOMMENDATION

We recommend a multi-layer approach using multiple non-pharmacologic interventions* in school settings to limit transmission of COVID-19 in schools. (Very low certainty of evidence, Strong recommendation)

The non-pharmacologic interventions are wearing of masks of students, physical distancing, engineering controls (ventilation, personal hygiene and handwashing, disinfection of surfaces), administrative controls (blended learning, phased reopening, no/reduced mixing of classes, restriction of class size, minimized or staggered breaks, symptom monitoring, self-quarantine, contact tracing, and early testing).

Consensus Issues
The recommendation is based on 17 studies done in first-world countries during the earlier phase of the pandemic. Although the evidence was judged to be very low due to issues on indirectness and risk of bias (descriptive), the consensus panel was unanimous in deciding that the burden of the problem and the equity of the issue deserved a strong recommendation for the use of multi-layer approach coupled with multiple NPIs. The specific NPIs noted above were voted on individually by the consensus panel members and only those that reached a vote of at least 75% were included. The panel noted that these NPIs were the minimum preventive measures for schools to open considering the equity, accessibility and feasibility of the interventions. Despite the low to moderate certainty of evidence favoring the HEPA filters and carbon dioxide monitors respectively, these NPIs did not reach consensus vote due to issues on cost and accessibility especially for public schools in more rural areas. However, the panel noted that these devices are indirect ways to ensure that there is adequate air exchange in enclosed spaces.

Conducted in several countries, 16 cross-sectional and 1 intervention studies on the impact of school re-opening on transmission of COVID-19 were included in this review. All countries put in place multiple-layered prevention strategies–- from community to school to classroom to individual level. Multiple preventive measures were instituted in all the schools with the minimum health protocols of masking, personal hygiene and physical distancing mentioned as NPIs in only 7 studies, which were done in 4 countries (including 2 US counties). Variable combinations of NPIs were used.

Outcomes measured also varied among countries with all studies showing a decrease in transmission in terms of number of cases, transmission rates, number of outbreaks per week, number of cases per outbreak, attack rate, incidence and/or prevalence rates. Two studies found low transmission even in a setting of high community incidence. One study reported a major outbreak due to a breach in the NPI protocols.

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CHAPTER 4: DISCUSSION

4.1 Outputs of the Philippine Pediatric COVID-19 Living CPG Project

Clinical Practice Questions

COVID-19 management issues and questions were collected from the different subspecialty societies of the PPS, the Steering Committee members and Consensus Panelists during the organizational meetings and consensus panel meetings. The topics were reviewed and prioritized. Priority topics were then assigned to the evidence reviewers for evidence reviews. A total of 15 priority topics were identified.

Consensus Meetings, Evidence Summaries, and Recommendations

For the first phase of this project, there were a total of 15 evidence summaries presented and 24 recommendations generated during the consensus panel presentations.

4.2 Applicability Issues

The members of the Consensus Panel provided information on the facilitators, barriers, and resource implications for the implementation of the recommendations. They used their expertise and experience to identify these issues, which were discussed in more detail in the *Consensus Issues* section of each evidence summary. These were considered in the final wording of the recommendations. The following subsections summarize the overall discussion of the panelists.

Organizational Considerations to Implementation

The availability of testing kits and medical equipment for the screening and diagnostic tests for COVID-19 would likely vary at the regional, provincial, or even municipal/city level. These issues were especially relevant to RT-PCR testing, rapid antibody, and antigen testing, chest imaging (X-ray, CT-Scan, and ultrasound), and laboratory parameters (LDH, CRP, Ferritin, D-dimer). Clinical risk assessment and using the 14-day symptom test were useful tools for screening for COVID-19, especially if there was a limitation in the availability of screening tests. Specially trained personnel were needed to do the more specialized tests, such as pooled testing using RT-PCR.

Aside from the availability of various testing modalities, there would be some limitations in the availability of treatment and critical care interventions also, most especially those investigational drugs only being accessible through the public via FDA's emergency use authorization. Medical specialists, especially those from infectious diseases, pulmonary medicine, and critical care medicine, were important to effectively lead in the use of these treatments for the management of COVID-19 patients. These limitations would be further compounded by the limitations in available isolation beds, hospital ward beds, and ICU beds.

For non-pharmacologic and prophylactic interventions for COVID-19, one potentially major barrier was the public's perceptions of these interventions and their actual compliance. This was evident in many instances of violations of the minimum public health standards set by DOH: wearing of face mask, physical distancing, and hand hygiene. In addition to these, there were rising trends in the use of non-proven prophylactic interventions and ineffective medical devices (such as ionizing air filters).

Resource Implications

As a low-middle-income country, our limited resources needed to be allocated and used efficiently. The cost of the tests and interventions being done for COVID-19 management was one important consideration discussed in the panel meetings, especially the investigational drugs (such as remdesivir, tocilizumab and the monoclonal antibodies). Health technology assessment should be a key gatekeeping mechanism to ensure that all payments by the government (through PhilHealth) are cost-effective.

4.3 Monitoring

The recommendations and evidence summaries of the Philippine Pediatric COVID-19 Living Clinical Practice Guidelines were published on the PSMID website last April 4, 2022, in order to maintain a single repository of all local clinical recommendations on COVID-19, both for the adult and pediatric populations. Since the addition of the pediatric recommendations, there were 92,952 views.

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CHAPTER 5: 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. This emphasized the need for further primary research to be conducted.

While existing studies on investigational treatment interventions identified the subset of patients that would benefit best (such as tocilizumab with dexamethasone for patients with elevated inflammatory biomarkers), many of these studies were performed on adult patients. Studies on treatment for pediatric patients were sorely lacking especially when it comes to dosing frequency of administration, combinations with other drugs, etc.

Diagnosis and treatment were sometimes overemphasized in the management of COVID-19. Equally important were the prophylactic and non-pharmacologic interventions that are more proximal steps in the national strategy of prevention, detection, isolation, treatment, and reintegration. However, these areas were still not very much studied. These studies were also crucial to prove the lack of effectiveness of interventions that many may subscribe to.

Finally, the living CPG methodology used in this project was the second local adoption known to the project team, the first being the Philippine COVID-19 Living CPG for adults. Research into streamlining the living CPG process is important to make it more efficient. The impact measurement of this living CPG, as described in the *Guideline Monitoring and Evaluation Criteria* subsection, would be another study to formally demonstrate the effects of CPG implementation in the country.

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CHAPTER 6: CONCLUSIONS

The Philippine Pediatric COVID-19 Living CPG identified 15 priority questions on COVID-19 management, infection prevention, and control, generated 15 evidence summaries, and came up with 24 recommendations. Thematic areas included in this CPG were screening and diagnosis, treatment, prophylactic interventions, adjunct interventions and non-pharmacologic interventions.

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 Pediatric COVID-19 Living CPG:

1. Retain consensus panel members who wish to continue contributing their time and expertise to the COVID-19 Living CPG.
2. Continue holding capacity building workshops on CPG development, systematic reviews, and evidence-based medicine to increase the pool of skilled evidence reviewers.
3. As much as possible, allow a longer project cycle for both the implementation of the Living CPG development and capacity building activities. This will ensure that adequate preparation is done by the task forces and consensus panelists prior to the *en banc* meeting.

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