

PHILIPPINE PEDIATRIC COVID-19

LIVING CLINICAL PRACTICE GUIDELINES

As of March 2022



Disclaimer

As a living guideline, the recommendations will be updated, and new recommendations will be added as the evidence evolves. The living recommendations are based on the best evidence available in scientific literature at the time of its formulation. However, this living CPG is not a comprehensive guide to all practice questions and management options on COVID-19 in children. 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.

Contact Us

Send us an email at pediacovidcpq.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 Philippine Pediatric COVID-19 Living Clinical Practice Guidelines Taskforce.

Acknowledgements

The Philippine Pediatric COVID-19 Living Clinical Practice Guidelines was funded and supported by the Philippine Pediatric Society (PPS) and the Pediatric Infectious Disease Society of the Philippines (PIDSP). The support of the following people from PPS and PIDSP were most valued: PPS Presidents, Dr. Joselyn A. Eusebio (2020–2022) and Dr. Florentina U. Ty (2022–2024), and PIDSP Presidents, Dr. Mary Ann C. Bunyi (2020–2022), and Dr. Fatima I. Gimenez (2022–2024). We would also like to thank the subspecialty societies of the PPS for helping identify priority clinical questions that needed to be addressed by this CPG.

The project was completed with the valuable contribution of each of the 42 people involved in the CPG project, including the Steering Committee, Evidence Reviewers, Consensus Panelists, Expert Facilitator, Technical Coordinators, Technical Writer, Oversight Committee, and Project Manager.

The Philippine Pediatric COVID-19 Living CPG team dedicates this work to the pediatric patients and their families who are 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.

Participating Professional Societies and Institutions



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I. 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.

A. Summary of Recommendations

Recommendation	Strength of Recommendation	Certainty of Evidence
Screening and Diagnosis		
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.	Strong	Moderate
*The use of three specific saliva RT-PCR assays is recommended: Allplex 2019-nCOV assay, Cobas 6800, QuantStudio 7 system.		
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.	Weak	Moderate
*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.		
We suggest against the use of nasopharyngeal aspirate as an alternative clinical specimen among non-hospitalized children suspected of COVID-19 infection.	Weak	Moderate

Recommendation	Strength of Recommendation	Certainty of Evidence
Treatment		
We suggest the against routine use of intravenous immunoglobulin for children with COVID-19 infection.	Weak	Very low
We suggest the use of systemic corticosteroids (dexamethasone) among children with severe and critical COVID-19 infection.	Weak	Very low
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
We suggest the use of remdesivir in hospitalized children with severe COVID-19 infection.	Weak	Very low
We suggest the use of remdesivir in non-hospitalized children with COVID-19 infection with at least one (1) risk factor* for disease progression.	Weak	Low
<p><i>*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.</i></p>		
We suggest against the routine use of anticoagulation in children with COVID-19 infection or MIS-C.	Weak	Very low
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
<p><i>*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.</i></p>		
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
<p><i>*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.</i></p>		

Recommendation	Strength of Recommendation	Certainty of Evidence
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
*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.		
There is insufficient evidence to recommend the use of sotrovimab as treatment of non-hospitalized children with COVID-19 infection.	--	Low
We suggest against the use of sotrovimab as treatment of hospitalized children with COVID-19 infection.	Weak	Low
We suggest against the use of amubarvimab plus romlusevimab as treatment of children with COVID-19 infection.	Weak	Low
We suggest against the use of regdanvimab as treatment of children with COVID-19 infection.	Weak	Low
Prophylactic Interventions		
We suggest against the routine use of vitamin D for the prevention of COVID-19 infection in children.	Weak	Very low
We suggest against the routine use of vitamin C for the prevention of COVID-19 infection in children.	Weak	Very low
We suggest against the routine use of zinc for the prevention of COVID-19 infection in children.	Weak	Low
Adjunct Interventions		
We suggest against the use of vitamin D as adjunctive treatment for COVID-19 infection in children.	Weak	Very low
We suggest against the use of vitamin C as adjunctive treatment for COVID-19 infection in children.	Weak	Very low
We suggest against the use of zinc as adjunctive treatment for COVID-19 in children.	Weak	Low

Recommendation	Strength of Recommendation	Certainty of Evidence
Non-Pharmacologic Interventions		
We recommend the implementation of supportive strategies* to optimize mental health among children and adolescents during the COVID-19 pandemic.	Strong	Low
<i>*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 peers, and health-promoting activities.</i>		
We recommend a multi-layer approach using multiple non-pharmacologic interventions* in school settings to limit transmission of COVID-19 in schools.	Strong	Very low
<i>*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).</i>		

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 $\text{SpO}_2 \geq 95\%$ 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 $\text{SpO}_2 < 95\%$; 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

II. 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.

A. 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

B. 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.

C. 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

III. CPG 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].

A. 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.

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

Key Clinical Issues and Questions

The Philippine 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
<ul style="list-style-type: none"> • Alternative clinical specimens to nasopharyngeal swab for RT-PCR 	<ul style="list-style-type: none"> • Intravenous immunoglobulin (IVIG) • Corticosteroids • Tocilizumab • Remdesivir • Anticoagulation • Monoclonal antibodies
Prophylactic Interventions	Adjunct Interventions
<ul style="list-style-type: none"> • Vitamin D • Vitamin C • Zinc 	<ul style="list-style-type: none"> • Vitamin D • Vitamin C • Zinc
Non-Pharmacologic Interventions	
<ul style="list-style-type: none"> • Supportive strategies to optimize mental health • Preventive interventions used in school settings to reduce transmission 	

B. 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. 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 (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.

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	<ul style="list-style-type: none">• Risk of Bias• Inconsistency• Indirectness• Imprecision• Publication Bias	<ul style="list-style-type: none">• 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.

C. 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	<ul style="list-style-type: none"> • Sensitivity and specificity • Positive and negative predictive values • Likelihood ratio 	<ul style="list-style-type: none"> • Adverse events
Treatment	<ul style="list-style-type: none"> • Mortality • Recovery • Hospitalization • Adverse events • Clinical improvement • Duration of ICU stay • Need for mechanical ventilation • Duration of hospital stay 	<ul style="list-style-type: none"> • Negative viral conversion
Treatment – Anticoagulation	<ul style="list-style-type: none"> • Mortality • Thrombosis • Bleeding events 	
Prophylactic Interventions	<ul style="list-style-type: none"> • Forward transmission • Adverse events • Incidence of COVID-19 • Viral load 	
Non-Pharmacologic Interventions – School Setting	<ul style="list-style-type: none"> • Transmission rates • Number of outbreaks • Attack rate • Incidence rate • Prevalence rate • Number of cases 	
Non-Pharmacologic Interventions – Mental Health	<ul style="list-style-type: none"> • Depression • Perception of overall well-being • Anxiety • Resilience 	<ul style="list-style-type: none"> • 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.

D. 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 (Figure 1) 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 (Figure 2).



Philippine COVID-19 Living Clinical Practice Guidelines

Institute of Clinical Epidemiology, National Institutes of Health, UP Manila

In cooperation with the Philippine Society for Microbiology and Infectious Diseases

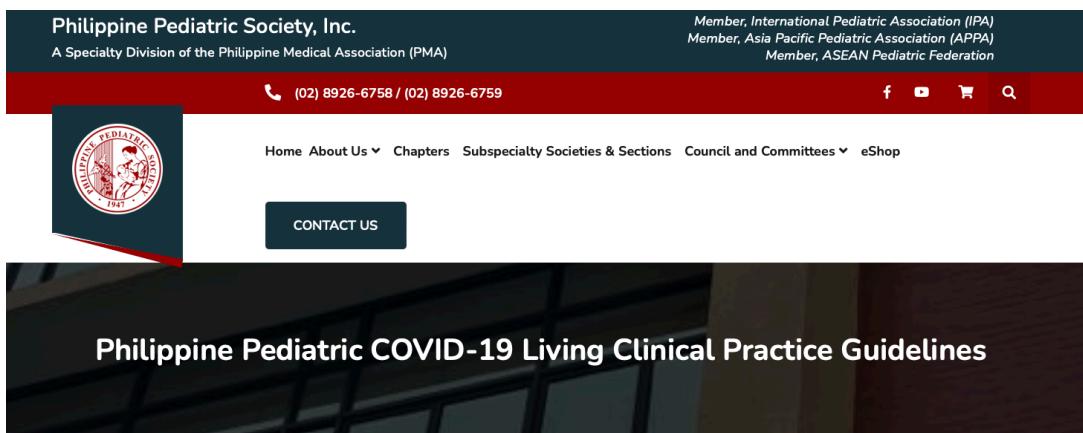
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CONTACT US

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.

Figure 1. Contact details in the Webpage for the Philippine COVID-19 Living CPG.



The COVID-19 pandemic has inflicted 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 2,127 cases as of December 31, 2021, with 89.5% requiring hospitalization and 40.5% 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. The development process followed the Manual for Clinical Practice Guideline Development of the Department of Health and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Approach. The pediatric recommendations can be found in the last section of the Philippine COVID-19 Living Clinical Practice Guidelines.

[View](#)

Figure 2. Philippine Pediatric COVID-19 Living CPG in the PPS Website.

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.

E. 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 (Figure 3). It has undergone improvements from the feedback of CPG users and members of the Living CPG task force.



Philippine COVID-19 Living Recommendations

Updated March 9, 2022.

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The Philippine COVID-19 Living Recommendations document is brought to you by the Institute of Clinical Epidemiology, National Institutes of Health, UP Manila in cooperation with the Philippine Society of Microbiology and Infectious Diseases (PSMID). This was funded by the Department of Health (DOH) AHEAD Program through the DOST-Philippine Council for Health Research and Development (PCHR) and the DOH-Disease Prevention and Control Bureau.

Pediatric Recommendations

SECTION LINKS:

Screening and Diagnosis ▾

Treatment ▾

Critical Care and Respiratory Management ▾

Non-Pharmacologic Interventions ▾

Vaccines and Prophylactic Interventions ▾

Adjunct Interventions ▾

Pediatric Recommendations ▾

- ▶ Which **clinical specimens** can be used as an alternative to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 infection in children?
- ▶ Should **anticoagulation** be used in the treatment of children with COVID-19 infection?
- ▶ Should **corticosteroids** be used in the treatment of children with COVID-19 infection?
- ▶ Should **intravenous immunoglobulin** be used in the treatment of children with COVID-19 infection?
- ▶ Should **monoclonal antibodies** be used in the treatment of children with COVID-19 infection?
- ▶ Should **remdesivir** be used in the treatment of children with COVID-19 infection?
- ▶ Should **tocilizumab** be used in the treatment of children with COVID-19 infection?
- ▶ Should **vitamin C** be used as a preventive measure for COVID-19 infection in children?
- ▶ Should **vitamin D** be used as a preventive measure for COVID-19 infection in children?
- ▶ Should **zinc** be used as a preventive measure for COVID-19 infection in children?
- ▶ Should **vitamin C** be used as an adjunctive treatment for COVID-19 infection in children?
- ▶ Should **vitamin D** be used as an adjunctive treatment for COVID-19 infection in children?
- ▶ Should **zinc** be used as an adjunctive treatment for COVID-19 infection in children?
- ▶ What are the **supportive strategies to optimize mental health** among children during the COVID-19 pandemic?
- ▶ What **preventive interventions should be used in school settings** to reduce transmission of COVID-19?

Figure 3. Pediatric recommendations in the Webpage for the Philippine COVID-19 Living CPG.

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.

F. 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.

G. 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 4.

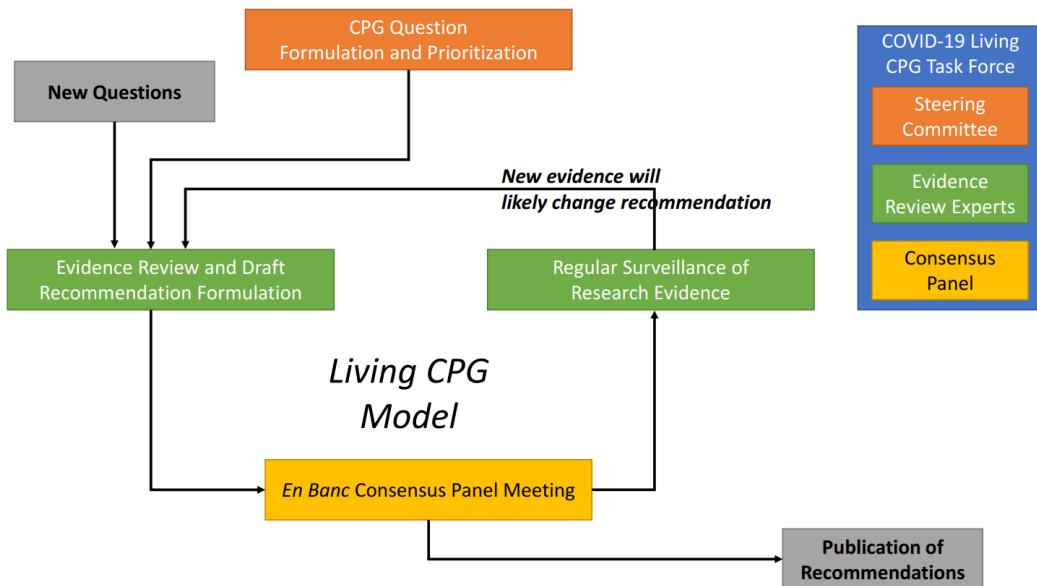


Figure 4. Philippine Pediatric COVID-19 Living CPG Development Process.

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.

H. 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 Appendix B. The other members of the Consensus Panel and Evidence Review Experts did not have any conflicts of interest.

IV. Evidence Summaries and Recommendations

A. Screening and Diagnosis of COVID-19 in Children

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

RECOMMENDATION
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)
<i>*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.</i>
<i>Consensus Issues</i> There were no consensus issues noted.

RECOMMENDATION
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)
<i>*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.</i>
<i>Consensus Issues</i> There were no consensus issues noted.

RECOMMENDATION
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)
<i>Consensus Issues</i> 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.

Evidence Summary

Key Findings

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.

Introduction

The RT-PCR of the nasopharyngeal swab (NPS) is the current reference standard for diagnosis of SARS-CoV-2 infection [1]. However, NPS collection causes difficulty and discomfort in children as it is invasive, requires trained healthcare personnel, and the use of protective personal equipment (PPE). Recommended alternative specimens like nasal swab, oropharyngeal/ pharyngeal swab, mid-turbinate swab, and saliva are based on studies in adults [1-3]. Saliva sample collection is easy, non-invasive, and can be performed by non-healthcare professionals or individuals themselves who are properly instructed.

Recent studies have evaluated several alternative specimens to NPS for RT-PCR in children. The sensitivity of these specimens has shown considerable variability compared with NPS, ranging from 0.60 to 0.93 [4,5]. Reported heterogeneity is likely to reflect differences in sampling techniques, symptom duration, type of population being tested and assay kit. This review was conducted to determine the diagnostic performance of alternative specimens that may be easier and safer to collect in children.

Review Methods

We searched Medline through PubMed, Cochrane CENTRAL, ChinaXiv.org, MedRxiv.org, BioRxiv, COVID-19 Open Living Evidence, Living Evidence on COVID-19, and UptoDate on January 05, 2022 (Appendix 1) using free text and MeSH terms. Our inclusion criteria may be found in Table 1. We excluded studies with incomplete data on the accuracy of the index tests, with less than 30 participants. Included studies were appraised using QUADAS 2 tool and Joanna Briggs Criteria for the study on safety of obtaining saliva specimen. Subgroup analysis was planned for age group, symptomatology (symptomatic/ asymptomatic), setting (hospital/outpatient), method of specimen collection, and type of assay kit. (Appendix 4E-4M). However, data was unavailable for subgroup analysis on age group and symptomatology (symptomatic/asymptomatic).

Table 1. PICO criteria for alternative clinical specimen.

Population	Children with COVID-19
Intervention/Exposure	Alternative clinical specimen for RT-PCR for the diagnosis of COVID-19
Comparison	Nasopharyngeal RT-PCR
Outcomes	Accuracy, true positives, false positives, false negatives, true negatives, adverse events

Results

Summary of characteristics of included studies

Out of the 1, 404 studies screened, we included 9 observational studies in this review [4-12] (Appendix 2A).

Saliva RT-PCR

Seven studies were retrieved but only three studies with no serious risk for bias were included in the meta-analysis to determine the diagnostic accuracy of using saliva specimen in the diagnosis of COVID-19. These three studies included 1,043 non-hospitalized children 1 month to 18 years old suspected of COVID-19 based on the presence of symptoms or history of exposure to confirmed COVID-19 individuals. Saliva was collected either by a healthcare professional, a caregiver or self-collected under supervision. The studies used different assays, namely 1) Allplex 2019-nCoV assay 2) Cobas 6800, and 3) QuantStudio 7 system.

Mid-turbinate swab RT-PCR

One study included 569 non-hospitalized symptomatic children suspected of COVID-19, median age was 5 years (range 1 month to < 18 y/o), and with a median time between symptom onset and specimen collection of 4 days (range 1 to 14 days). Specimen were collected by trained clinical staff. They used either RealStar SARS-CoV-2 RT-PCR kit or Aptima SARS-CoV-2 Assay [12].

Nasopharyngeal aspirate RT-PCR

One study evaluated the diagnostic performance of NPA on 136 hospitalized children suspected of COVID-19 provided 300 paired NPS/NPA specimens for analysis. They used either AllplexTM 2019-nCoV assay or GeneFinder COVID-19 Plus RealAmp Kit [9].

Methodological quality

Saliva RT-PCR

The three studies were without serious risk of bias with outcomes having moderate certainty of evidence due to imprecision (Appendix 4).

Mid-turbinate swab

The certainty of evidence for mid-turbinate swab RT-PCR was rated moderate due to imprecision (Appendix 4).

Nasopharyngeal aspirate

The certainty of evidence for the sensitivity of nasopharyngeal aspirate RT-PCR was low. There was a serious risk of bias due to timing of specimen collection, and imprecision (Appendix 4).

Diagnostic accuracy (Appendices 5 & 6)

Saliva RT-PCR

Three studies were pooled to check for diagnostic accuracy of saliva as specimen. Pooled sensitivity was 0.87 (95% CI 0.81, 0.91) with wide confidence interval and specificity of 0.98 (95% CI 0.97, 0.99). It demonstrated high positive PV of 91.75% (95% CI 87.02, 94.86) and negative PV of 96.82% (95% CI 95.41, 97.81). The LRs for a positive and a negative saliva RT-PCR were 45.48 (95% CI 40.17, 51.49) and 0.13 (95% CI 0.12, 0.14), respectively. (moderate certainty of evidence).

Mid-turbinate swab RT-PCR

One study on mid-turbinate RT-PCR showed a sensitivity of 0.82 (95% CI 0.74, 0.89) (n= 569) while its specificity was high at 1.00 (95% CI 0.99, 1.00). The positive and negative PVs were 100% (95% CI 96, 100) and 96% (95% CI 94, 97), respectively and the LR for a negative test was 0.18 (95% CI 0.16, 0.19) (n= 569). The certainty of evidence was moderate.

Nasopharyngeal aspirate RT-PCR

One study on NPA RT-PCR showed sensitivity: 0.81 (95% CI 0.63, 0.93) (n = 136 with 300 paired specimen). Its specificity was high: 0.93 (95% CI 0.90, 0.94). Its positive and negative PVs were 58% (95% CI 43, 72) and 98% (95% CI 95, 99). The LR was 12 (95% CI 11, 14) for a positive test and 0.21 (95% CI 0.15, 0.29) for a negative test (n = 136 with 300 paired specimens. The certainty of evidence was low.

Adverse events

There were no reported adverse events with saliva specimen collection among hospitalized children (n= 156, one study, low certainty of evidence) (Appendix 4). There were no studies that reported adverse events on the use of mid-turbinate swab and NPA specimens.

Harms associated with false negative and false positive saliva RT-PCR results

With a sensitivity of 81-91%, saliva RT-PCR will detect 81-91 out of every 100 with COVID-19, but 9-19 will be missed as they will have false negative test. With a specificity of 97-99 %, out of every 100 individuals without COVID-19, 1-3 will be wrongly diagnosed as having COVID-19.

Other Considerations (Evidence to Decision)

Table 2. Evidence to Decision Considerations

Cost	<p>Philhealth benefit package rates for COVID-19 testing:</p> <ul style="list-style-type: none"> a) plate-based NPS RT-PCR: Php 800- 2,800 b) cartridge-based NPS RT-PCR: Php 500- 2,450 [14]. <p>There is no Philhealth benefit package for saliva, NPS and mid-turbinate for RT-PCR [14].</p> <p>Philippine Red Cross offers saliva RT-PCR test for Php 2,000 [15].</p>
Availability	<p>There are FDA-approved, available test kits for saliva RT-PCR, mid-turbinate swab and nasopharyngeal aspirate RT-PCR. For saliva RT-PCR, these are Allplex, Argene SarsCoV-2 R gene, Molaccu and TaqPath CE-IVD. For mid-turbinate swab RT-PCR, these are Xpert Xpress, 1 copy qPCR 4plex, TaqPath FluA FluB combo kit and TaqPath CE-IVD. For NPA RT-PCR, these are Opti, Aptima, Triplex RT qPCR, CoviPath and TaqPath CE-IVD. Of these kits, only the saliva RT-PCR Allplex assay was used in the study by Trobajo-San Martin.</p>
Patient's Values or Preferences; Social Impact	<p>398 (77%) children preferred saliva specimen collection to NPS/ OPS/ mid turbinate swab/ throat swab specimens. These included 2- 11 y/o suspected to have COVID-19 and among asymptomatic children attending school day care centers. (n=516, from three cross-sectional studies, low certainty of evidence) [16-18].</p>
Factors to Impact Acceptability or Compliance	<p>Saliva: In 2,088 children, 97% provided adequate saliva samples for RT-PCR. These included hospitalized children suspected of COVID-19 (n=461) and asymptomatic school children (n= 1,627) from four cross-sectional studies, very low certainty of evidence) [17, 19-21].</p> <p>The minimum age for adequate saliva sample collection was 5 y/o in hospitalized children suspected to have COVID-19 (n= 461, one cross sectional preprint, very low certainty [20].</p> <p>With a sensitivity of 81-91%, saliva RT-PCR will detect 81-91 out of every 100 with COVID-19, but 9-19 will be missed as they will have false negative test. With a specificity of 97-99 %, out of every 100 individuals without COVID-19, 1-3 will be wrongly diagnosed as having COVID-19.</p> <p>Mid-turbinate swab: Among 67 children 2 years and older with influenza-like illness, a median discomfort score of 1 was obtained for mid-turbinate specimen collection compared with a score of 3 for NPS specimen. (validated 6-point Faces Pain scale with zero being no discomfort and 6 being worst imaginable) [22].</p>

	NPA: In 86 adult patients with URTI, 26% complained that NPA procedure was very uncomfortable, majority (69%) said it was mildly uncomfortable and only 6% patients reported no discomfort. On a 10-point-scale, the median discomfort was 4 [23].
Cost	Philhealth benefit package rates for COVID-19 testing: a) plate-based NPS RT-PCR: Php 800- 2,800 b) cartridge-based NPS RT-PCR: Php 500- 2,450 [14]. There is no Philhealth benefit package for saliva, NPS and mid-turbinate for RT-PCR [14]. Philippine Red Cross offers saliva RT-PCR test for Php 2,000 [15].
Availability	There are FDA-approved, available test kits for saliva RT-PCR, mid-turbinate swab and nasopharyngeal aspirate RT-PCR. For saliva RT-PCR, these are Allplex, Argene SarsCoV-2 R gene, Molaccu and TaqPath CE-IVD. For mid-turbinate swab RT-PCR, these are Xpert Xpress, 1 copy qPCR 4plex, TaqPath FluA FluB combo kit and TaqPath CE-IVD. For NPA RT-PCR, these are Opti, Aptima, Triplex RT qPCR, CoviPath and TaqPath CE-IVD. Of these kits, only the saliva RT-PCR Allplex assay was used in the study by Trobajo-San Martin.
Patient's Values or Preferences; Social Impact	398 (77%) children preferred saliva specimen collection to NPS/ OPS/ mid turbinate swab/ throat swab specimens. These included 2- 11 y/o suspected to have COVID-19 and among asymptomatic children attending school day care centers. (n=516, from three cross-sectional studies, low certainty of evidence) [16-18].
Factors to Impact Acceptability or Compliance	Saliva: In 2,088 children, 97% provided adequate saliva samples for RT-PCR. These included hospitalized children suspected of COVID-19 (n=461) and asymptomatic school children (n= 1,627) from four cross-sectional studies, very low certainty of evidence) [17, 19-21]. The minimum age for adequate saliva sample collection was 5 y/o in hospitalized children suspected to have COVID-19 (n= 461, one cross sectional preprint, very low certainty [20]). With a sensitivity of 81-91%, saliva RT-PCR will detect 81-91 out of every 100 with COVID-19, but 9-19 will be missed as they will have false negative test. With a specificity of 97-99 %, out of every 100 individuals without COVID-19, 1-3 will be wrongly diagnosed as having COVID-19. Mid-turbinate swab: Among 67 children 2 years and older with influenza-like illness, a median discomfort score of 1 was obtained for mid-turbinate specimen collection compared with a score of 3

for NPS specimen. (validated 6-point Faces Pain scale with zero being no discomfort and 6 being worst imaginable) [22].

NPA: In 86 adult patients with URTI, 26% complained that NPA procedure was very uncomfortable, majority (69%) said it was mildly uncomfortable and only 6% patients reported no discomfort. On a 10-point-scale, the median discomfort was 4 [23].

Recommendations from Other Groups

The US-CDC (28 Dec 2021), American Academy of Pediatrics (AAP) (17 Nov 2021) and the Philippine Pediatric Society (PPS) (08 Jan 2022) along with the Pediatric Infectious Disease Society of the Philippines (PIDSP) recommend nasal mid turbinate, nasopharyngeal aspirate, and saliva as alternative specimens to NPS in the diagnosis of COVID-19 using RT-PCR [1-3].

The Infectious Disease Society of America (IDSA) (06 May 2021) suggests mid turbinate swab, and saliva as alternative specimens to NPS in the diagnosis of COVID-19 using RT-PCR [24].

The World Health Organization (WHO) (11 Sept 2020) does not recommend the use of saliva as the sole specimen type for routine clinical diagnostics. Due to a large variety of collection methods and processing steps, WHO recommends that laboratories must collect their own performance data linked to the local method of collection and in the relevant population for testing [25].

European CDC states that further clinical studies are warranted on the sensitivity of saliva for RT-PCR for symptomatic and asymptomatic children, and to standardize the sampling collection [26].

Research Gaps

As of January 2022, there are no ongoing studies. Further studies on the sensitivity of saliva, nasopharyngeal aspirate and mid-turbinate swab specimens for RT-PCR for COVID-19 diagnosis in children are needed, stratified by age, illness duration, setting, type of assay, and method of specimen collection. Studies on other specimens like oropharyngeal, pharyngeal or nasal swab and sputum are also recommended.

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Evidence Summary Appendices

Appendix 1. Search Yield and Results

Table 1. Search Yield and Results from different databases

Database	Search Strategy	Search Yield
Medline through PubMed	((COVID-19) AND ((pediatric) OR (children)) AND (((((saliva) OR (nasal swab)) OR (oropharyngeal swab)) OR (throat swab)) OR (nasopharyngeal)) OR (nasopharyngeal swab)) OR (upper respiratory tract))) AND (((((sensitivity) OR (accuracy)) OR (concordance)) OR (cost effectiveness)) OR (acceptability)) 19 AND 20	248
Cochrane CENTRAL database https://clinicaltrials.gov/ https://www.who.int/clinical-trials-registry-platform PubMed Embase	COVID-19 as Population (PICO search, Advanced Search) Search Results There are 11 results for your search on MeSH descriptor: COVID-19 Nucleic Acid Testing Explode all trees	24
ChinaXiv.org	Abstract: (COVID-19) AND Subjects::("Medicine, Pharmacy" OR "Clinical Medicine")	9
MedRxiv.org (with BioRxiv)	for term "COVID-19 AND (pediatric OR children) AND RT-PCR AND (Sensitivity OR accuracy OR cost-effectiveness OR feasibility)" and posted between "01 Jan, 2020 and 05 Jan, 2022"	376
Cross-referencing http://www.chictr.org.cn/searchprojen.aspx	Hoch	12
COVID-19 Open Living Evidence Synthesis	COVID-19	0
Living Evidence on COVID-19 zika	COVID-19	0
Australia: https://covid19evidence.net.au/		736
		0

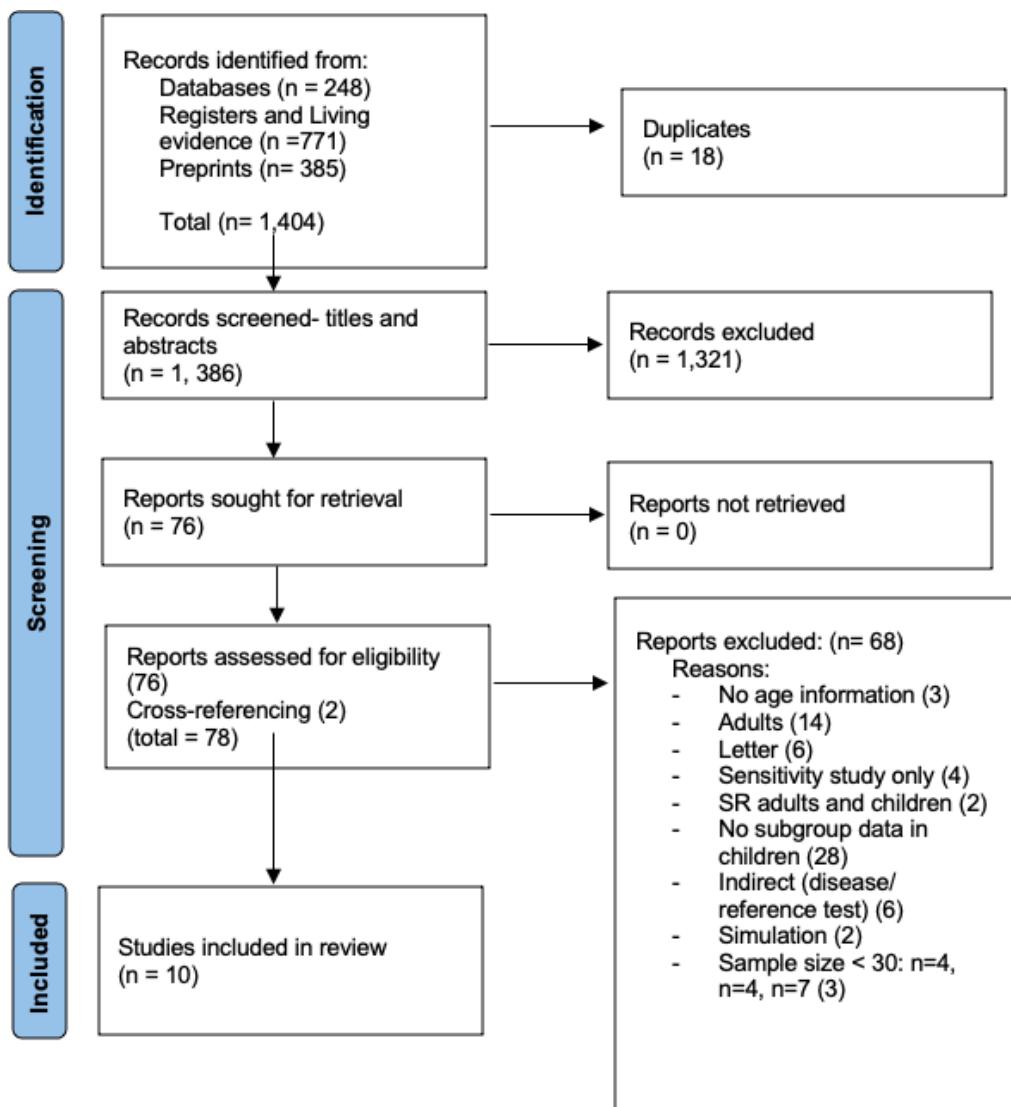


Figure 1. PRISMA flow diagram |

Appendix 2A. Characteristics of Included Studies

Author	Study design	Population	Index test Assay	Reference standard	Outcome
Al-Suwaidi 2021 UAE	Cross-sectional	476 suspected COVID-19 Mean age 10.8 y/o SD 3.9 years (range 3- 18 y/o) • Outpatient	Saliva RT-PCR Allplex 2019-nCoV assay (Seegene, Seoul, South Korea)	NPS RT-PCR	Sn Sp
Fougere 2021 Switzerland	Cross-sectional	397 suspected COVID-19 • Outpatient	Saliva RT-PCR Cobas 6800 (Roche, Basel, Switzerland) or QuantStudio 7 system (Applied Biosystems, Waltham, United States)	NPS RT-PCR	Sn Sp
Huber 2021 Switzerland	Cross-sectional	170 suspected COVID-19 Median age -13 (range 5-17 y/o) Median days of symptoms 2 days (range 1-21 days) • Outpatient	saliva RT-PCR Cobas SARS-CoV-2 IVD test (Roche) on a Cobas 6800	NPS RT-PCR	Sn Sp
Felix 2021 Brazil	Cross-sectional	50 suspected COVID-19 Mean 10.24 (+- 3.52 years) Mean days of symptoms 4.76 (+- 1.31 days) • Outpatient	Saliva RT-PCR Altona Realstar Kit	NPS RT-PCR	Sn Sp
Alenquer 2021 Portugal	Cross-sectional	85 suspected COVID-19 and causes unrelated to COVID-19 (other medical pathologies or surgeries) (1- 10 y/o) Saliva collected within 48 hours from NPS collection • Hospital	Saliva RT-PCR iTaq Universal Probes One-Step Kit (BIORAD, #12013250)	NPS RT-PCR	Sn Sp
Banerjee 2021 USA	Cross-sectional	109 suspected COVID-19 Mean age 10.8 years (range 5-14 y/o) • Outpatient	Saliva RT-PCR Aptima SARS-CoV-2-Assay	NPS RT-PCR	Sn Sp
Trojano-Samartín 2021 Spain	Cross-sectional	103 suspected of COVID-19 (subgroup) • Outpatient	Saliva RT-PCR AllplexTM 2019-nCoV assay (Seegene, Seoul, Korea)	NPS RT-PCR	Sn Sp
Sahni 2021 USA	Cross-sectional	569 children suspected COVID-19 median age 5 y/o (range 1 month to <18 y/o) Median onset of symptoms 2 days (range 0-13 days) • Outpatient	Mid turbinate swab RealStar SARS-CoV-2 Rt-PCR kit (Germany) or Aptima SARS-CoV-2 Assay on the Hologic Panther System (Massachusetts)	NPS RT-PCR	Sn Sp
Di Pietro 2021 Italy	Cross-sectional	136 suspected COVID-19 children (600 paired specimens) • Hospital	nasopharyngeal aspirate AllplexTM 2019-nCoV assay with Seegene NIMBUS & STARlet instrument (C _t cut-off value for a positive test was ≤ 40) or GeneFinder COVID-19 Plus RealAmp Kit adapted to the ELITE InGenius® (ELITechGroup) (C _t cut-off value for a positive test was ≤ 45)	NPS RT-PCR	Sn Sp

Appendix 2B. Method of Saliva Collection for RT-PCR

Study	Saliva collection
Alenquer 2021	1 ml of saliva collected with the help of a healthcare worker, after food and water abstinence for 30 minutes, by pooling saliva in the mouth and gently spitting it into a sterile container without coughing or clearing their throats For < 1 y/o- saliva was aspirated from the mouth with a suction tube
Al Suwaidi 2021	1- 3 ml of self-collected saliva, after food and water abstinence, by pooling saliva in the mouth for 1-2 minutes and spitting into a sterile container.
Banerjee 2021	2 ml of self-collected saliva, after food and water abstinence for 30 minutes by pooling saliva in the mouth and using a straw to fill the collection tube. A saliva collection kit was provided with a straw and 10 ml conical tube.
Felix 2021	The children were asked to spit into a sterile container for a collection of about 1 ml of saliva.
Fougere 2021	Saliva was either self-collected or collected by a healthcare professional or caregiver by asking the child to drool at least 10 uL of saliva in a tube.
Huber 2021	Participants were asked to clear their throat thoroughly and collect 0.5 - 1 ml of saliva (approximately a teaspoon full) one or two times into the same tube
Trobajo-Sanmartin 2021	Self-collection of saliva after 1 hour of food and water abstinence by pooling saliva in the mouth for a few seconds, and expelling the saliva into a sterile tube amounting to approximately one finger has been collected. If the amount is less, you should generate more saliva and expel it into the same tube.
Sahni 2021	The MT swab was inserted into one nostril by trained clinical staff (medical assistants, licensed vocational nurses, registered nurses, and respiratory therapists). Age specific swab was used (pediatric size for < 2 y/o and adult size for > 2 y/o). The head of the child is tilted to an angle of 70 degrees and the personnel gently insert the swab into the nares, rotating the swab 2-3 times then holding the swab in place for 5 seconds. The swab is then inserted into the viral transport medium.
Di Pietro 2021	The nasopharyngeal aspirates were collected from both nostrils using a standard protocol and the Medicoplast mucus extractor 440- ch08.

Appendix 3. Detailed Study Appraisal

	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Alenquer 2021	+	+	+	-	+	+	+
Al Suwaidi 2021	+	+	+	+	+	+	+
Banerjee 2021	+	?	?	-	+	+	+
Di Petro 2021	+	+	+	-	+	+	+
Felix 2021	+	?	?	+	+	+	+
Fougere 2021	+	+	+	+	+	+	+
Huber 2021	+	+	+	+	+	+	+
Sahni 2021	+	+	+	+	+	+	+
Trobaño-Sanmartín 2021	+	+	+	-	+	+	+

- High ? Unclear + Low

Figure 1. Risk of bias and applicability concerns summary of the included studies (QUADAS-2).

Table 1. Appraisal of studies using Joanna Briggs Critical Appraisal Instrument for Studies Reporting Prevalence Data

	Guzman-Ortiz
1. Was the sample frame appropriate to address the target population?	Yes
2. Were study participants sampled in an appropriate way?	Yes
3. Was the sample size adequate?	Yes
4. Were the study subjects and the setting described in detail?	Yes
5. Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
6. Were valid methods used for the identification of the condition?	Yes
7. Was the condition measured in a standard, reliable way for all participants?	Yes
8. Was there appropriate statistical analysis?	Yes
9. Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes
Overall appraisal	Include

Appendix 4A. GRADE Evidence Profile: Saliva RT-PCR

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD

Question: Should Saliva RT-PCR be used to diagnose COVID-19 in children?

Setting: Hospital and Outpatient

Sensitivity	0.85 (95% CI: 0.76 to 0.91)	Prevalence	8 %*	33%**	
Specificity	0.99 (95% CI: 0.97 to 0.99)				

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%		
True positives (patients with COVID-19)	7 studies 364 patients	cross-sectional (cohort type accuracy study)	serious ^{1,2,3,a,b}	not serious	serious ^{2,4,c}	serious ^{2,3,4,5,d,e}	none	68 (61 to 73)	281 (251 to 300)	Very low	Critical
False negatives (patients incorrectly classified as not having COVID-19)								12 (7 to 19)	49 (30 to 79)		Critical
True negatives (patients without COVID-19)	7 studies 1027 patients	cross-sectional (cohort type accuracy study)	serious ^{1,2,4,a,b,d}	not serious	not serious	not serious	none	911 (892 to 911)	663 (650 to 663)	Moderate	Critical
False positives (patients incorrectly classified as having COVID-19)								9 (9 to 28)	7 (7 to 20)		Critical

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%		
Positive Predictive Value	7 studies 325 patients	cross-sectional (cohort type accuracy study)	serious ^{1,2,3,a,b}	Not serious	serious ^{3,4,,5,f}	Not serious	none	94% (95% CI 91, 96)		⊕⊕○○ Low	Critical
Negative Predictive Value	7 studies 1066 patients	cross-sectional (cohort type accuracy study)	serious ^{1,2,3,a,b}	Not serious	serious ^{3,4,,5,6,f}	Not serious	none	94% (95% CI 92, 96)		⊕⊕○○ Low	Critical
Likelihood ratio for a (+) test	7 studies 1391 patients	cross-sectional (cohort type accuracy study)	serious ^{1,2,3,a,b}	Not serious	serious ^{1, 5, f}	Not serious	none	48 (95% CI 43, 53)		⊕⊕○○ Low	Critical
Likelihood ratio for a (-) test	7 studies 391 patients	cross-sectional (cohort type accuracy study)	serious ^{1,2,3,a,b}	Not serious	serious ^{1, 5, 7, f}	Not serious	none	0.16 (95% CI 0.16, 0.17)		⊕⊕○○ Low	Critical

Explanations

- a. Saliva specimen was collected within 24-48 hours from NPS collection
- b. 109/ 335 (33%) children were analyzed.
- c. High heterogeneity ($I^2 = 77\%$). Differences in the methods of specimen collection, setting, type of assay.
- d. Wide confidence interval
- e. small sample size

References

- 1.Banerjee D, et al. 2021;
- 2.Trobajo-Sanmartín C, et al. 2021;
3. Alenquer M, et al. 2021;
- 4.Felix AC, et al. 2021;
- 5.Huber M, et al. 2021.
6. Al Suwaldi, 2021
7. Fougere, 2021

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]

**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4B. GRADE Evidence Profile: Saliva RT-PCR in studies without serious risk of bias

Author(s): Eva I. Bautista, MD, Maria Teresa S. Tolosa, MD, Ma. Lucila M. Perez, MD

Question: Should saliva RT-PCR be used to diagnose COVID-19 in children based on studies without serious risk of bias?

Setting: Ambulatory

Sensitivity	0.87 (95% CI: 0.81 to 0.91)					Prevalence	8% *	33% **
Specificity	0.98 (95% CI: 0.97 to 0.99)							

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%	pre-test probability of 0%		
True positives (patients with COVID-19)	3 studies 205 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	serious ^{1,a}	none	70 (65 to 73)	287 (267 to 300)	0 (0 to 0)	⊕⊕⊕○ Moderate	Critical
False negatives (patients incorrectly classified as not having COVID-19)								10 (7 to 15)	43 (30 to 63)	0 (0 to 0)		Critical
True negatives (patients without COVID-19)	3 studies 838 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	not serious	none	902 (892 to 911)	657 (650 to 663)	980 (970 to 990)	⊕⊕⊕⊕ High	Critical
False positives (patients incorrectly classified as having COVID-19)								18 (9 to 28)	13 (7 to 20)	20 (10 to 30)		Critical

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%	pre-test probability of 0%		
Positive Predictive Value	3 studies 194 patients	cross-sectional (cohort type accuracy study)	Not serious	Not serious	Serious ^{1,2, b}	Not serious	none	92 % (95% CI 87, 95)			⊕⊕⊕○ Moderate	Critical
Negative Predictive Value	3 studies 849 patients	cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	none	97% (95% CI 95, 98)			⊕⊕⊕⊕ High	Critical
Likelihood ratio for a (+) test	3 studies 1043 patients	cross-sectional (cohort type accuracy study)	Not serious	Not serious	Serious ^{1,2, b}	Not serious	none	45 (95% CI 40, 51)			⊕⊕⊕○ Moderate	Critical
Likelihood ratio for a (-) test	3 studies 1043 patients	cross-sectional (cohort type accuracy study)	Not serious	Not serious	serious ^{1,2, b}	Not serious	none	0.13 (95% CI 0.12, 0.14)			⊕⊕⊕○ Moderate	Critical

Explanations

a. wide confidence interval

References

1. Huber M, et al. 2021.

2. Fougere, 2021

3. Al Suwaldi, 2021

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]

**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4C. GRADE Evidence Profile: Mid-turbinate swab RT-PCR

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD

Question: Should mid-turbinate RT-PCR be used to diagnose COVID-19 in children?

Setting: Ambulatory

Sensitivity	0.82 (95% CI: 0.74 to 0.89)						Prevalence	8%*	33% **
Specificity	1.00 (95% CI: 0.99 to 1.00)								

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%		
True positives (patients with COVID-19)	1 study 114 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	serious ^{1,a}	none	66 (59 to 71)	271 (244 to 294)	⊕⊕⊕○ Moderate	Critical
False negatives (patients incorrectly classified as not having COVID-19)								14 (9 to 21)	59 (36 to 86)		Critical
True negatives (patients without COVID-19)	1 study 453 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	not serious	none	920 (911 to 920)	670 (663 to 670)	⊕⊕⊕⊕ High	Critical
False positives (patients incorrectly classified as having COVID-19)								0 (0 to 9)	0 (0 to 7)		Critical
Positive Predictive Value	1 study 94 patients	cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	none	100 % (95% CI 96, 100)		⊕⊕⊕⊕ High	Critical

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%		
Negative Predictive Value	1 study 473 patients	cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	none	96% (95% CI 94, 97)		⊕⊕⊕⊕ High	Critical
Likelihood ratio for a (+) test	1 study 567 patients	cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	none	undefined			Critical
Likelihood ratio for a (-) test	1 study 567 patients	cross-sectional (cohort type accuracy study)	Not serious	Not serious	Not serious	Not serious	none	0.18 (95% CI 0.16, 0.19)		⊕⊕⊕⊕ High	Critical

Explanations

a. Wide confidence interval

References

1.DiPietro GM, et al.;2021

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]

**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4D. GRADE Evidence Profile: Nasopharyngeal aspirate RT-PCR

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD

Question: Should NPA RT-PCR be used to diagnose COVID-19 in children?

Setting: Hospital

Sensitivity	0.81 (95% CI: 0.63 to 0.93)					Prevalence	8 %*	33%**	
Specificity	0.93 (95% CI: 0.90 to 0.94)								

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%		
True positives (patients with COVID-19)	1 studies 31 specimens	cross-sectional (cohort type accuracy study)	serious ^{1,a}	not serious	not serious	serious ^{1,b}	none	65 (50 to 74)	267 (208 to 307)	⊕⊕○○ Low	Critical
False negatives (patients incorrectly classified as not having COVID-19)								15 (6 to 30)	63 (23 to 122)		Critical
True negatives (patients without COVID-19)	1 studies 269 specimens	cross-sectional (cohort type accuracy study)	serious ^{1,a}	not serious	not serious	not serious	none	856 (828 to 865)	623 (603 to 630)	⊕⊕⊕○ Moderate	Critical
False positives (patients incorrectly classified as having COVID-19)								64 (55 to 92)	47 (40 to 67)		Critical

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%		
Positive Predictive Value	1 study 43 specimens	cross-sectional (cohort type accuracy study)	serious ^{1,a}	Not serious	Not serious	Not serious	none	58% (95% CI 43, 72)		⊕⊕⊕○ Moderate	Critical
Negative Predictive Value	1 study 257 specimens	cross-sectional (cohort type accuracy study)	serious ^{1,a}	Not serious	Not serious	Not serious	none	98% (95% CI 95, 99)		⊕⊕⊕○ Moderate	Critical
Likelihood ratio for a (+) test	1 study 567 specimens	cross-sectional (cohort type accuracy study)	serious ^{1,a}	Not serious	Not serious	Not serious	none	undefined		⊕⊕⊕○ Moderate	Critical
Likelihood ratio for a (-) test	1 study 567 specimens	cross-sectional (cohort type accuracy study)	serious ^{1,a}	Not serious	Not serious	Not serious	none	0.18 (95% CI 0.16, 0.19)		⊕⊕⊕○ Moderate	Critical

Explanations

a. Timing of specimen collection. NPS was either collected before NPA collection or after NPA collection on follow-up.

b. wide Confidence Interval

References

1.DiPietro GM, et al.; 2021

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]

**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4E. GRADE Evidence Profile: Saliva RT-PCR among hospitalized children

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD

Question: Should saliva RT-PCR be used to diagnose COVID-19 in hospitalized children?

Setting: Hospital

Sensitivity	0.85 (95% CI: 0.71 to 0.94)	Prevalence	8% *	33% *
Specificity	1.00 (95% CI: 0.91 to 1.00)			

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%		
True positives (patients with COVID-19)	1 study 46 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	not serious	not serious	serious ^{1,b}	none	68 (57 to 75)	281 (234 to 310)	⊕⊕○○ Low	Critical
								12 (5 to 23)	49 (20 to 96)		Critical
True negatives (patients without COVID-19)	1 study 39 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	not serious	not serious	not serious	none	920 (837 to 920)	670 (610 to 670)	⊕⊕⊕○ Moderate	Critical
								0 (0 to 83)	0 (0 to 60)		Critical

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%		
Positive Predictive Value	1 study 39 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	Not serious	Not serious	Not serious	none	100% (95% CI 91, 100)		⊕⊕⊕○ Moderate	Critical
Negative Predictive Value	1 study 46 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	Not serious	Not serious	serious ^b	none	85% (95% CI 72, 92)		⊕⊕○○ Low	Critical
Likelihood ratio for a (+) test	1 study 85 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	Not serious	Not serious	Not serious	none	undefined			Critical
Likelihood ratio for a (-) test	1 study 85 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	Not serious	Not serious	Not serious	none	0.15 (95% CI 0.12, 0.20)		⊕⊕⊕○ Moderate	Critical

Explanations

a. Saliva specimen was collected within 24-48 hours from

b. Wide confidence interval

References

1.Alenquer M, et al. 2021

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]

**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4F. GRADE Evidence Profile: Saliva RT-PCR among non-hospitalized children

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD

Question: Should saliva RT-PCR be used to diagnose COVID-19 in children in outpatient setting?

Setting: Ambulatory

Sensitivity	0.85 (95% CI: 0.75 to 0.92)	Prevalence	8% *	33 %**
Specificity	0.98 (95% CI: 0.97 to 0.99)			

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%		
True positives (patients with COVID-19)	6 studies 318 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	not serious	serious ^{2,3,b}	serious ^{3,c,d}	none	68 (60 to 74)	281 (248 to 304)	⊕○○○ Very low	Critical
								12 (6 to 20)	49 (26 to 82)		Critical
True negatives (patients without COVID-19)	6 studies 988 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	not serious	not serious	not serious	none	902 (892 to 911)	657 (650 to 663)	⊕⊕⊕○ Moderate	Critical
								18 (9 to 28)	13 (7 to 20)		Critical

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability	pre-test probability		
Positive Predictive Value	6 studies 286 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	not serious	serious ^{2,3,d}	Not serious	none	94% (95% CI 90, 96)		⊕⊕○○ Low	Critical
Negative Predictive Value	6 studies 1020 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	Not serious	Serious ^{1,2,d}	Not serious	none	95% (95% CI 93, 96)		⊕⊕○○ Low	Critical
Likelihood ratio for a (+) test	6 studies 1306 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	Not serious	Serious ^{1,4,d}	Not serious	none	46 (95% CI 41, 51)		⊕⊕○○ Low	Critical
Likelihood ratio for a (-) test	6 studies 1306 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	Not serious	Serious ^{1,2,4,d}	Not serious	none	0.17 (95% CI 0.16, 0.17)		⊕⊕○○ Low	Critical

Explanations

a. 109 (33%) participants were included in the analysis out of 335 included children.

b. I²= 80 %

c. small sample size

References

1.Banerjee D, et al. 2021

2.Trobajo-Sanmartín, et al. 2021

3.Felix AC, et al. 2021

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]

**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4G. GRADE Evidence Profile: Self-collected saliva for RT-PCR

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD

Question: Should self-collected saliva for RT-PCR be used to diagnose COVID-19 in children?

Setting: Ambulatory

Sensitivity	0.83 (95% CI: 0.77 to 0.88)					Prevalence	8% *	33% **	
Specificity	0.98 (95% CI: 0.97 to 0.99)								

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%		
True positives (patients with COVID-19)	5 studies 219 patients	cross-sectional (cohort type accuracy study)	serious ^{1,2,a}	not serious	serious ^{1,2,3,4,5, b, d}	serious ^{4,c}	none	66 (62 to 70)	274 (254 to 290)	⊕○○○ Very low	Critical
False negatives (patients incorrectly classified as not having COVID-19)								14 (10 to 18)	56 (40 to 76)		Critical
True negatives (patients without COVID-19)	5 studies 690 patients	cross-sectional (cohort type accuracy study)	serious ^{1,2,a}	not serious	not serious	not serious	none	902 (892 to 911)	657 (650 to 663)	⊕⊕⊕○ Moderate	Critical
False positives (patients incorrectly classified as having COVID-19)								18 (9 to 28)	13 (7 to 20)		Critical

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%		
Positive Predictive Value	5 studies 195 patients	cross-sectional (cohort type accuracy study)	serious ^{1,2,a}	not serious	serious ^{1,2,3,4,5,b, d}	serious ^{4,c}	none	93% (95% CI 89, 96)		⊕○○ Very low	Critical
Negative Predictive Value	5 studies 714 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	Not serious	Serious ^{1, 2, 5, d}	Not serious	none	95% (95% CI 93, 96)		⊕⊕○○ Low	Critical
Likelihood ratio for a (+) test	5 studies 909 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	Not serious	Serious ^{2, 5, , d}	Not serious	none	44 (95% CI 38, 51)		⊕⊕○○ Low	Critical
Likelihood ratio for a (-) test	5 studies 909 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	Not serious	Serious ^{1, 2, 5, d}	Not serious	none	0.17 (95% CI 0.16, 0.18)		⊕⊕○○ Low	Critical

Explanations

- a. non-inclusion of some children in the analysis
- b. different RT-PCR assays used
- c. small sample size

References

- 1.Trobajo-Sanmartín, et al. 2021;
- 2.Banerjee D, et al. 2021.;
- 3.Huber M, et al. 2021.;
- 4.Felix AC, et al. 2021.
- 5.Alenquer, et al. 2021.

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]

**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4H. GRADE Evidence Profile: HCW/Caregiver-collected saliva for RT-PCR

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD

Question: Should saliva collected by healthcare worker or caregiver for RT-PCR be used to diagnose COVID-19 in children?

Setting: Hospital

Sensitivity	0.85 (95% CI: 0.71 to 0.94)					Prevalence	8% *	33% **	
Specificity	1.00 (95% CI: 0.91 to 1.00)								

Outcome	Nº of studies (Nº of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%		
True positives (patients with COVID-19)	1 studies 46 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	not serious	not serious	serious ^{1,b}	none	68 (57 to 75)	281 (234 to 310)	$\oplus\oplus\circ\circ$ Low	Critical
False negatives (patients incorrectly classified as not having COVID-19)								12 (5 to 23)	49 (20 to 96)		Critical
True negatives (patients without COVID-19)	1 studies 39 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	not serious	not serious	not serious	none	920 (837 to 920)	670 (610 to 670)	$\oplus\oplus\oplus\circ$ Moderate	Critical
False positives (patients incorrectly classified as having COVID-19)								0 (0 to 83)	0 (0 to 60)		Critical

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%		
Positive Predictive Value	1 study 39 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	not serious	not serious	Not serious	none	100% (95% CI 91, 100)		⊕⊕⊕○ Moderate	Critical
Negative Predictive Value	1 study 46 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	Not serious	Not serious	serious ^b	none	85% (95% CI 72, 92)		⊕⊕○○ Low	Critical
Likelihood ratio for a (+) test	1 study 85 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	Not serious	Not serious	Not serious	none	undefined			Critical
Likelihood ratio for a (-) test	1 study 85 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	Not serious	Not serious	Not serious	none	0.15 (95% CI 0.12, 0.20)		⊕⊕⊕○ Moderate	Critical

Explanations

a. Saliva specimen was collected 24-48 hours after NPS collection.

b. wide confidence interval

References

1. Alenquer M, et al. 2021

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]

**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4I. GRADE Evidence Profile: Saliva Allplex nCoV assay

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD

Question: Should saliva Allplex nCoV assay be used to diagnose COVID-19 in children?

Setting: Outpatient

Sensitivity	0.76 (95% CI: 0.68 to 0.83)					Prevalence	8% *	33% **	
Specificity	0.99 (95% CI: 0.97 to 1.00)								

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%		
True positives (patients with COVID-19)	2 studies 122 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	not serious	Serious ^{1,2,b}	not serious	none	61 (54 to 66)	251 (224 to 274)		Critical
False negatives (patients incorrectly classified as not having COVID-19)								19 (14 to 26)	79 (56 to 106)		Critical
True negatives (patients without COVID-19)	2 studies 457 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	not serious	not serious	not serious	none	911 (892 to 920)	663 (650 to 670)		Critical
False positives (patients incorrectly classified as having COVID-19)								9 (0 to 28)	7 (0 to 20)		Critical
Inconclusive	0 studies patients	-	-	-	-	-	-			-	
Complications	0 studies patients									-	

Explanations

a. Unclear in the number of patients excluded in the analysis

b. 95 % confidence intervals do not overlap.

References

1.Trobajo-Sanmartín C, et al. 2021.

2. Al-Suwaidi H, et al. 2021

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]

**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4J. GRADE Evidence Profile: Cobas 6800 assay

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD

Question: Should saliva Cobas 6800 assay be used to diagnose COVID-19 in children?

Setting: Outpatient

Sensitivity	0.93 (95% CI: 0.78 to 0.99)				Prevalence	8% *	33% **	
Specificity	0.96 (95% CI: 0.92 to 0.99)							

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%		
True positives (patients with COVID-19)	1 studies 101 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	serious ^{1,a}	none	74 (62 to 79)	307 (257 to 327)	⊕⊕⊕○ Moderate	Critical
False negatives (patients incorrectly classified as not having COVID-19)								6 (1 to 18)	23 (3 to 73)		Critical
True negatives (patients without COVID-19)	1 studies 296 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	not serious	none	883 (846 to 911)	643 (616 to 663)	⊕⊕⊕⊕ High	Critical
False positives (patients incorrectly classified as having COVID-19)								37 (9 to 74)	27 (7 to 54)		Critical
Inconclusive	0 studies patients	-	-	-	-	-	-			-	
Complications	0 studies patients									-	

Explanations

a. wide Confidence Interval

References

1.Fougere, et al. 2021.

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]

**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4K. GRADE Evidence Profile: Altona Realstar Kit assay

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD

Question: Should saliva Altona Realstar kit assay be used to diagnose COVID-19 in children?

Setting: Outpatient

Sensitivity	0.80 (95% CI: 0.44 to 0.97)					Prevalence	8% *	33% **
Specificity	1.00 (95% CI: 0.91 to 1.00)							

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%		
True positives (patients with COVID-19)	1 studies 10 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	not serious	not serious	serious	none	64 (35 to 78)	264 (145 to 320)	⊕⊕○○ Low	Critical
False negatives (patients incorrectly classified as not having COVID-19)								16 (2 to 45)	66 (10 to 185)		Critical
True negatives (patients without COVID-19)	1 studies 40 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	not serious	not serious	not serious	none	920 (837 to 920)	670 (610 to 670)	⊕⊕⊕○ Moderate	Critical
False positives (patients incorrectly classified as having COVID-19)								0 (0 to 83)	0 (0 to 60)		Critical
Inconclusive	0 studies patients	-	-	-	-	-	-			-	
Complications	0 studies patients									-	

Explanations

a. unclear if reference test was interpreted independently from the index test

References

1.Felix AC, et al. 2021.

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]

**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4L. GRADE Evidence Profile: ITaq Universal Probes assay

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD

Question: Should saliva Itaq Universal Probes assay be used to diagnose COVID-19 in children?

Setting: Hospital

Sensitivity	0.85 (95% CI: 0.71 to 0.94)					Prevalence	8% *	33% **
Specificity	1.00 (95% CI: 0.91 to 1.00)							

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%		
True positives (patients with COVID-19)	1 studies 46 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	not serious	not serious	serious ^{1,b}	none	68 (57 to 75)	281 (234 to 310)	⊕⊕○○ Low	Critical
False negatives (patients incorrectly classified as not having COVID-19)								12 (5 to 23)	49 (20 to 96)		Critical
True negatives (patients without COVID-19)	1 studies 39 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	not serious	not serious	not serious	none	920 (837 to 920)	670 (610 to 670)	⊕⊕⊕○ Moderate	Critical
False positives (patients incorrectly classified as having COVID-19)								0 (0 to 83)	0 (0 to 60)		Critical
Inconclusive	0 studies patients	-	-	-	-	-	-			-	
Complications	0 studies patients									-	

Explanations

a. Timing of specimen collection. Saliva specimen was collected 24- 48 hours after NPS collection.

b. small sample size

References

1. Alenquer M, et al. 2021.

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]

**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4M. GRADE Evidence Profile: Aptima SARS-CoV-2-Assay

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD

Question: Should saliva Aptima SARS-CoV-2 assay be used to diagnose COVID-19 in children?

Setting: Outpatient

Sensitivity	0.93 (95% CI: 0.83 to 0.98)				Prevalence	8% *	33% **	
Specificity	0.96 (95% CI: 0.87 to 1.00)							

Outcome	No of studies (No of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested		Test accuracy CoE	Importance
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 8%	pre-test probability of 33%		
True positives (patients with COVID-19)	1 studies 57 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	not serious	not serious	Serious ^b	none	74 (66 to 78)	307 (274 to 323)	⊕⊕○○ Low	Critical
False negatives (patients incorrectly classified as not having COVID-19)								6 (2 to 14)	23 (7 to 56)		Critical
True negatives (patients without COVID-19)	1 studies 53 patients	cross-sectional (cohort type accuracy study)	serious ^{1,a}	not serious	not serious	not serious	none	883 (800 to 920)	643 (583 to 670)	⊕⊕⊕○ Moderate	Critical
False positives (patients incorrectly classified as having COVID-19)								37 (0 to 120)	27 (0 to 87)		Critical
Inconclusive	0 studies patients	-	-	-	-	-	-			-	
Complications	0 studies patients									-	

Explanations

a. non-inclusion of other participants in the analysis

b. wide Confidence Interval

References

1.Banerjee D, et al. 2021.

* 8 % pretest probability of COVID-19 among children 0-14 y/o. [27]

**33% pretest probability of ICU admission among hospitalized COVID-19 children [28,29]

Appendix 4N. GRADE Evidence Profile: Adverse events of saliva RT-PCR

Author(s): Eva I. Bautista, MD, Ma. Lucila M. Perez, MD, Maria Teresa S. Tolosa, MD

Question: Should Saliva for RT-PCR compared to NPS/OPS RT-PCR be used to diagnose COVID-19?

Setting: Hospitalized

Certainty assessment							Impact	Certainty	Importance	
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Adverse events										
1	observational studies	not serious	not serious	not serious	not serious	none	There were no reported adverse events in 156 hospitalized children suspected of COVID-19 who had saliva and NPS/OPS RT-PCR. ¹	⊕⊕○○ Low	IMPORTANT	

Reference

1. Guzman-Ortiz AL, et al. 2021

Appendix 5. Forest Plots

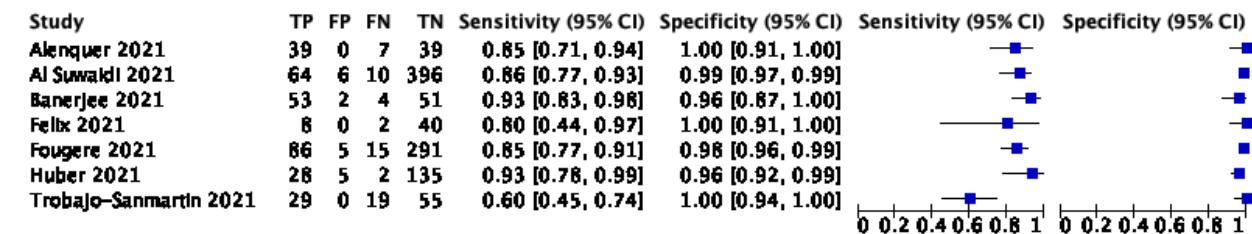


Figure 1. Forest plot of the sensitivity and specificity of saliva RT-PCR

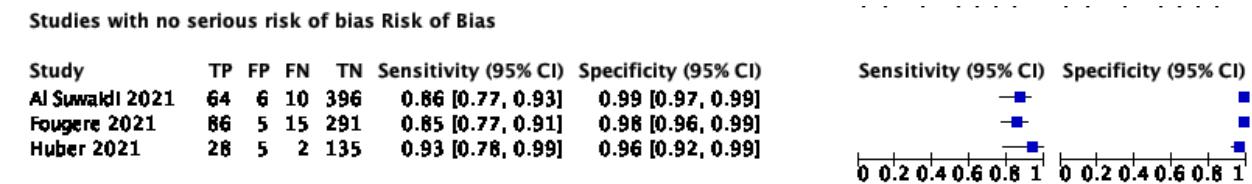


Figure 2. Forest plot of the sensitivity analysis of saliva RT-PCR: Studies with no serious risk of bias

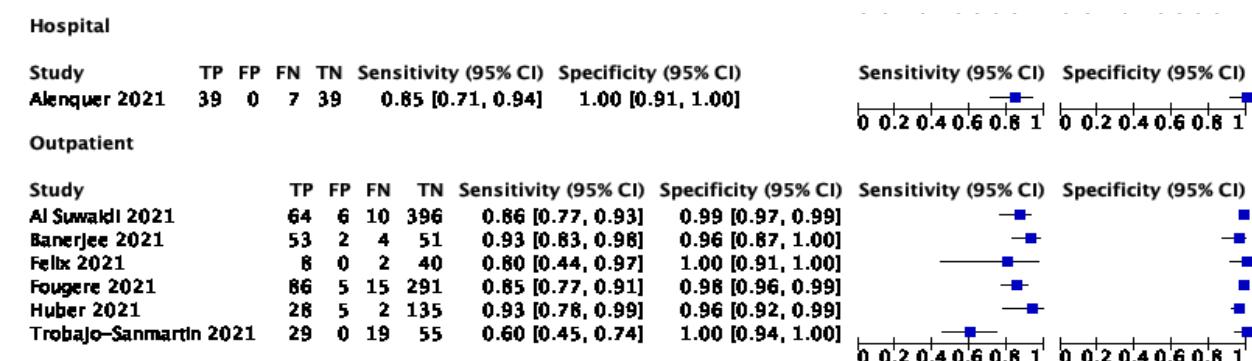


Figure 3. Forest plot of the sensitivity and specificity of saliva RT-PCR according to setting (hospital vs outpatient)

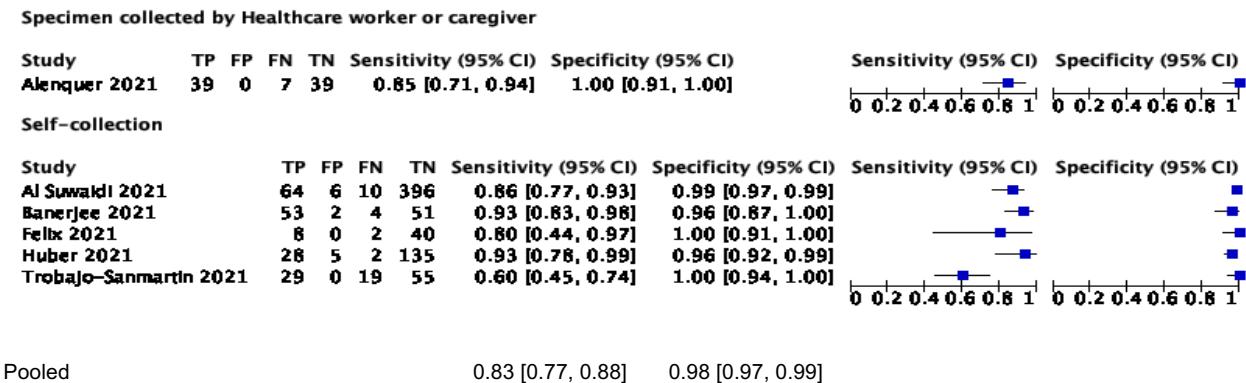


Figure 4. Forest plot of the sensitivity and specificity of saliva RT-PCR by method of collection

Appendix 6. Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 10)

FACTORS		JUDGEMENT (N = 10)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (10)		Varies		Uncertain		
Benefits	Large (1)	Moderate (9)	Small	Trivial	Varies	Uncertain		<ul style="list-style-type: none"> • Saliva specimen is preferred by majority of children 2-11 years old
Harm	Large	Moderate	Small (10)	Trivial	Varies	Uncertain		<ul style="list-style-type: none"> • Median score: 4/10 for discomfort
Certainty of evidence	High	Moderate (6)		Low (4)		Very low		<ul style="list-style-type: none"> • Saliva: moderate • Mid-turbinate: moderate • NPA: low
Balance of effects	Favors test (5)	Probably favors test (5)	Does not favor test or no test	Probably favors no test	Favors no test	Varies	Uncertain (8)	
Accuracy	Very accurate	Accurate (7)	Inaccurate	Very inaccurate	Varies	Uncertain (3)		<ul style="list-style-type: none"> • Saliva and mid-turbinate: moderate Sn, high Sp, wide CI • Insufficient for NPA
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (3)		Probably no important uncertainty or variability (6)		No important uncertainty or variability		
Resources required	Uncertain (1)	Varies	Large costs (2)	Moderate costs (7)	Negligible costs or savings	Moderate savings	Large savings	
Certainty of evidence of resources required	No included studies (9)		Very low	Low (1)	Moderate	High		
Cost-effectiveness	No included studies (9)	Varies	Favors the comparison (1)	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention	Favors the intervention	
Equity	Uncertain (1)	Varies (2)	Reduced	Probably reduced (4)	Probably no impact	Probably increased (3)	Increased	
Acceptability	Uncertain (3)	Varies (1)	No	Probably no	Probably yes (5)	Yes (1)		
Feasibility	Uncertain (3)	Varies	No	Probably no	Probably yes (6)	Yes (1)		

Additional Comments

- Equity, acceptability and feasibility depend on whether there will be enough Philhealth/government support to shoulder these costs.

B. Treatment of COVID-19 in Children

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.

Evidence Summary

Key Findings

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.

Introduction

Intravenous immunoglobulin has been considered as a treatment for COVID-19 due to its anti-inflammatory and immunomodulatory effects. It is used as first line treatment for Kawasaki disease due to its anti-inflammatory effect [1].

MIS-C is a newly defined clinical syndrome associated with SARS-CoV-2 infection characterized by fever, systemic inflammation, and multiple organ dysfunction [2-4]. As reported in studies, the incidence of MIS-C is 316 per 1 million SARS-CoV-2 infections or approximately 1 in 3000 children and adolescents or patients less than 21 years old who had SARS-CoV-2 infection with a median age of 9 years old (75% of cases with no comorbidities) and highest among Black and Hispanic/Latino children [5-8]. Patients with MIS-C often have severe symptoms of cardiac injury or dysfunction [9], critically ill with as high as 80% of children requiring ICU admission and a mortality rate of 1% to 2% for hospitalized patients as reported in the United States [10]. Due to the similarity of the features of Kawasaki disease and MIS-C such as fever, rash, conjunctivitis, mucosal symptoms, and swollen hands and feet, IVIG was proposed as a potential drug of choice for the treatment of MIS-C [11,12].

Despite several clinical trials done in adults on the use of IVIG for the treatment of COVID-19 infection, there has been insufficient evidence to recommend IVIG as treatment [13]. This review looks into the effectiveness of IVIG as treatment of pediatric COVID-19 infection and MIS-C.

Review Methods

A systematic search was conducted from January 3, 2022 to January 5, 2022 in the following sites: Pubmed (Medline), Cochrane Library, Google Scholar, COVID-NMA Living Data and the Living Evidence on COVID-19. Ongoing studies were checked in the WHO clinical trial registry, NIH *clinicaltrials.gov* and various trial registries, and preprints from MedRxiv, chinaXiv and bioRxiv. MeSH and free text search were done. Search terms included coronavirus infections, COVID-19, severe acute respiratory syndrome, coronavirus 2 or SARS-CoV-2, intravenous immunoglobulin, immunoglobulin, IVIG, children, pediatric and adolescent. Only randomized trials and cohort studies and studies were included. The inclusion criteria were as follows:

Table 1. PICO criteria for IVIG and COVID-19.

Population	Children with COVID-19
Intervention/Exposure	Intravenous immunoglobulin
Comparison	Usual care, standard of care, placebo, any active control
Outcomes	Mortality, clinical improvement, hospitalization, ICU admission

Since few to no studies in children were found, indirect evidence was obtained using the Philippine COVID 19 Adult Living Clinical Practice Guideline (ALCPG) Phase II. To update the CPG, newer RCTs in adults were located using the same search terms but, this time with adults as population. All studies were appraised using Newcastle Ottawa Scale (NOS) for the cohort study, Cochrane RoB for RCTs and AGREE II for the Philippine ALCPG II.

Planned subgroup analysis for age, dose and COVID severity was not done due to unavailability of data in the pediatric population.

Results

During the search, there were no randomized clinical trials found in children on the use of IVIG for the treatment of COVID-19 infection, however there were cohort studies found on the use of IVIG compared with IVIG+CS for the treatment of MIS-C [14-17]. Among the cohort studies found, only one retrospective cohort study investigated the use of IVIG alone, corticosteroids alone and IVIG+CS for the treatment of MIS-C. The remaining three (3) retrospective cohort studies investigated the use of IVIG compared with IVIG plus corticosteroids for the treatment of MIS-C which did not fit the PICO criteria (intervention and comparison), thus only one cohort study was included in this review. Outcomes of interest included in the cohort study were reduction in the score for disease severity on the ordinal scale and composite outcome: inotropic support or mechanical ventilation or death. This cohort study was appraised as poor using the Newcastle-Ottawa Scale with a total score of 6 stars (Appendix 3).

Since there were no other studies found in children aside from the cohort study on MIS-C, indirect evidence was used in the form of the Philippine COVID 19 Adult Living Clinical Practice Guideline (ALCPG) Phase II which had an overall good quality using AGREE II. (Appendix 3) Three (3) new RCTs (Appendix 2) were added to update the ALCPG making a total of seven (7) RCTs.

The included studies have a very low overall certainty of evidence due to very serious risk of bias, for being an observational study and imprecision in 2 critical outcomes for the study on MIS-C and for the adult RCTs were downgraded due to indirectness, inconsistency and imprecision in 2 critical outcomes (Appendix 4).

Efficacy

MIS-C

Patient outcomes from the single cohort study on the use of IVIG alone compared with CS alone among patients with MIS-C showed inconclusive findings for the composite outcome: use of inotropic support or mechanical ventilation on or after day two (2) or death and for the outcome reduction in the score for disease severity on the ordinal scale by day 2 (RR 0.75, 95% CI [0.42, 1.33], n=237 and RR 0.94, 95% CI [0.58, 1.54], n=212, respectively).

Among patients with MIS-C, studies showed that addition of IVIG to CS resulted in a tendency to increased risk for the composite outcome: use of inotropic support or mechanical ventilation on or after day 2 or death (RR 1.89, 95% CI [1.08, 3.30], n=230) compared to CS alone. Findings were inconclusive for the outcome reduction in the score for disease severity on the ordinal scale by day 2 (RR 1.28, 95% CI [0.80, 2.06], n=212). The outcomes have very low certainty of evidence.

Adult Studies

Pooled estimates of patient outcomes on the use of IVIG showed statistically significant benefit for clinical deterioration or WHO progression level 7 or above (RR 0.39, 95% CI [0.20, 0.79], n=84, 2 RCTs), with shorter duration of hospital stay (MD -9.80, 95% CI [-11.38, -8.22], n=100, 1 RCT) and duration of ICU admission (MD -1.00, 95% CI [-1.92, -0.08], n=100, 1 RCT). Pooled estimates however, were inconclusive for all-cause mortality at Day 28 (RR 0.73, 95% CI [0.45, 1.19], n=533, 7 RCTs), clinical improvement at Day 28 (RR 1.35, 95% CI [0.93, 1.95], n=230, 3 RCTs), need for ICU admission (RR 0.89, 95% CI [0.72, 1.10], n=84, 1 RCT), and need for mechanical ventilation (RR 0.85, 95% CI [0.46, 1.59], n=264, 3 RCTs). The rest of the outcomes namely clinical improvement at Day 7, viral clearance at Day 3 and Day 8 were likewise inconclusive. The forest plots are shown in Appendix 5.

Safety

Risk for adverse events (RR 1.06, 95% CI [0.89, 1.27], n=356, 4 RCTs) and serious adverse events (RR 1.39, 95% CI [0.82, 2.38], n=340, 4 RCTs) were not statistically significant.

Adverse events reported include hypersensitivity reaction (e.g. mild rash and lip swelling, anaphylaxis), infusion reactions (e.g. headache, chills, myalgia, wheezing, tachycardia, lower back pain, nausea, hypotension), transfusion related acute lung injury (TRALI), hemolysis, thrombotic events, renal failure, aseptic meningitis syndrome, transmission of infectious pathogens [13].

The cohort study on children reported adverse events or IVIG-related complications which occurred in approximately 1.8% of patients treated with IVIG [4]. Adverse events reported in the study include mild rash and lip swelling and other complications which were not specified [16].

Other Considerations (Evidence to Decision)

Intravenous immunoglobulin and methylprednisolone have been available and used locally for the treatment of Kawasaki disease and systemic lupus erythematosus (SLE) respectively. IVIG has been available in hospitals and various suppliers and methylprednisolone is mostly available in hospitals and local drugstores. The estimated cost of IVIG and methylprednisolone was retrieved from the 2020 Philippine Drug Price Reference Index [18]. Table 2 shows the estimated cost of IVIG and methylprednisolone.

Table 2. Estimated Cost of IVIG and Methylprednisolone

	IVIG 2 g/kg over 8-12 hours (maximum dose:100g) [15]	Methylprednisolone 1-2 mg/kg/dose (max: 30 mg/dose) IV q12h for 3-5 days [15]
Preparations available:	50mg/ml (100ml) or 5g per vial	125mg/ml(2ml)

Cost per preparation based on 2020 DPRI (Range of Cost from lowest to highest)	9,650 (1,600 – 16,000)	613.77 (613.77-995)
Total Cost of Treatment (Range)	20 vials: 193,000 (32,000 – 320,000)	3 vials: 1,841.31 (1,841.31-2,985)
Total Cost of Treatment [IVIG + Steroid] (Range)	194,841.31 (33,841.31 – 322,985)	

*Values were taken from the 2020 Philippine Drug Price Reference Index; Dosages were based on the PPS and PIDSP INTERIM GUIDELINES ON THE SCREENING, CLASSIFICATION, AND MANAGEMENT OF PEDIATRIC PATIENTS WITH SUSPECTED OR CONFIRMED CORONAVIRUS DISEASE 2019 (COVID-19) Ver. 5. Updated 1/8/2022.

There were no studies found on patient's values and preference, equity, acceptability and feasibility in the literature search done but based on the availability and the varied use of IVIG and methylprednisolone, it can somehow be inferred that they are widely acceptable.

Recommendations from Other Groups

There were no available guidelines on the use of IVIG for the treatment of COVID-19 infection in children; however, the PIDSP and PPS interim guidelines recommend the use of IVIG plus steroids for the treatment of MIS-C [12]. The Australian guideline taskforce is currently developing recommendations [18].

Since there were no available guidelines on the use of IVIG in children with COVID 19 infection, guidelines in adults were used. The Philippine COVID 19 Adult Living CPG suggests against the use of IVIG in moderate to severe COVID 19 [19] while the Surviving Sepsis Campaign Guidelines also suggest against its routine use but in critically-ill adults with COVID-19 (updated March 2021) [20]. The Australian Living Guidelines allow the use of immunoglobulin for the treatment of COVID-19, only in the context of randomized trials with appropriate ethical approval (updated December 2021) [19]. The US NIH found insufficient evidence to support its use pending results of clinical trials (updated April 2021) [13]. WHO, IDSA, and American Thoracic Society/European Respiratory Society have no recommendation on the use of IVIG for the treatment of COVID 19 infection.

Research Gaps

Currently, there are no randomized trials on the use of IVIG for the treatment of COVID 19 in children, hence the available sources of data are from observational studies in children and from randomized trials in adults which is an indirect form of evidence.

As of January 13, 2022, there are 26 ongoing studies during the search of which only two studies are conducted in children. One of the two studies is a randomized open label study of COVID-19 Therapy in Children with Pediatric Inflammatory Multisystem

Syndrome –Temporally Associated with SARS COV 2 (PIMS-TS) in Switzerland or the SWISSPED-RECOVERY trial with the expected completion date on July 2022. The other one is an observational study on MIS-C (Appendix 6).

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Evidence Summary Appendices

Appendix 1. Search Yield and Results

	"adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "adolescence"[All Fields] OR "adolescents"[All Fields] OR "adolescent s"[All Fields]))			
CENTRAL	"COVID-19" OR "COVID-19 diagnostic testing" OR "COVID-19 drug treatment" OR "COVID-19 serotherapy" OR "COVID-19 vaccine" OR "severe acute respiratory syndrome coronavirus 2" OR "2019-nCoV" OR "2019nCoV" OR "cov 2" OR "Covid-19" OR "sars coronavirus 2" OR "sarscov 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" in All Text AND Intravenous Immunoglobulin OR IVIG OR Immunoglobulin in Title Abstract Keyword AND children OR child OR pediatrics OR pedia OR adolescent OR infant OR neonate OR newborn in Title Abstract Keyword - (Word variations have been searched)	1/4/22 8 PM	33	Adults
COVID-NMA Initiative		1/4/22 9:30 PM	7	Adults
ClinicalTrials.gov		1/4/22 11PM	568	26 (24 on adults)
WHO database COVID-19 studies		1/4/22	0	0
China Registry		1/5/22	0	0
MedRxiv.org		1/5/22 8AM	217	1 (MIS-C)
BioRxiv.org		1/5/22	24	0
ChinaRxiv.org		1/5/22	0	0
Google Scholar		1/5/22	967	4 (MIS-C)
EU Clinical Trials Register		1/5/22		0
Republic of Korea - Clinical Research Information Service		1/5/22	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search		1/5/22	0	0

Appendix 2. Characteristics of Included Studies

Study ID	Design	Sample Size	Participants	Comparisons		Outcomes
Treatment of Multisystem Inflammatory Syndrome in Children McArdle et al 2021 (UK)	Observational (cohort)	N=420	pediatric patients who met the World Health Organization (WHO) criteria for MIS-C	1. IVIG (dose not specified) 2. IVIG (dose not specified) + Glucocorticoids	Glucocorticoids	Composite of inotropic support or mechanical ventilation (invasive or noninvasive) by day 2 or later or death. The reduction in disease severity on a seven-point ordinal scale between day 0 and day 2.
ADULT STUDIES						
Gharebaghi et al 2020	RCT	59	adult patients with severe COVID-19 who did not respond to initial treatments, ARDS	4 vials of 5g IVIg x 3 days	placebo	In-hospital mortality
Tabarsi et al 2020	RCT	84	Severely ill COVID-19 adult patients	400 mg/Kg daily for three doses	Standard of care	invasive mechanical ventilation and oxygenation, the need for admission to the Intensive Care Unit (ICU), and the mortality rate
Sakoulas et al 2020	RCT, open label	33	Adult patients with Moderate to severe COVID-19	500 mg/kg daily for 3 days	Standard of care	Need for mechanical ventilation, length of hospital stay, length of ICU stay
Raman et al 2021	RCT open label	100	Adult patients with Moderate COVID-19	400 mg/kg daily for 5 days	Standard of care	Number of days hospitalized, time to clinical improvement, duration of mechanical ventilation, 28-day mortality, proportion of patients with negative RT PCR (day 14, 28)
Marezaud et al 2021 (new)	RCT double blind	146	Adult patients with COVID-19 associated Moderate	2 g/kg over 4 days or 0.5g/kg per day for 4 days	Placebo	The primary outcome was the number of ventilator-free days at day 28, defined as the number of days between the last

			to severe ARDS			extubation day and day 28 The key secondary outcomes were the sequential organ failure assessment score at day 14 and day 28; the occurrence of grade 3 or 4 adverse events or serious adverse events attributed to IVIG; the time to intensive care unit or hospital discharge; the clinical status at day 28 and day 90 as assessed by the seven-category ordinal scale; 90-day mortality; and lung injury score at day 28.
Parikh, D. et al 2021 (preprint) (new)	RCT open label	60	Admitted patients with moderate to critical COVID 19 infection	C-IVIG 30 ml IV on day 1 and 2	Standard of Care	Mean change from Day 1 to Day 8 in an 8-point ordinal scale
Ali et al 2021 (new)	RCT open label	50	Patients with confirmed with COVID 19 (moderate to severe) admitted to a center in Pakistan	C-IVIG 0.15-0.3g/kg IV x 1 dose	Standard of Care	Mortality at D28, WHO Score of 7 and above at D28, Clinical improvement at D28, Adverse events

Appendix 3A. Study Appraisal

Newcastle Ottawa Scale

McArdle et al. 2021		
Domain	Assessment	Score
Selection		
1) Representativeness of the exposed cohort	Truly representative (one star)	*
2) Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort (one star)	*
3) Ascertainment of exposure	Secure record (one star)	*
4) Demonstration that outcome of interest was not present at start of study	Yes (one star)	*
TOTAL		4 STARS
Comparability		
Comparability of cohorts on the basis of the design or analysis controlled for confounders	Cohorts are not comparable on the basis of the design or analysis controlled for confounders	-
TOTAL		0 STAR
Outcome		
1) Assessment of outcome	Record linkage (one star)	*
2) Was follow-up long enough for outcomes to occur	Yes (one star)	-
3) Adequacy of follow-up of cohorts	Complete follow up- all subject accounted for (one star) Subjects lost to follow up unlikely to introduce bias-number lost less than or equal to 20% or description of those lost suggested no different from those followed (one star)	*
TOTAL		2 STARS =POOR

OVERALL TOTAL	6 STARS
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Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor): **Poor** (**Since it failed or zero star in the comparability domain**)

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Appendix 3B. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ali 2021	+	+	+	+	?	+	+
Gharebaghi 2020	+	+	+	+	?	?	?
Mazeraud 2021	+	+	+	+	-	+	+
Parikh 2021	+	?	-	-	-	?	+
Raman 2021	+	+	-	-	-	-	+
Sakoulas 2020	+	+	-	-	+	+	+
Tabarsi 2020	+	?	?	?	+	+	+

Appendix 4A: GRADE Evidence Summary: IVIG vs. Glucocorticoids for MIS-C

Author(s): Liza Bejemino, MD, Maria Theresa Tolosa, MD, Ma. Lucila Perez, MD

Reference(s): Mcardle AJ, et al..Treatment of Multisystem Inflammatory Syndrome in Children. N Engl J Med 2021;385:11-22.

№ of studies	Study design	Certainty assessment					№ of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glucocorticoids	IVIG	Relative (95% CI)	Absolute (95% CI)		
Use of inotropic support or mechanical ventilation on or after day 2 or death												
1 (N=237)	observational studies	very serious ^a	not serious	not serious	serious ^b	none	12/68 (17.6%)	40/169 (23.7%)	RR 0.75 (0.42 to 1.33)	59 fewer per 1,000 (from 137 fewer to 78 more)	⊕○○○	Very low
Reduction in the score for disease severity on the ordinal scale by day 2												
1 (N= 212)	observational studies	very serious ^a	not serious	not serious	serious ^b	none	16/60 (26.7%)	43/152 (28.3%)	RR 0.94 (0.58 to 1.54)	17 fewer per 1,000 (from 119 fewer to 153 more)	⊕○○○	Very low

CI: confidence interval; RR: risk ratio

Explanations

a. Failed to meet the criteria for the comparability domain of the Newcastle-Ottawa Scale

b. Wide confidence interval

Appendix 4B: GRADE Evidence Summary: IVIG + glucocorticoids vs. Glucocorticoids for MIS-C

Author(s): Liza Bejemino, MD, Maria Theresa Tolosa, MD, Ma. Lucila Perez, MD

Reference(s): Mcardle AJ, et al..Treatment of Multisystem Inflammatory Syndrome in Children. N Engl J Med 2021;385:11-22.

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVIG + Glucocorticoids	Glucocorticoids	Relative (95% CI)	Absolute (95% CI)		

Composite: Use of inotropic support or mechanical ventilation on or after day 2 or death

1 (N=237)	observational studies	very serious ^a	not serious	not serious	not serious	none	54/162 (33.3%)	12/68 (17.6%)	RR 1.89 (1.08 to 3.30)	157 more per 1,000 (from 14 more to 406 more)	⊕○○○	Very low	Critical
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Reduction in the score for disease severity on the ordinal scale by day 2

1 (N=212)	observational studies	very serious ^a	not serious	not serious	serious ^b	none	52/152 (34.2%)	16/60 (26.7%)	RR 1.28 (0.80 to 2.06)	75 more per 1,000 (from 53 fewer to 283 more)	⊕○○○	Very low	Important
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CI: confidence interval; RR: risk ratio

Explanations

a. Failed to meet the criteria for the comparability domain of the Newcastle-Ottawa Scale.

b. Wide confidence interval

Appendix 4C: GRADE Evidence Summary: IVIG vs. SOC or placebo for COVID-19 infection

Author(s): Gharebaghi, et. al. 2020, Tabarsi, et. al. 2020, Sakoulas, et. al. 2020, Raman, et. al. 2021, Marezaud, et. al. 2021, Parikh, D. 2021, Ali, et. al. 2021

Reference(s): PHILIPPINE COVID-19 LIVING CLINICAL PRACTICE GUIDELINES. Updated June 30, 2021; Intravenous immunoglobulins in patients with COVID-19-associated moderate-to-severe acute respiratory distress syndrome (ICAR): multicentre, double-blind, placebocontrolled, phase 3 trial. Lancet Respir Med 2021; Safety and efficacy of COVID-19 hyperimmune globulin (HIG) solution in the treatment of active COVID-19 infection: Findings from a Prospective, Randomized, Controlled, MultiCentric Trial. 2021; Hyperimmune anti-COVID-19 IVIG (C-IVIG) treatment in severe and critical COVID-19 patients: A phase I/II randomized control trial. EClinicalMedicine 36 (2021).

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVIG	SOC or Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
7 (N=533)	randomised trials	not serious	not serious	serious ^a	serious ^b	none	66/288 (22.9%)	59/245 (24.1%)	RR 0.73 (0.45 to 1.19)	65 fewer per 1,000 (from 132 fewer to 46 more)	⊕⊕○○ Low	Critical
Clinical Improvement D28												
3 (N=230)	randomised trials	not serious	not serious	serious ^a	serious ^b	none	61/126 (48.4%)	33/104 (31.7%)	RR 1.35 (0.93 to 1.95)	111 more per 1,000 (from 22 fewer to 301 more)	⊕⊕○○ Low	Critical
Clinical improvement D7												
1 (N=50)	randomised trials	not serious	not serious	serious ^a	very serious ^c	none	15/40 (37.5%)	0/10 (0.0%)	RR 8.32 (0.54 to 128.34)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕○○○ Very low	Critical
Clinical Deterioration or WHO progression level 7 or above at D28												
2 (N=84)	randomised trials	not serious	not serious	serious ^a	not serious	none	11/57 (19.3%)	10/27 (37.0%)	RR 0.39 (0.20 to 0.79)	226 fewer per 1,000 (from 296 fewer to 78 fewer)	⊕⊕⊕○ Moderate	Important
Viral Clearance D3												
1(n=60)	randomised trials	not serious	not serious	serious ^a	serious ^b	none	14/30 (46.7%)	11/30 (36.7%)	RR 1.27 (0.69 to 2.33)	99 more per 1,000 (from 114 fewer to 488 more)	⊕⊕○○ Low	Important
Viral Clearance D14												
2(n=160)	randomised trials	not serious	serious ^d	serious ^a	serious ^c	none	69/80 (86.3%)	36/80 (45.0%)	RR 1.89 (0.37 to 9.73)	400 more per 1,000 (from 284 fewer to 1,000 more)	⊕○○○ Very low	Importatny

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVIG	SOC or Placebo	Relative (95% CI)	Absolute (95% CI)		

Adverse Events

4(n=356)	randomised trials	not serious	not serious	serious ^a	not serious	none	97/189 (51.3%)	75/167 (44.9%)	RR 1.06 (0.89 to 1.27)	27 more per 1,000 (from 49 fewer to 121 more)	⊕⊕⊕○ Moderate	Critical
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Serious Adverse Events

4(n=340)	randomised trials	not serious	not serious	serious ^a	serious ^b	none	24/166 (14.5%)	20/174 (11.5%)	RR 1.39 (0.82 to 2.38)	45 more per 1,000 (from 21 fewer to 159 more)	⊕⊕○○ Low	Critical
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Need for Mechanical Ventilation

3(n=264)	randomised trials	not serious	not serious	serious ^a	serious ^b	none	38/138 (27.5%)	37/126 (29.4%)	RR 0.85 (0.46 to 1.59)	44 fewer per 1,000 (from 159 fewer to 173 more)	⊕⊕○○ Low	Critical
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Duration of Hospitalization

1(n=100)	randomised trials	not serious	not serious	serious ^a	not serious	none	50	50	-	MD 9.8 lower (11.38 lower to 8.22 lower)	⊕⊕⊕○ Moderate	Critical
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Duration of ICU Admission

1(n=100)	randomised trials	not serious	not serious	serious ^a	not serious	none	50	50	-	MD 1 lower (1.92 lower to 0.08 lower)	⊕⊕⊕○ Moderate	Critical
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Need for ICU Admission

1(n=84)	randomised trials	not serious	not serious	serious ^a	not serious	none	39/52 (75.0%)	27/32 (84.4%)	RR 0.89 (0.72 to 1.10)	93 fewer per 1,000 (from 236 fewer to 84 more)	⊕⊕⊕○ Moderate	Critical
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CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

a. The subjects in the included studies are not children but adults.

b. Wide Confidence Interval

c. Very wide confidence interval

d. High heterogeneity

Appendix 5. Forest Plots

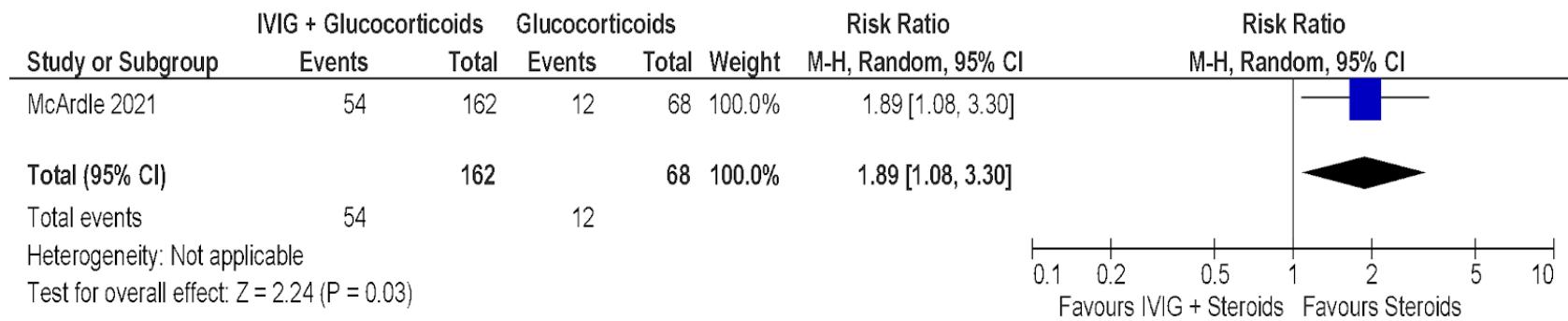


Figure 1. IVIG + Glucocorticoids vs Glucocorticoids in pediatric patients: Use of inotropic support or mechanical ventilation on or after day 2 or death.

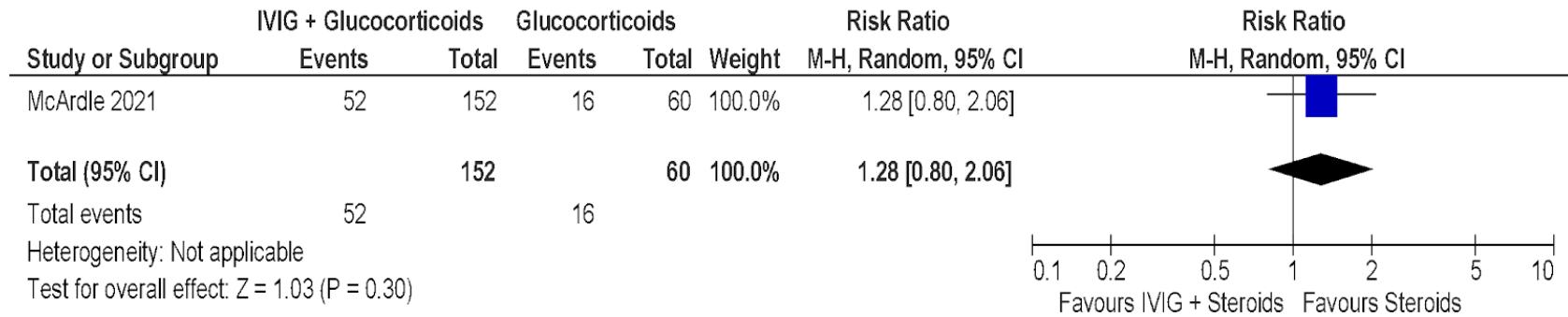


Figure 2. IVIG + Glucocorticoids in pediatric patients: Reduction in the score for disease severity on the ordinal scale by day 2.

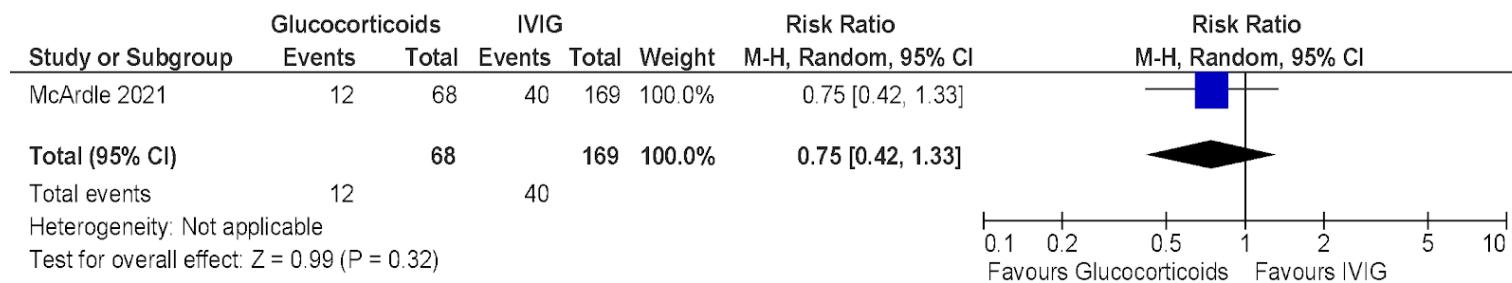


Figure 3. IVIG vs. Glucocorticoids in pediatric patients: Use of inotropic support or mechanical ventilation on or after day 2 or death.

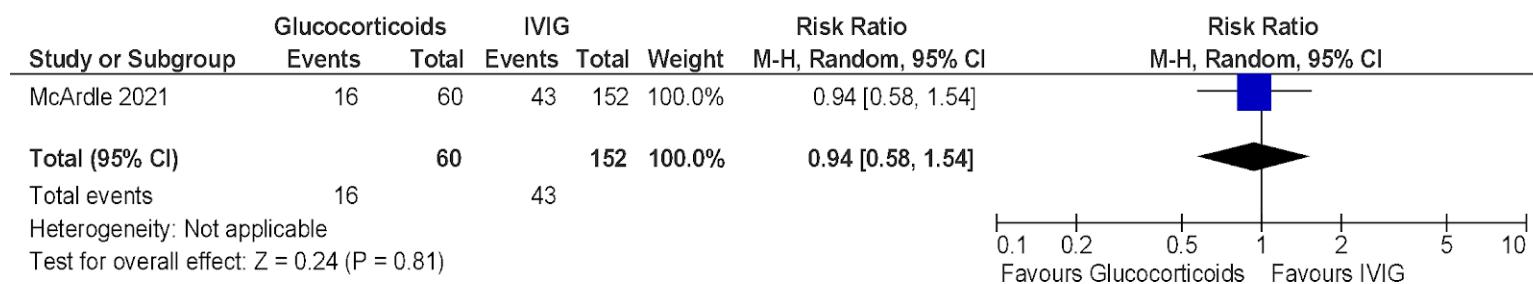


Figure 4. IVIG vs. Glucocorticoids in pediatric patients: Reduction in the score for disease severity on the ordinal scale by day 2.

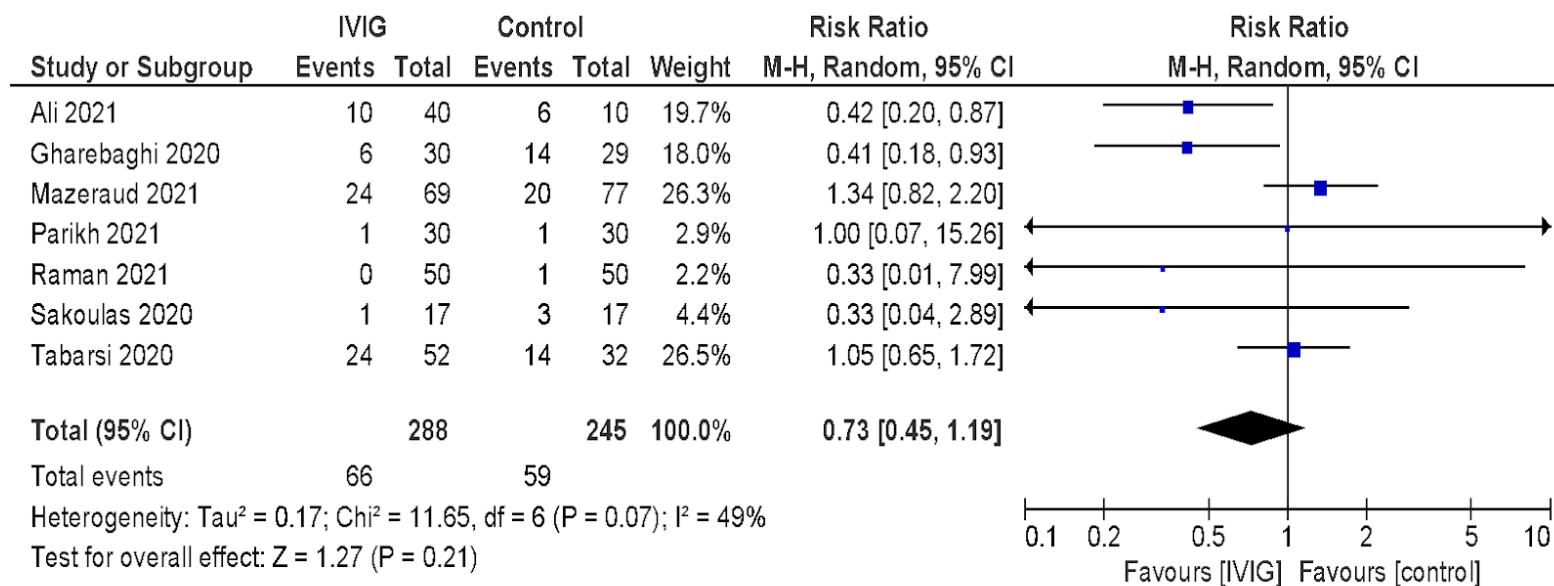


Figure 5. IVIG vs SOC or Placebo in adults: Mortality.

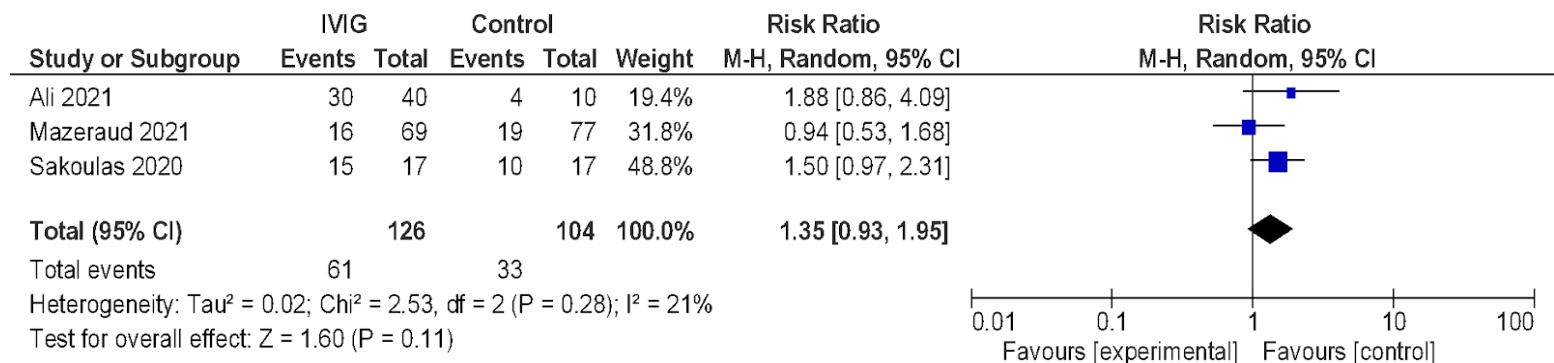


Figure 6. IVIG vs SOC or Placebo in adults: Clinical Improvement D28.

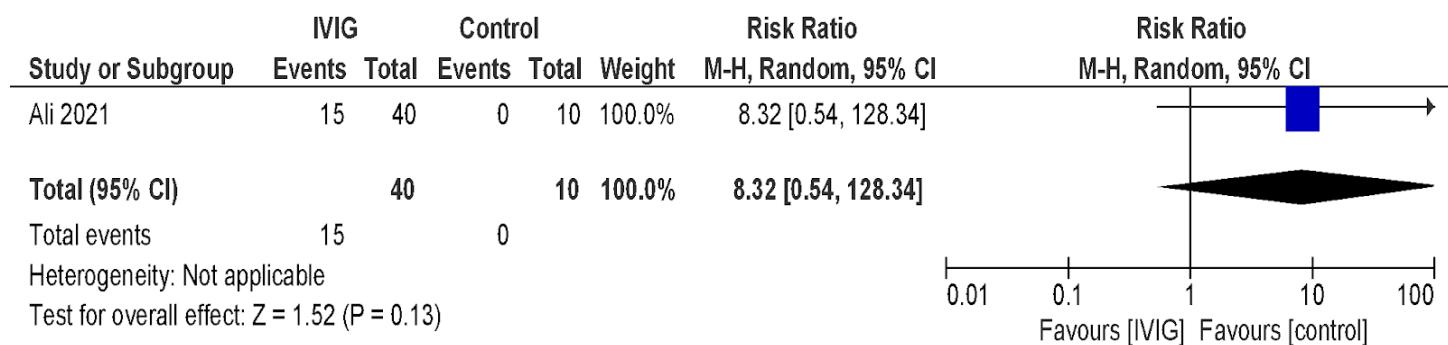


Figure 7. IVIG vs SOC or Placebo in adults: Clinical improvement D7.

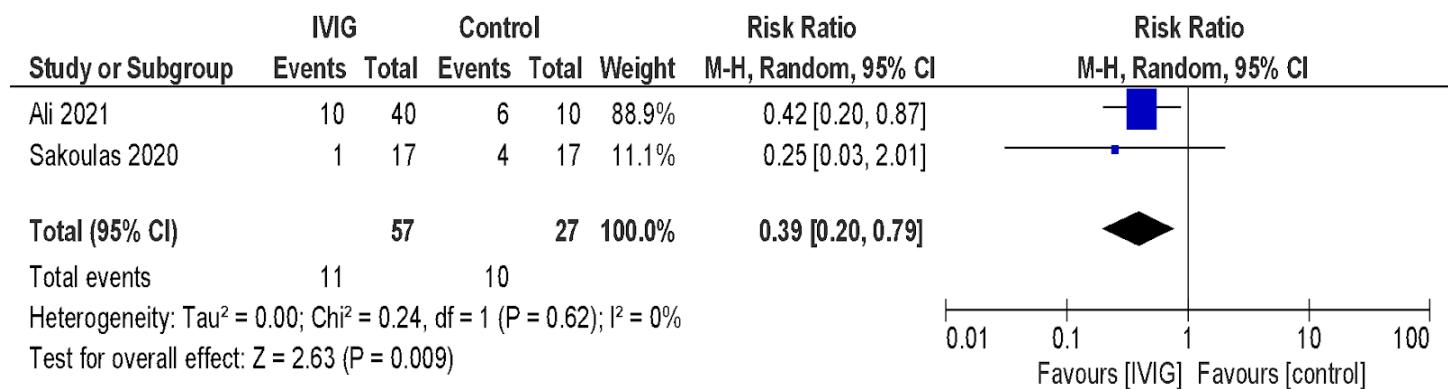


Figure 8. IVIG vs SOC or Placebo in adults: Clinical Deterioration or WHO progression level 7 or above at D28.

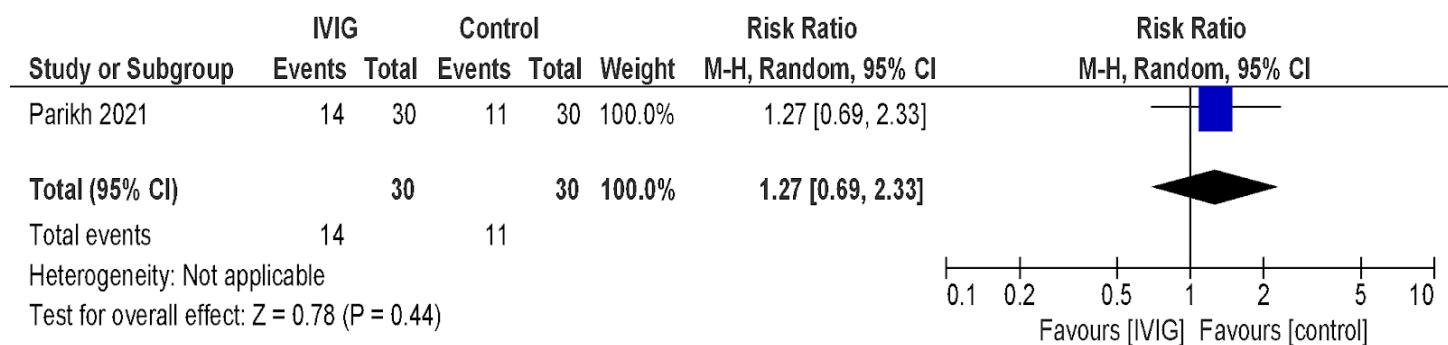


Figure 9. IVIG vs SOC or Placebo in adults: Viral Clearance D3.

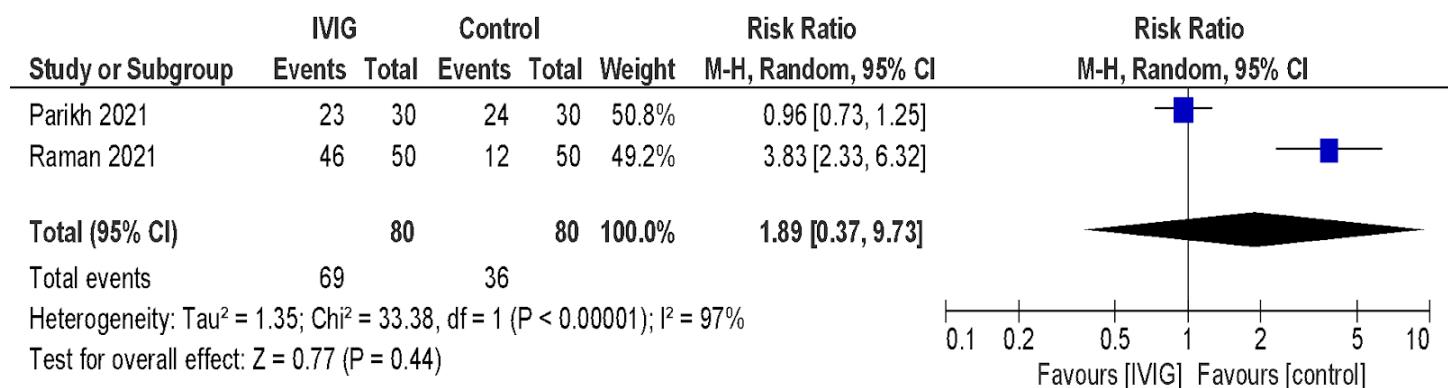


Figure 10. IVIG vs SOC or Placebo in adults: Viral Clearance D14.

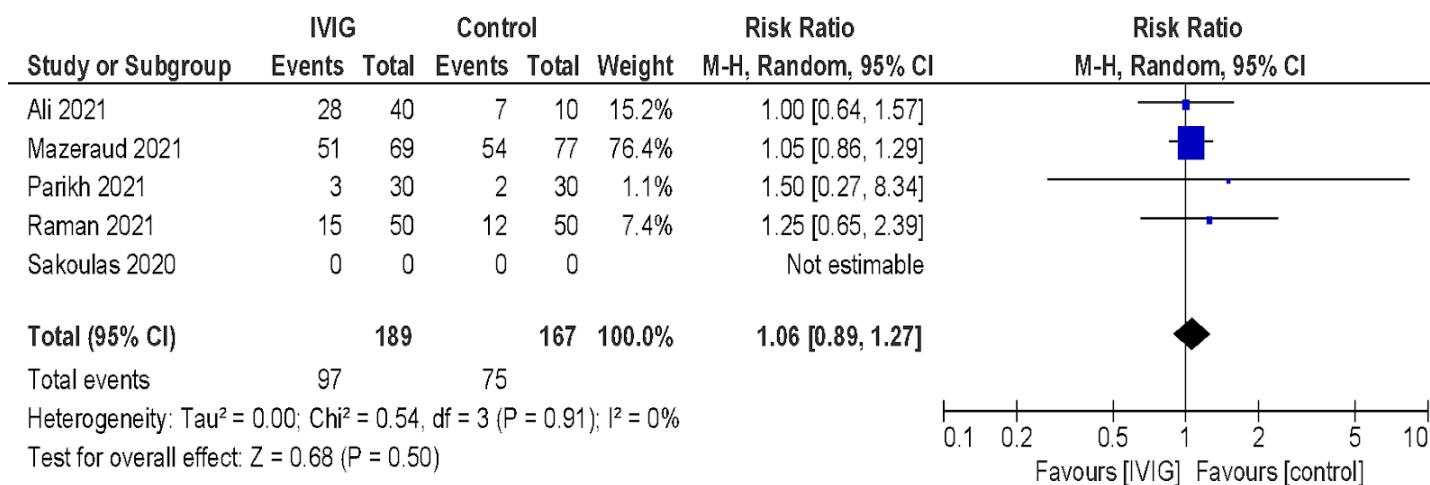


Figure 11. IVIG vs SOC or Placebo in adults: Adverse Events

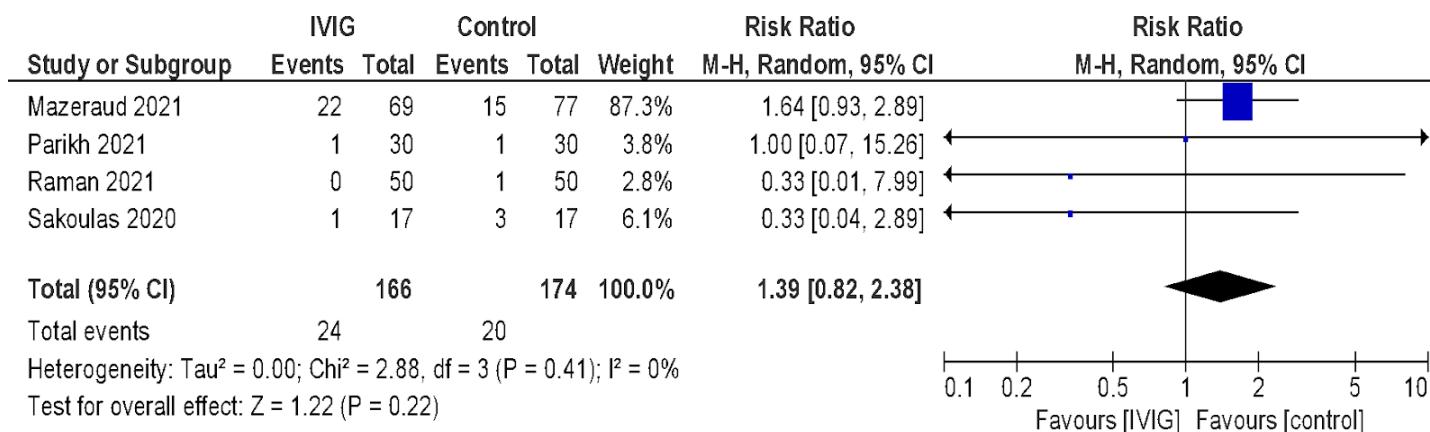


Figure 12. IVIG vs SOC or Placebo in adults: Serious Adverse Events.

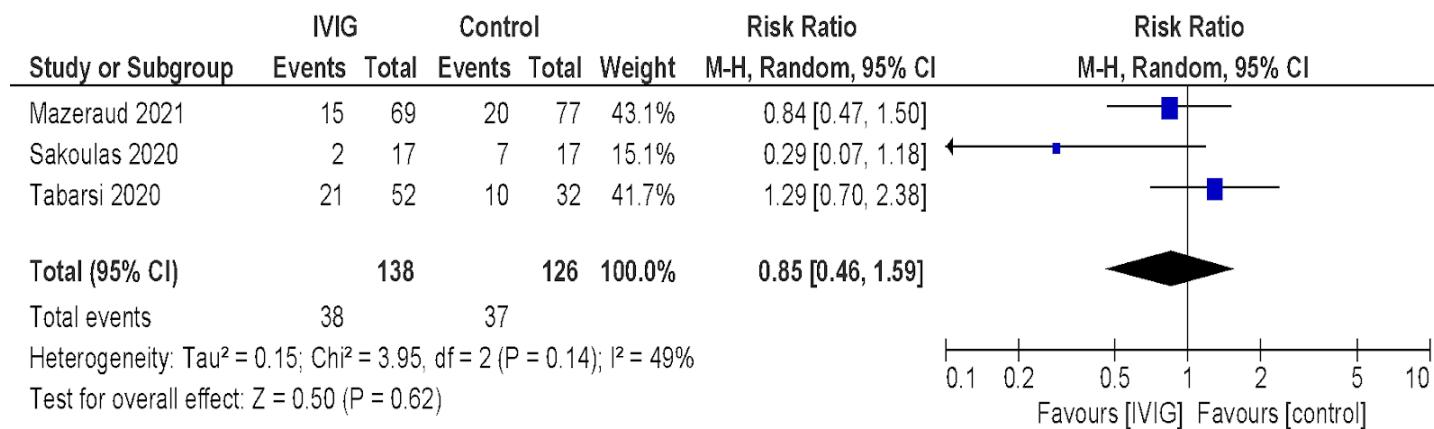


Figure 13. IVIG vs SOC or Placebo in adults: Need for Mechanical Ventilation.

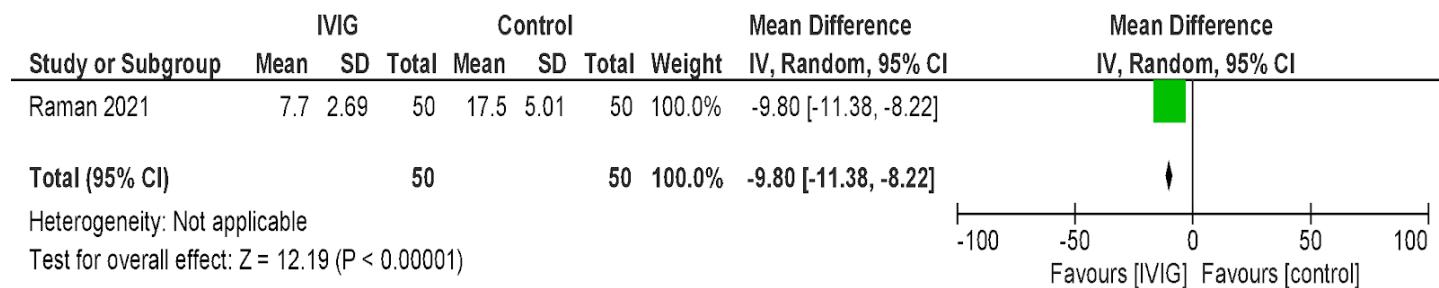


Figure 14. IVIG vs SOC or Placebo in adults: Duration of Hospitalization.

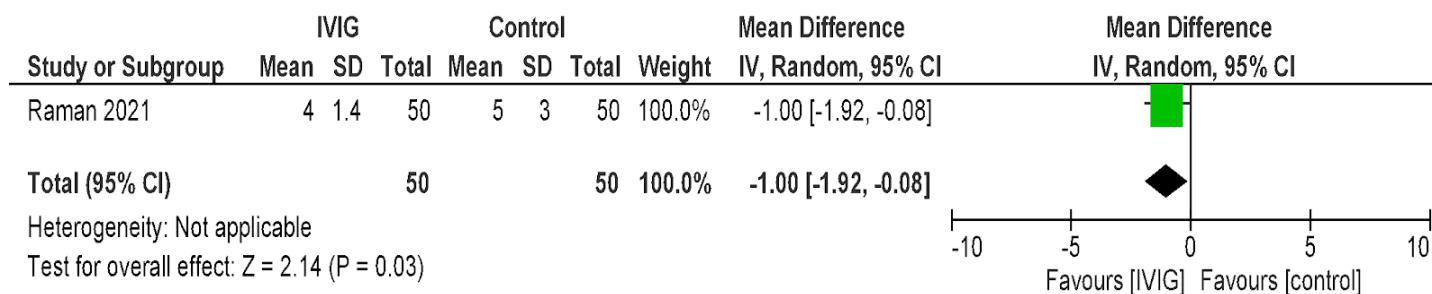


Figure 15. IVIG vs SOC or Placebo in adults: Duration of ICU Admission.

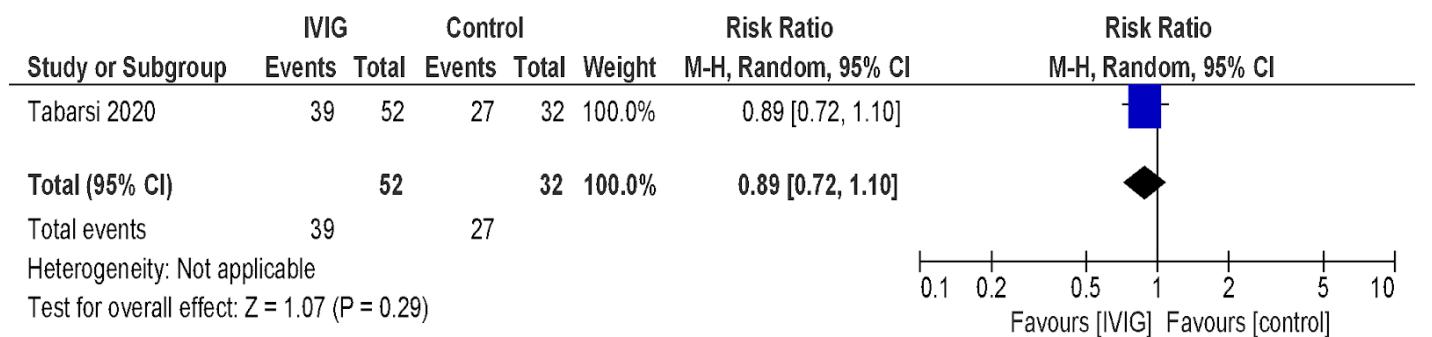


Figure 16. IVIG vs SOC or Placebo in adults: Need for ICU Admission.

Appendix 6. Summary of Recommendations from Other Groups

CPGs/ Expert Group	Recommendation	CPGs/ Expert Group
Interim Guidelines on the Screening, Classification, and Management Of Pediatric Patients With Suspected Or Confirmed Coronavirus Disease 2019 (Covid-19) Version 5, PPS, PIDSP	<p>Recommend intravenous immunoglobulin (IVIG) with corticosteroids for the treatment of MIS-C at a dose of 2 g/kg over 8-12 hours (max 100 g)*</p> <p>*Assess cardiac function and fluid status before giving IVIG; should only be administered when cardiac function is restored</p>	08 January 2022
Australian Guidelines	<p>The Taskforce is currently developing recommendations in children and adolescents with COVID-19*. The Australian Living Guidelines for adults allow the use of IVIG for the treatment of COVID-19, only in the context of clinical trials</p> <p>*Do not use combination of immunoglobulin plus methylprednisolone to treat COVID-19 in children and adolescents unless they are eligible to be enrolled in trials.</p>	17 December 2021
US NIH Guidelines	There is currently insufficient evidence for the Panel to recommend either for or against any specific therapeutic strategy for the management of MIS-C.	21 April 2021
Philippine Covid-19 Living Clinical Practice Guidelines (Adult)	Suggest against the use of IVIG as treatment for moderate to severe COVID-19 (Conditional, Very low)	30 June 2021
Surviving Sepsis Guideline (Adult)	Suggest against the routine use of standard IV immunoglobulin in critically-ill adults with COVID-19	March 2021
WHO	No recommendation for children and adults	
IDSA		
American Thoracic Society		
European Respiratory Society		

Appendix 7. Characteristics of Ongoing Studies

	Title	Population	Interventions	Characteristics	Outcome Measures
1	Randomised Evaluation of COVID-19 Therapy (RECOVERY) in Children With PIMS-TS in Switzerland (SWISSPEDRECOVERY)	Age: 44 Weeks to 18 Years (Child, Adult)	•Drug: Methylprednisolone sodium succinate 10 mg/ kg intravenously •Biological: Human normal immunoglobulin (IVIg) •Drug: Methylprednisolone sodium succinate 2 mg/ kg	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Hospital length of stay •All-cause mortality among patients •Composite endpoint of death or need for mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
2	Human COVID-19 immunoglobulin (COVID HIG) Therapy for COVID 19 Patients	18 Years to 65 Years (Adult, Older Adult)	•Biological: Human COVID-19 immunoglobulin (pH4) for intravenous injection •Drug: Placebo	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment	Outcome Measures: •Time to clinical improvement •Changes of 7-point ordinal scale for COVID-19 clinical improvement •COVID-19-Related Symptoms •Discharge Status •Length of hospital stay •All-cause Mortality •Negativization rate of SARS-CoV-2 nucleic acid •Changes of leukocyte count, lymphocyte count, C-reactive protein, IL-6 and SARS-CoV-2 nucleic acid (quantitative) •Treatment in ICU •SARS-CoV-2 Neutralizing Antibody Level •and 3 more
3	A COVID-19 Study to Evaluate Safety and PK of COVID-HIG Administered Through IM, SC, or IV Routes as a Single Dose Regimen to SARS-CoV-2 Uninfected Adults	Age: 18 Years to 59 Years (Adult)	•Biological: COVID-HIG	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Adverse events within 72 hours post-dosing •Adverse events leading to discontinuation or temporary suspension of study treatment administration •Adverse events up to 85 days post-administration of a single dose •Serious adverse events up to 85 days post-administration of a single dose •Pharmacokinetic parameter of area under the concentration-time curve (AUC) from time 0 to infinity •Pharmacokinetic parameter of maximum observed concentration after dosing (Cmax) •Pharmacokinetic parameter of time at (Tmax) which Cmax occurs after dosing •Pharmacokinetic parameter of observed or estimated

					<p>concentration at 28 days (C28d) after dosing</p> <ul style="list-style-type: none"> • Pharmacokinetic parameter of AUC0-inf ratios (bioavailability) compared between routes for comparable dose levels • Pharmacokinetic parameter of AUC0-last after COVID-HIG Dosing • and 6 more
4	Outpatient Treatment With AntiCoronavirus Immunoglobulin	Age: 18 Years and older (Adult, Older Adult)	<ul style="list-style-type: none"> • Biological: Hyperimmune Immunoglobulin to SARSCoV-2 (hIVIG) • Other: Placebo 	<p>Study Design:</p> <ul style="list-style-type: none"> • Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) • Primary Purpose: Treatment 	<p>Outcome Measures:</p> <ul style="list-style-type: none"> • Clinical Status • All-cause hospitalization or death through 28 days. • All-cause mortality through 28 days. • Significant Disease Progression • Ordinal Scale Distribution • Disease Progression Through 7 Days • Significant Disease Progression Through 7 Days • Disease Progression at Followup • Activity Limitations at Follow-up • Change in Viral Burden from Serum Antigen • and 6 more
5	MISC COVID-19 Study in Pediatric Population	Age: 1 Year to 15 Years (Child)		<p>Study Design:</p> <ul style="list-style-type: none"> • Observational Model: CaseControl • Time Perspective: CrossSectional 	<p>Outcome Measures:</p> <p>Characterization of immuneresponses</p>
6	Clinical Study in the Treatment of Patients With Moderate Course of COVID-19	Age: 18 Years to 65 Years (Adult, Older Adult)	<ul style="list-style-type: none"> • Drug: COVID-globulin • Drug: Placebo 	<p>Study Design:</p> <ul style="list-style-type: none"> • Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: Double (Participant, Investigator) • Primary Purpose: Treatment 	<p>Outcome Measures:</p> <ul style="list-style-type: none"> • The proportion of subjects in the study groups in whom, during the first 7 days after drug administration, one of the following events developed according to the laboratory/instrumental methods or on the basis of a clinical presentation • All-cause mortality • The elimination time of the SARS-CoV-2 virus • The median time to clinical improvement on the WHO Ordinal Scale for Clinical Improvement • The incidence of severe and extremely severe COVID-19 disease • The need for respiratory support • The need for invasive mechanical ventilation of the lungs, ECMO

					<ul style="list-style-type: none"> •Time to cancellation of oxygen support •The need to stay at the intensive care unit •Duration of fever (# 380C), days •and 3 more
7	A COVID-19 Study to Evaluate Safety and Pharmacokinetics of COVID-HIGIV Administered in Healthy Adults	Age: 18 Years to 60 Years (Adult)	<ul style="list-style-type: none"> •Biological: COVID-HIGIV •Other: Placebo (saline) 	Study Design: <ul style="list-style-type: none"> •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment 	<ul style="list-style-type: none"> •Outcome Measures: •Number of Subjects with Adverse Events (AEs) postdosing •Number of Subjects with Adverse Events that Led to Discontinuation or Temporary Suspension of IV Infusion •Number of Subjects with AEs after IV Infusion •Number of Subjects with SAEs after IV Infusion •Pharmacokinetics parameter of area under the concentration-time curve (AUC) from time0 to the last quantifiable concentration (AUC0-t) of SARSCoV-2 antibodies after dose of COVID-HIGIV •Pharmacokinetics parameter of area under the concentration-time (AUC) from time 0 to the last quantifiable concentration(AUC0-t) of SARS-CoV-2 antibodies plus the additional area extrapolated to infinity(AUC0-inf) after dose of COVIDHIGIV •Pharmacokinetics parameter of area under the concentration-time curve (AUC) from time 0 to 14 days (AUC0-14d) after dose of COVID-HIGIV •Pharmacokinetics parameter of area under the concentration-time curve (AUC) from time 0 to 28 days (AUC0-28d) after dose of COVID-HIGIV •Pharmacokinetics parameter of maximum observed concentration (Cmax) of SARSCoV-2 antibodies observed after dose of COVID-HIGIV •Pharmacokinetics parameter of time at which Cmax occurs after dose of COVID-HIGIV •and 5 more
8	IVIG in Patients With Severe COVID-19 Requiring Mechanical Ventilation	Age: 18 Years and older (Adult, Older Adult)	•Drug: IVIG	Study Design: <ul style="list-style-type: none"> •Allocation: N/A •Intervention Model: Single Group Assignment 	<ul style="list-style-type: none"> •Outcome Measures: •Hospital length of stay •Human metabolome and proteome

				<ul style="list-style-type: none"> •Masking: None (Open Label) •Primary Purpose: Treatment 	
9	TREATMENT WITH ANTI-SARS-COV-2 IMMUNOGLOBULIN IN PATIENTS WITH COVID-19	Age: 18 Years to 75 Years (Adult, Older Adult)	•Biological: Anti-SARSCoV-2 immunoglobulin	<p>Study Design:</p> <ul style="list-style-type: none"> •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment 	<p>Outcome Measures:</p> <ul style="list-style-type: none"> •Rate of adverse events related to the infusion of anti-SARS-CoV-2 immunoglobulin through CTCAEv4.0. •Clearance of viral RNA evaluated by RT-PCR •Reduction of viral load evaluated by area under the curve of RTPCR values •Length of hospital stay •Orotracheal Intubation Rate •Infusional reaction rate •Mortality rate •Assessment of adverse events •Evaluation of clinical status •Modulation of serum and cellular inflammatory marker
10	COVIDIG (COVID-19 HyperImmunoGlobulin	Age: 19 Years and older (Adult, Older Adult)	•Biological: GC5131 •Other: Placebo	<p>Study Design:</p> <ul style="list-style-type: none"> •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment 	<p>Outcome Measures:</p> <ul style="list-style-type: none"> •Ordinal scale outcome •Viral negative •Change in NEWS2 (National Early Warning Score 2) •mortality
11	Intravenous Immunoglobulins for the Treatment of Covid-19 Patients: a Clinical Trial	Age: 18 Years to 90 Years (Adult, Older Adult)	•Biological: intravenous immunoglobulin therapy	<p>Study Design:</p> <ul style="list-style-type: none"> •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Double (Investigator, Outcomes Assessor) •Primary Purpose: Treatment 	<p>Outcome Measures:</p> <ul style="list-style-type: none"> •In hospital days •14 day mortality •D-dimers •C-reactive protein •Oxygen saturation •TNF alpha •IL-6 •Ferritin •Number of participants with treatment-related adverse events as assessed by CTCAE v4.0
12	Inpatient Treatment of COVID-19 With Anti-Coronavirus Immunoglobulin (ITAC)	Age: 18 Years and older (Adult, Older Adult)	•Biological: Hyperimmune immunoglobulin to SARSCoV-2 (hIVIG) •Other: Placebo •Drug: Remdesivir	<p>Study Design:</p> <ul style="list-style-type: none"> •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment 	<p>Outcome Measures:</p> <ul style="list-style-type: none"> •Ordinal Outcome Scale - Day 7 •All-cause mortality through Day 28 •Ordinal Outcome Scale •Change in National Early Warning Score (NEWS) •Time to Worsening •Discharge Status •Days Alive Outside the Hospital •Pulmonary-only Components of the Primary Ordinal Outcome •Thrombotic Components of the Primary Ordinal Outcome •Time to recovery •and 6 more

13	SARS-CoV-2 Antibodies Based IVIG Therapy for COVID-19 Patients	Age: 18 Years and older (Adult, Older Adult)	•Biological: SARS-CoV-2 antibody based IVIG therapy	Study Design: •Allocation: Randomized •Intervention Model: Sequential Assignment •Masking: Single (Participant) •Primary Purpose: Treatment	Outcome Measures: •28 Days mortality •Requirement of supplemental oxygen support •Number of days on assisted ventilation •Days to step down •Days to Hospital Discharge •Adverse events during hospital stay •Change in C-Reactive Protein(CRP) levels •Change in neutrophil lymphocyte ratio •Change in Ferritin levels •Change in lactatedehydrogenase (LDH) levels •and 8 more
14	Intravenous Immunoglobulin (IVIG, Bioven) Efficacy Assess for COVID-19 / SARS-CoV-2 Severe Pneumonia Complex Treatmen	Age: 18 Years and older (Adult, Older Adult)	•Drug: IVIG	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Period duration (in days) to clinical improvement •O2 saturation (SPO2percentage), with self-breathing •Respiratory movements rate(amount per minute), with selfbreathing •Body temperature without antipyretics use •Lymphocyte count •Time from the onset of the disease to discharge, in days •Duration of the need for ventilatory support, in days •Duration of the need for intensive care, in days •Duration of need for oxygenationin days (SPO2 # 93% with selfbreathing) •The C-reactive protein (CRPlevel •and 10 more
15	Study to Evaluate the Safety and Efficacy of High Dose Intravenous Immune Globulin (IVIG) Plus Standard Medical Treatment (SMT) Versus SMT Alone in Participants in Intensive Care Unit (ICU) With Coronavirus Disease (COVID-19)	Age: 18 Years and older (Adult, Older Adult)	•Biological: GAMUNEX-C •Drug: Standard Medical Treatmen	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •All-Cause Mortality Rate Through Day 29 •Time to Actual ICU Discharge •Duration of Mechanical Ventilation •Time to Actual Hospital Discharge •Duration of Any Oxygen Use •Mean Change from Baseline in Ordinal Scale •Absolute Value Change from Baseline in Ordinal Scale •Percentage of Participants in Each Severity Category of the 7-Point Ordinal Scale •Overall Number of Participants who Develop Acute Respiratory Distress Syndrome (ARDS)

					•Number of Participants whoDevelop ARDS Distributed by Severity •and 3 more
16	Study to Evaluate the Safety and Efficacy of High Dose IVIG in Hospitalized Participants With Coronavirus Disease (COVID-19)	Age: 18 Years and older (Adult, Older Adult)	•Biological: Intravenous Immune Globulin •Drug: Standard Medical Treatment	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Percentage of Participants Dying or Requiring ICU Admission •Percentage of Participants Who are Dependent on High Flow Oxygen Devices or Invasive Mechanical Ventilation •Change from Baseline in National Early Warning Score (NEWS) •Time to Clinical Response as Assessed by: NEWS # 2 Maintained for 24 hours •Time to Hospital Discharge •Duration of ICU Stay •Duration of Any Oxygen Use •Duration of Mechanical Ventilation •Mean Change from Baseline in Ordinal Scale •Absolute Value Change from Baseline in Ordinal Scale •and 5 more
17	Convalescent Antibodies Infusion in COVID 19 Patients	Age: 18 Years and older (Adult, Older Adult)	•Biological: Anticoronavirus antibodies (immunoglobulins) obtained with DFPP from convalescent patients	Study Design: •Allocation: N/A •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Time to weaning of oxygen support •Chest XR or CT scan evaluation •Survival, •Viral titer •Anti COVID 19 IgG antibodies •Anti COVID 19 IgM antibodies •C5a concentration •C3a concentration •Serum C5b-9 concentration Marker of complement activation •Serum IL-6 levels •and 7 more
18	Study of SOC Plus IVIG Compared to SOC Alone in the Treatment of COVID-19	Age: 18 Years and older (Adult, Older Adult)	•Drug: Octagam	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Mechanical Ventilation •Oxygen Therapy •Length of Stay
19	NORMAL HUMAN IMMUNOGLOBULINS (IVIG) IN PATIENTS AGED 75 YEARS AND OVER, COVID-19 WITH SEVERE	Age: 75 Years and older (Older Adult)	•Drug: IgIV	Study Design: •Allocation: N/A •Intervention Model: Single Group Assignment	Outcome Measures: •Mortality •Total number of days of full hospitalization •Duration of oxygen therapy •Ferritin level in the blood •CRP level in the blood

	ACUTE RESPIRATORY FAILURE			<ul style="list-style-type: none"> •Masking: None (Open Label) •Primary Purpose: Treatment 	<ul style="list-style-type: none"> •LDH level in the blood •Lymphocyte level in the blood •PNN level in the blood •platelet level in the blood •WHO performance index •and 4 more
20	Octagam 10% Therapy in COVID-19 Patients With Severe Disease Progression	Age: 18 Years and older (Adult, Older Adult)	<ul style="list-style-type: none"> •Biological: Octagam 10% •Other: Placebo 	<ul style="list-style-type: none"> •Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Prevention 	<ul style="list-style-type: none"> •Outcome Measures: •Stabilization or Improvement in Clinical Status •Descriptive Clinical Status Analysis •Clinical Status Assessment •Time to death •Mechanical Ventilation Initiation •Mechanical Ventilation Duration •SARS-CoV-2 Test Result •Incidence of all AEs •Incidence of AEs considered related to the IMP •Incidence of serious adverse events (SAEs) •and 45 more
21	Convalescent Plasma (PC) and Human Intravenous Anti-COVID-19 Immunoglobulin (IV Anti COVID-19 IgG) in Patients Hospitalized for COVID-19.	Age: 18 Years and older (Adult, Older Adult)	<ul style="list-style-type: none"> •Biological: COVID-19 convalescent plasma •Biological: Anti-COVID-19 human immunoglobulin •Drug: Standard (specific) therapy for COVID-19 	<ul style="list-style-type: none"> •Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment 	<ul style="list-style-type: none"> •Outcome Measures: •Admission to ICU and/or mechanical ventilation •Length of hospital stay •Neutralizing antibody (IgG) titers against COVID-19 •Safety - Adverse events •Death
22	Clinical Study for Efficacy of AntiCorona VS2 Immunoglobulins Prepared From COVID19 Convalescent Plasma Prepared by VIPS Mini-Pool IVIG Medical Devices in Prevention of SARS-CoV-2 Infection in High Risk Groups as Well as Treatment of Early Cases of COVID19 Patients	Age: 21 Years to 50 Years (Adult)	<ul style="list-style-type: none"> •Other: hyper immunoglobulins containing anti-Corona VS2 immunoglobulin 	<ul style="list-style-type: none"> •Study Design: •Allocation: N/A •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment 	<ul style="list-style-type: none"> •Outcome Measures: •Efficacy of COVID19 hyperimmunoglobulins for patients •Efficacy of COVID19 hyperimmunoglobulins for high risk groups •Safety of anti-SARS-CoV-2 hyper immunoglobulins assessed by percentage of adverse events
23	Convalescent Plasma vs Human Immunoglobulin to Treat COVID-19 Pneumonia	Age: 16 Years to 90 Years (Child, Adult, Older Adult)	<ul style="list-style-type: none"> •Drug: Plasma from COVID-19 convalescent patient •Drug: Human immunoglobulin 	<ul style="list-style-type: none"> •Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Double (Participant, Outcomes Assessor) •Primary Purpose: Treatment 	<ul style="list-style-type: none"> •Outcome Measures: •Mean hospitalization time •Mean Oxygenation index evolution •Rate of severe ARDS •Rate and time to death •Mean time with invasive mechanical ventilation •Time to Viral PCR Negativization

24	Polyvalent Immunoglobulin in COVID-19 Related ARDs	Age: 18 Years and older (Adult, Older Adult)	•Drug: Human immunoglobulin •Drug: Placebo	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Double (Participant, Care Provider) •Primary Purpose: Treatment	Outcome Measures: •Ventilator-free days •Mortality •Sequential Organ Failure Assessment Score •P/F ratio •Lung compliance •Radiological score •Biological efficacy endpoints - Creative protein •Biological efficacy endpoints - Procalcitonin •Immunological profile •Number of patients using other treatments for COVID-19 related ARDS •and 6 more
25	Treatment of Acute Severe 2019-nCoV Pneumonia With Immunoglobulin From Cured Patients	Age: 18 Years and older (Adult, Older Adult)	•Drug: Immunoglobulin of cured patients •Drug: #-Globulin	Study Design: •Allocation: Non-Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Time to Clinical Improvement(TTCI) •Clinical status assessed by the ordinal scale •The differences in oxygen intake methods •Duration (days) of supplemental oxygenation •Duration (days) of mechanical ventilation •The mean PaO ₂ /FiO ₂ •The lesions of the pulmonary segment numbers involved in pulmonary CT [every 7 days] •Time to 2019-nCoV RT-PCR negativity in respiratory tract specimens [every 3 days] •Dynamic changes of 2019-nCoV antibody titer in blood •Length of hospital stay (days) •All cause mortality
26	The Efficacy of Intravenous Immunoglobulin Therapy for Severe 2019-nCoV Infected Pneumonia	Age: 18 Years and older (Adult, Older Adult)	•Drug: Intravenous Immunoglobulin •Other: Standard care	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Clinical improvement based on the 7-point scale •Lower Murray lung injury score •28-day mortality •Duration of mechanical ventilation •Duration of hospitalization •Proportion of patients with negative RT-PCR results •Proportion of patients in each category of the 7-point scale •Proportion of patients with normalized inflammation factors •Frequency of Adverse Drug Events •Frequency of Serious Adverse Drug Events

Appendix 8. Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 11)

FACTORS		JUDGEMENT (N = 11)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS	
Problem	No	Yes (11)		Varies		Uncertain			
Benefits	Large (1)	Moderate (2)	Small (2)	Trivial	Varies (1)	Uncertain (5)		<ul style="list-style-type: none"> Pedia studies: Inconclusive for inotropic support, use of mechanical ventilators Indirect evidence from adult studies: benefit for clinical deterioration, duration of hospital stay, ICU admission; no significant effect for all-cause mortality 	
Harm	Large (1)	Moderate (1)	Small (5)	Trivial	Varies	Uncertain (4)		<ul style="list-style-type: none"> No significant adverse events 	
Certainty of evidence	High	Moderate		Low (2)		Very low (9)		<ul style="list-style-type: none"> Rated very low due to very serious risk of bias, indirectness and imprecision 	
Balance of effects	Favors drug (1)	Probably favors drug (1)	Does not favor drug or no drug	Probably favors no drug	Favors no drug (1)	Varies	Uncertain (8)		
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (3)		Probably no important uncertainty or variability (4)		No important uncertainty or variability (1)			
Resources required	Uncertain	Varies	Large costs (10)	Moderate costs (1)	Negligible costs or savings	Moderate savings	Large savings	<ul style="list-style-type: none"> Dose 2g/kg; max dose: 100g 1 vial IVIG: Php 9650.00 1 course IVIG: Php 33,841.31 to Php 322,985.00 	
Certainty of evidence of resources required	No included studies (8)		Very low	Low (1)	Moderate (6)	High			
Cost-effectiveness	No included studies (8)	Varies	Favors the comparison	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention (3)	Favors the intervention		
Equity	Uncertain (7)	Varies (1)	Reduced (1)	Probably reduced	Probably no impact (3)	Probably increased (1)	Increased		
Acceptability	Uncertain (5)	Varies (2)	No	Probably no (1)	Probably yes (2)	Yes (1)			
Feasibility	Uncertain (4)	Varies (2)	No (2)	Probably no	Probably yes (3)	Yes (1)			

Additional Comments

- The drug is costly.
- There is questionable accessibility and availability in far-flung areas.

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.

Evidence Summary

Key Findings

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.

Introduction

In the Philippines, 9.6% of total confirmed cases of COVID-19 are 19 years old or younger [1]. Once infected, the body initiates a systemic inflammatory response which could lead to excessive release of cytokines and inflammatory markers. This process may cause severe organ damage manifesting as acute respiratory distress syndrome (ARDS), renal failure, shock, or multisystem inflammatory syndrome in children (MIS-C) **Error! Reference source not found.** Corticosteroids are widely used drugs with potent anti-inflammatory effects which have been used to treat other severe viral infections (e.g., SARS, MERS). While CS have reputable efficacy and safety profiles, they may still cause several adverse effects such as immunosuppression, hyperglycemia, and fungal infection. As COVID-19 persists in both out-patient and in-patient settings, the potential effects of CS must be further investigated **Error! Reference source not found..**

Review Methods

We searched Cochrane Library, PubMed, MEDLINE, Google Scholar, JSTOR, HERDIN, WHO ICTRP and ClinicalTrials.gov using a combined MeSH and free text search with the terms “SARS-CoV-2”, “COVID-19”, “dexamethasone”, “hydrocortisone”, “methylprednisolone”, “prednisone”, “prednisolone”, “mortality”, “hospitalization”, “recovery”, “clinical improvement”, “need for mechanical ventilation”, “duration of hospital stay”, “duration of ICU stay”, “adverse events”, “negative viral conversion”. Table 1 illustrates our PICO. Randomized controlled trials were prioritized in the search; and if none were found, non-randomized and observational studies were screened as well. When systematic reviews or meta-analyses were found, the individual studies were assessed for possible inclusion.

Table 1. PICO criteria for corticosteroids and COVID-19.

Population	Pediatric patients with COVID-19
Intervention	Corticosteroids
Comparison	Standard of care, placebo
Outcome	Mortality, hospital admission rate, length of hospital stay, length of ICU stay, mechanical ventilator rate, adverse events

Results

We found 20 RCTs done on adult populations which used different CS as treatment for COVID-19. A total of 10,031 COVID-19 patients with all levels of disease severity were analyzed in this review. The included studies compared either systemic CS with standard care or placebo [4,17], two different systemic CS **Error! Reference source not found..**

different doses of the same systemic CS [19, 21], or inhaled plus intranasal CS with standard care or placebo **Error! Reference source not found.**.. The CS used were dexamethasone (8 RCTs) [5,7,11,13,18,21], hydrocortisone (3 RCTs) [4,6,14], methylprednisolone (8 RCTs) [7,8,10,12,15,21], prednisolone (1 RCT) **Error! Reference source not found.**, and ciclesonide (1 RCT) [22].

Systemic Corticosteroids

We found indirect evidence from 15 RCTs that compared systemic CS with standard care or placebo in adult COVID-19 patients [4-17] with only one study including patients aged 15-18 years old [13]. All-cause mortality from the pooled estimate of 14 studies was significantly reduced in the systemic CS group (RR 0.90, 95% CI 0.82 to 0.98, I² = 7%, 13 studies) [4-17]; among the individual CS, only DEX was able to show the same significant benefit (RR 0.90, 95% CI 0.83 to 0.98, I² = 0%, 4 studies) [5,7,11,13]. COVID-19-related mortality in particular did not differ significantly between the groups (RR 1.04, 95% CI 0.29 to 3.73, 1 study) [15].

For the other outcomes, the results were inconclusive: time to death (all-cause) (HR 0.80, 95% CI 0.24 to 2.61, 1 study) [15], time to death (COVID-19-related) (HR 0.96, 95% CI 0.24 to 3.84, 1 study) [15], time to clinical improvement (HR 0.93, 95% CI 0.65 to 1.33, 2 studies) [15,16], length of hospital stay (MD 0.80, 95% CI -0.81 to 2.41, 4 studies) [9,11,12,15], ICU admission rate (RR 0.78, 95% CI 0.32 to 1.90, 2 studies) [9,16], intubation rate (RR 0.69, 95% CI 0.40 to 1.18, 2 studies) [4,9], ECMO rate (RR 0.96, 95% CI 0.14 to 6.64, 1 study) [4], life support-free days (MD -12.68, 95% CI -40.28 to 14.92, 2 studies) [6,14], and SOFA score (MD -0.49, 95% CI -2.18 to 1.20, 2 studies) [5,11]. The rest of the outcomes showed a significant increase for the systemic CS group: length of ICU stay (MD 4.2, 95% CI -3.26 to 5.14, 1 study) [11] and ventilator-free days (MD 2.26, 95% CI 0.2 to 2.38, 1 study) [5].

Another outcome which was increased for the systemic CS group was Glasgow Coma Scale (GCS) score (CS: 15, Control: 10), however, the article did not include specific statistical figures [17]. One study by Ranjbar et al. compared MP with DEX. The MP group had significantly lower WHO OS scores (MD -1.81, 95% CI -2.8 to -0.82) and shorter hospital stay (MD -3.09, 95% CI -5.06 to -1.12) while mortality (RR 0.51, 95% CI 0.24 to 1.07) and need for MV (RR 0.48, 95% CI 0.23 to 1.00) were similar for both groups [18].

Regarding AEs, there was no significant difference found between the systemic CS group and the control group (RR 0.95, 95% CI 0.86 to 1.05, 7 studies) [4,6-10,14]. Likewise, the specific AEs did not show a significant difference: nosocomial infection (RR 0.91, 95% CI 0.61 to 1.36, 2 studies) [4,8], shock (RR 0.17, 95% CI 0.01 to 3.32, 1 study) [8], need for insulin therapy (RR 1.20, 95% CI 0.99 to 1.46, 1 study) [12], and GI symptoms (RR 0.91, 95% CI 0.47 to 1.78, 2 studies) [8,9].

Across the outcomes, the certainty of evidence was very low to moderate; downgrading was done for risk of bias (due to issues of blinding and selective reporting), indirectness, and imprecision (Appendix D). Eleven RCTs were either open-label trials or lacked blinding of the personnel and the outcome assessors [5,7-10,13-16].

Dexamethasone Doses

We found indirect evidence from three RCTs that compared different doses of DEX on adult patients with COVID-19 [19-21]. The included studies varied in the doses used: COVID STEROID 2 – 6 mg DEX OD or 12 mg DEX OD for 10 days [19]; Toroghi et al. – 8 mg OD, BID, or TID for 10 days [20]; Taboada et al. – 6 mg OD for 10 days (low-dose) or 20 mg OD for 5 days then 10 mg OD for 5 days (high-dose) [21].

The COVID STEROID 2 trial showed significantly fewer ventilator-free days (MD -1, 95% CI -1.79 to -0.21), cardiovascular support-free days (MD -1.5, 95% CI -2.12 to -0.88), and renal replacement therapy-free days (MD -1.1, 95% CI -1.54 to -0.66) in the 6 mg/day DEX group. The rest of the outcomes did not show a significant difference between the two doses: mortality (RR 1.18, 95% CI 0.99 to 1.40), life support-free days (MD -2.8, 95% CI -5.8 to 0.2). Adverse events did not significantly differ between the doses: patients who experienced ≥ 1 AE (RR 1.19, 95% CI 0.85 to 1.66), septic shock (RR 1.22, 95% CI 0.83 to 1.80), invasive fungal infection (RR 1.43, 95% CI 0.75 to 2.75), GI bleeding (RR 0.57, 95% CI 0.19 to 1.69) [19].

For the three-arm study done by Toroghi et al., the BID and TID groups' results were analyzed with the OD group results as the common comparator. Mortality rate was significantly higher (RR 0.41, 95% CI 0.20 to 0.85) and length of ICU stay was significantly longer (MD -2.00, 95% CI -3.07 to -0.93) in the TID group. Time to clinical response was significantly longer for both BID and TID groups (BID: MD -1.00, 95% CI -1.82 to -0.18; TID: MD -1.80, 95% CI -2.90 to -0.70). The rest of the outcomes did not differ significantly: duration of MV (BID: MD 0, 95% CI -0.84 to 0.84; TID: MD -1.00, 95% CI -2.04 to 0.04), length of hospital stay (BID: MD -0.80, 95% CI -2.16 to 0.56; TID: MD -1.30, 95% CI -2.65 to 0.05), need for MV (BID: RR 0.51, 95% CI 0.13 to 2.01; TID: RR 0.49, 95% CI 0.13 to 1.84), ICU admission rate (BID: RR 0.85, 95% CI 0.27 to 2.73; TID: RR 0.54, 95% CI 0.20 to 1.50), hospital readmission rate (BID: RR 0.85, 95% CI 0.05 to 13.17; TID: RR 0.98, 95% CI 0.06 to 15.19). Similarly, AEs did not show significant difference between the groups: acute kidney injury (BID: RR 5.98, 95% CI 0.32 to 112.39; TID: RR 2.94, 95% CI 0.32 to 27.21), acute hepatic injury (BID: RR 1.42, 95% CI 0.36 to 5.57; TID: RR 1.22, 95% CI 0.35 to 4.27), arrhythmia (BID: RR 1.28, 95% CI 0.39 to 4.21; TID: RR 0.53, 95% CI 0.22 to 1.32), myocardial infarction (BID: RR 4.27, 95% CI 0.21 to 86.44; TID: RR 1.96, 95% CI 0.18 to 20.85), hyperglycemia (BID: RR 0.79, 95% CI 0.44 to 1.44; TID: RR 0.62, 95% CI 0.37 to 1.06), secondary infection (BID: RR 0.85, 95% CI 0.05 to 13.17; TID: RR 0.24, 95% CI 0.03 to 2.11) [20].

The study done by Taboada et al. showed that the low-dose DEX group had significantly more patients who worsened clinically within 11 days (RR 1.92, 95% CI 1.13 to 3.27). It was also observed that length of ICU stay (MD 1.63, 95% CI 1.00 to 2.26) and duration of MV (MD 4.02, 95% CI 3.44 to 4.60) were prolonged in the low-dose DEX group. In contrast, length of hospital stay was significantly shorter for this group (MD -0.63, 95% CI -1.21 to -0.05). Other outcomes did not differ significantly: mortality (RR 1, 95% CI 0.98 to 1.02), recovery (RR 1, 95% CI 0.37 to 2.71), time to recovery (MD -0.05, 95% CI -0.54 to 0.44), ICU admission rate (RR 1, 95% CI 0.98 to 1.02), need for MV (RR 1, 95% CI

0.98 to 1.02). Complications and adverse events were also similar for the two groups: nosocomial infection (RR 1.08, 95% CI 0.43 to 2.75), need for insulin (RR 1, 95% CI 0.57 to 1.74), thrombosis (RR 0.17, 95% CI 0.02 to 1.43) [21].

Altogether, the studies did not show results which consistently favor either lower or higher doses of DEX. The certainty of evidence from these studies were very low to moderate due to risk of bias (lack of blinding), indirectness and imprecision (Appendix 4). All studies involved adult COVID-19 patients and most outcomes had confidence intervals which crossed the null value.

Inhaled plus Intranasal Corticosteroids

From the search, one study was found which compared inhaled plus intranasal CIC with placebo.

The results were inconclusive for the outcomes of respiratory symptom resolution at Day 7 (RR 0.87, 95% CI 0.61 to 1.24), respiratory symptom resolution at Day 14 (RR 0.89, 95% CI 0.71 to 1.10), overall feeling of improvement at Day 7 (RR 1.03, 95% CI 0.88 to 1.21), overall feeling of improvement at Day 14 (RR 1.03, 95% CI 0.94 to 1.11), symptom resolution at Day 7 (RR 0.94, 95% CI 0.57 to 1.56), symptom resolution at Day 14 (RR 0.83, 95% CI 0.62 to 1.10), hospital admission rate (RR 0.54, 95% CI 0.14 to 2.08), improvement in cough at Day 7 (RR 0.98, 95% CI 0.78 to 1.23), improvement in cough at Day 14 (RR 1.01, 95% CI 0.88 to 1.15), resolution of dyspnea at Day 7 (RR 0.77, 95% CI 0.57 to 1.04), and resolution of dyspnea at Day 14 (RR 0.96, 95% CI 0.81 to 1.14). There were no deaths observed during the study. Adverse events did not significantly differ between the groups (RR 0.70, 95% CI 0.39 to 1.26) [22].

Overall certainty of evidence was low due to indirectness and imprecision (Appendix 4). The study only included adult COVID-19 patients and all outcomes had confidence intervals which crossed the null value.

Other Considerations (Evidence to Decision)

From our literature search, we found one cost-effectiveness analysis done in South Africa on the use of DEX (6 mg oral or intravenous). The study showed that while there is a cost increase with the addition of DEX to standard care, its cost still falls below willingness-to-pay thresholds and approaches 100% cost-effectiveness for thresholds beyond \$500 [23]. Locally, CS are considered to be affordable drugs as the daily cost of medication is below the average daily wage in the Philippines (₱263.77) [24,25].

Table 2. Corticosteroid Prices in the Philippines [25-27]

Drug	Unit Price
Dexamethasone	₱39.88 per ampule (5 mg/mL, 1 mL ampule)
Hydrocortisone	₱21.06 per vial (100 mg powder, vial)
Methylprednisolone	₱289.93 per vial (40 mg, single dose vial)
Prednisolone	₱200 per bottle (20 mg/5 ml syrup, 60 ml bottle)
Ciclesonide	₱835 per nasal spray bottle (120 actuation bottle)

Recommendations from Other Groups

The Pediatric Infectious Disease Society of the Philippines guidelines updated last January 8, 2022 recommends the use of DEX 0.15 mg/kg IV once daily (maximum dose of 6mg) up to 10 days or until discharge for pediatric patients classified as severe or critical. Alternatives include IV MP, IV HCT, oral DEX, and oral PRDL [28]. Treatment guidelines published by the US NIH specifically recommend using DEX for children with COVID-19 who require high-flow oxygen, noninvasive ventilation, invasive MV, or ECMO [29]. The World Health Organization Guidelines for COVID-19 Therapeutics currently do not have recommendations on the use of CS for pediatric COVID-19 patients. For adult patients, they recommend the use of intravenous (IV) CS for severe or critical COVID-19. As their safety profiles are more familiar and more predictable, these can be monitored adequately by competent healthcare providers. For non-severe COVID-19, however, their use is not recommended as it was deemed unreasonable to obtain IV access just for CS [30].

Research Gaps

At present we need more randomized controlled trials enrolling children across all ages and severity of COVID-19 to investigate the efficacy and safety of CS, as well as the optimal dosing and frequency. As of January 21, 2022, there are 15 ongoing RCTs on CS use for COVID-19 registered on ClinicalTrials.gov: one of these trials seeks to compare MP vs. DEX in pediatric (15-18 years old) and adult participants.

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Evidence Summary Appendices

Appendix 1. Search Yield & Results

(Cochrane, PubMed, MEDLINE, Google Scholar, JSTOR, HERDIN, WHO ICTRP)

#	Query	Results
1	“steroids” OR “corticosteroids”	2,051,262
2	“dexamethasone” OR “hydrocortisone” OR “methylprednisolone” OR “prednisone” OR “prednisolone”	1,045,360
3	“SARS-CoV-2” OR “COVID-19”	215,638
4	“children” OR “pediatric”	7,699,280
5	“mortality”	4,842,015
6	“hospitalization” OR “recovery” OR “clinical improvement” OR “need for mechanical ventilation” OR “duration of hospital stay” OR “duration of ICU stay” OR “adverse events” OR “negative viral conversion”	582,688
7	#1 OR #2	1,594,434
8	#5 OR #6	2,704,236
9	#7 AND #8	11,709
10	#4 AND #9	4,775

Appendix 2. Characteristics of Included Studies

Study ID	Patients (n)	Intervention	Comparator	Outcomes	Method
CAPE COVID 2020	Critically-ill COVID-19 patients (n = 149)	Hydrocortisone (200 mg/day until day 7, then 100 mg/day x 4 days, then 50 mg/day x 3 days)	Saline	All-cause Mortality, Intubation Rate, ECMO Rate, Adverse Events, Nosocomial Infection	Multicenter Randomized Double-blind Trial
CoDEX 2020	COVID-19 patients with moderate to severe ARDS (n = 299)	Dexamethasone (20 mg/day x 5 days, then 10 mg/day x 5 days)	Standard Care	All-cause Mortality, Ventilator-free Days, SOFA Score	Multicenter Randomized Open-label Trial
COVID STEROID 2021	COVID-19 patients with severe hypoxia (n = 30)	Hydrocortisone (200 mg/day)	Saline	All-cause Mortality, Life Support-free Days, Adverse Events	Multicenter Randomized Blinded Trial
COVID STEROID 2 2021	COVID-19 patients with severe hypoxemia (n = 982)	Dexamethasone (6 or 12 mg/day x 10 days)		All-cause Mortality, Life Support-free Days, Ventilator-free Days, Cardiovascular Support-free Days, Renal Replacement Therapy-free Days, Adverse Events	Multicenter Randomized Blinded Trial
DEXA-COVID 19 2020	COVID-19 patients with moderate to severe ARDS (n = 19)	Dexamethasone (20 mg/day x 5 days, then 10 mg/day x 5 days)	Standard Care	All-cause Mortality, Adverse Events	Multicenter Randomized Open-label Trial
Edalatifard 2020	patients with severe COVID-19 (n = 62)	Methylprednisolone (250 mg/day x 3 days)	Standard Care	All-cause Mortality, Adverse Events, Nosocomial Infection, Shock, GI Symptoms	Multicenter Randomized Single-blind Trial

Ezer 2021	patients with polymerase chain reaction confirmed COVID-19, presenting with fever, cough, or dyspnea (n = 203)	Inhaled Ciclesonide (600 µg twice daily) and Intranasal Ciclesonide (200 µg daily)	Saline	Respiratory Symptom Resolution, Overall Feeling of Improvement, Symptom Resolution, Hospital Admission Rate, Improvement in Cough, Resolution of Dyspnea, Mortality, Adverse Events	Multicenter Randomized Double-blind Trial
Farahani 2020	COVID-19 patients with severe respiratory failure (n = 29)	Methylprednisolone (1000 mg/day x 3 days)	Standard Care	GCS	Single-center Randomized Double-blind Trial
Ghanei 2021	patients with severe COVID-19 (n = 336)	Prednisolone (25 mg/day)	Standard Care	All-cause Mortality, Length of Hospital Stay, Admission to ICU, Intubation Rate, Adverse Events, GI Symptoms	Multicenter Randomized Open-label Trial
GLUCOCOVID 2021	patients with severe COVID-19 (n = 64)	Methylprednisolone (40 mg BID x 3 days, then 20 mg TID x 3 days)	Standard Care	All-cause Mortality	Multicenter Randomized Open-label Trial
Jamaati 2021	COVID-19 patients with mild to moderate ARDS (n = 50)	Dexamethasone (20 mg/day x 5 days, then 10 mg/day x 5 days)	Standard Care	All-cause Mortality, Length of Hospital Stay, Length of ICU Stay, SOFA Score	Single-center Randomized Trial
Jeronimo 2021	patients with severe COVID-19 (n = 393)	Methylprednisolone (0.5 mg/kg/day)	Saline	All-cause Mortality, Length of Hospital Stay, Need for Insulin Therapy	Single-center Randomized Double-blind Trial
Ranjbar 2021	COVID-19 patients severe (n = 90)	Dexamethasone (6 mg/day) Methylprednisolone		WHO Ordinal Scale	Single-center Randomized Triple-blind Trial

		(2 mg/kg/day)			
RECOVERY 2021	COVID-19 patients (n = 6,425)	Dexamethasone (6 mg/day x 10 days)	Standard Care	All-cause Mortality	Multicenter Randomized Open-label Trial
REMAP-CAP 2020	patients with severe COVID-19 (n = 379)	Hydrocortisone Fixed 7-day Course (50 mg or 100 mg every 6 hours) Hydrocortisone Shock-Dependent Course (50 mg or 100 mg every 6 hours when in shock)	Standard Care	All-cause Mortality, Life Support-free Days, Adverse Events	Multicenter Randomized Open-label Trial
Solanich 2021	patients with severe COVID-19 (n = 55)	Methylprednisolone (120 mg/day x 3 days)	Standard Care	All-cause Mortality, COVID-19-related Mortality, Time to Death (All-cause), Time to Death (COVID-19-related), Time to Clinical Improvement, Length of Hospital Stay	Single-center Randomized Open-label Trial
Steroids-SARI 2020	ICU-admitted COVID-19 patients (n = 47)	Methylprednisolone (40 mg every 12 hours x 5 days)	Standard Care	All-cause Mortality, Adverse Events	Single-center Randomized Open-label Trial
Taboada 2021	hospitalised patients with moderate or severe COVID-19 pneumonia (n = 200)	Dexamethasone (6 mg OD x 10 days or 20 mg OD x 5 days then 10 mg OD x 5 days)		Clinical Worsening, Recovery, Time to Recovery, ICU Admission, Length of ICU Stay, Need for MV, Duration of MV, Length of Hospital Stay, Nosocomial Infection, Need for	Single-center Randomized Open-label Trial

				Insulin, Thrombosis, Mortality	
Tang 2021	COVID-19 patients with CT-confirmed pneumonia (n = 86)	Methylprednisolone (1 mg/kg/day)	Saline	All-cause Mortality, Time to Clinical Improvement, Admission to ICU	Multicenter Randomized Single-blind Trial
Toroghi 2021	patients with moderate to severe COVID-19 (n = 87)	Dexamethasone (8 mg OD, BID, or TID x 10 days)		Time to Clinical Response, Need for MV, Duration of MV, Length of Hospital Stay, ICU Admission Rate, Length of ICU Stay, Hospital Readmission Rate, 60-day Mortality	Single-center Randomized Single-blind Trial

Appendix 3A. GRADE Evidence Profile: Systemic corticosteroids vs. Standard of care or placebo

Authors: Grazielle S. Verzosa, MD, DPPS; Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS; Ma. Lucila M. Perez, MD, MSc, FPPS

Question: Should systemic corticosteroids be used in the treatment of children with COVID-19 infection?

Setting: In-patient and Out-patient

Bibliography:

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Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		

All-cause mortality (all corticosteroids)

14	randomized trials	not serious	not serious	serious	not serious	none	791/3130 (25.3%)	1408/5264 (26.7%)	RR 0.90 (0.82 to 0.98)	27 fewer per 1,000 (from 48 fewer to 5 fewer)	⊕⊕⊕○	MODERATE
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All-cause mortality (dexamethasone)

4	randomized trials	not serious	not serious	serious	not serious	none	585/2287 (25.6%)	1218/4506 (27.0%)	RR 0.90 (0.83 to 0.98)	27 fewer per 1,000 (from 46 fewer to 5 fewer)	⊕⊕⊕○	MODERATE
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All-cause mortality (hydrocortisone)

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
3	randomized trials	not serious	not serious	serious ^a	serious ^{b,c}	none	96/369 (26.0%)	56/188 (29.8%)	RR 0.85 (0.50 to 1.44)	45 fewer per 1,000 (from 149 fewer to 131 more)	⊕⊕○○ LOW	
All-cause mortality (methylprednisolone)												
4	randomized trials	not serious	not serious	serious ^a	serious ^b	none	106/357 (29.7%)	122/350 (34.9%)	RR 0.82 (0.59 to 1.16)	63 fewer per 1,000 (from 143 fewer to 56 more)	⊕⊕○○ LOW	
All-cause mortality (prednisolone)												
1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	4/116 (3.4%)	12/220 (5.5%)	RR 0.63 (0.21 to 1.92)	20 fewer per 1,000 (from 43 fewer to 50 more)	⊕⊕○○ LOW	
COVID-19-related mortality												
1	randomized trials	not serious	not serious	serious ^a	serious ^{b,d,e}	none	4/27 (14.8%)	4/28 (14.3%)	RR 1.04 (0.29 to 3.73)	6 more per 1,000 (from 101 fewer to 390 more)	⊕⊕○○ LOW	
Time to death (all-cause)												
1	randomized trials	serious ^f	not serious	serious ^a	serious ^b	none	27 participants	28 participants	HR 0.80 (0.24 to 2.61)	--	⊕○○○ VERY LOW	
Time to death (COVID-19 related)												
1	randomized trials	serious ^f	not serious	serious ^a	serious ^b	none	27 participants	28 participants	HR 0.96 (0.24 to 3.84)	--	⊕○○○ VERY LOW	
Time to clinical improvement												
2	randomized trials	serious ^f	not serious	serious ^a	serious ^b	none	70 participants	71 participants	HR 0.93 (0.65 to 1.33)	--	⊕○○○ VERY LOW	
Length of hospital stay (days)												
4	randomized trials	serious ^f	not serious	serious ^a	serious ^{b,c}	none	362	441	--	MD 0.8 days more (0.81 fewer to 2.41 more)	⊕○○○ VERY LOW	
ICU admission												

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
2	randomized trials	seriousf	not serious	seriousa	seriousb	none	7/159 (4.4%)	15/263 (5.7%)	RR 0.78 (0.32 to 1.90)	13 fewer per 1,000 (from 39 fewer to 51 more)	⊕○○○ VERY LOW	
Length of ICU stay (days)												
1	randomized trials	not serious	not serious	seriousa	not serious	none	25	25	--	MD 4.2 days more (3.26 more to 5.14 more)	⊕⊕⊕○ MODERATE	
Intubation rate												
2	randomized trials	seriousf	not serious	seriousa	seriousb	none	10/132 (7.6%)	16/236 (6.8%)	RR 0.69 (0.40 to 1.18)	21 fewer per 1,000 (from 41 fewer to 12 more)	⊕○○○ VERY LOW	
ECMO Rate												
1	randomized trials	not serious	not serious	seriousa	seriousb,e	none	2/76 (2.6%)	2/73 (2.7%)	RR 0.96 (0.14 to 6.64)	1 fewer per 1,000 (from 24 fewer to 155 more)	⊕⊕○○ LOW	
Life Support-free Days												
2	randomized trials	seriousf	not serious	seriousa	seriousb,c	none	294	115	--	MD 12.68 days fewer (40.28 fewer to 14.92 more)	⊕○○○ VERY LOW	
Ventilator-free Days												
1	randomized trials	seriousf	not serious	seriousa	not serious	none	151	148	--	MD 2.26 days more (0.2 more to 4.38 more)	⊕⊕○○ LOW	
SOFA Score												
2	randomized trials	seriousf	not serious	seriousa	seriousb	none	152	145	--	MD 0.49 points lower (2.18 lower to 1.2 higher)	⊕○○○ VERY LOW	
GCS Score												

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	seriousg	not serious	seriousa	seriousb	none	Methylprednisolone Group: GCS 15 Control Group: GCS 10				⊕○○○ VERY LOW	
Adverse events												
7	randomized trials	seriousf,i	not serious	seriousa	seriousb	none	113/538 (21.0%)	168/461 (36.4%)	RR 0.95 (0.86 to 1.05)	18 fewer per 1,000 (from 51 fewer to 18 more)	⊕○○○ VERY LOW	
Nosocomial Infection												
2	randomized trials	seriousf	not serious	seriousa	seriousb	none	29/110 (26.4%)	30/101 (29.7%)	RR 0.91 (0.61 to 1.36)	27 fewer per 1,000 (from 116 fewer to 107 more)	⊕○○○ VERY LOW	
Shock												
1	randomized trials	seriousf	not serious	seriousa	seriousb,d,e	none	0/34 (0.0%)	2/28 (7.1%)	RR 0.17 (0.01 to 3.32)	59 fewer per 1,000 (from 71 fewer to 166 more)	⊕○○○ VERY LOW	
Need for Insulin Therapy												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	103/173 (59.5%)	86/174 (49.4%)	RR 1.20 (0.99 to 1.46)	99 more per 1,000 (from 5 fewer to 227 more)	⊕⊕○○ LOW	
Gastrointestinal Symptoms												
2	randomized trials	seriousf	not serious	seriousa	seriousb	none	12/148 (8.1%)	23/236 (9.7%)	RR 0.91 (0.47 to 1.78)	9 fewer per 1,000 (from 52 fewer to 76 more)	⊕○○○ VERY LOW	

CI: Confidence interval; HR: hazard Ratio; MD: mean difference; RR: relative risk

Explanations

- a. The studies used adult subjects.
- b. CI crossed the null value.
- c. The pooled results were heterogenous.
- d. The study had low event rates within a small sample size.
- e. The result had a wide CI.
- f. Some studies were open-label.
- g. Specific figures are not reported.
- h. No available data for MD computation.
- i. Data was extracted from a secondary source.

Appendix 3B. GRADE Evidence Profile: Methylprednisolone vs. Dexamethasone

Authors: Grazielle S. Verzosa, MD, DPPS; Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS; Ma. Lucila M. Perez, MD, MSc, FPPS

Question: Should Methylprednisolone or Dexamethasone be used in the treatment of children with COVID-19 infection?

Setting: In-patient

Bibliography:

Ranjbar K, Moghadami M, Mirahmadizadeh A, Fallahi MJ, Khaloo V, Shahriarid R, et al. Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalized COVID-19 patients: A triple-blinded randomized controlled trial. BMC Infectious Diseases. 2021 Apr 10;21(1).

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	8/44 (18.2%)	15/46 (32.6%)	RR 0.51 (0.24 to 1.07)	160 fewer per 1,000 (from 248 fewer to 23 more)	⊕⊕○○ LOW	
WHO Ordinal Scale												
1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	44	46	--	MD 1.81 points lower (2.8 lower to 0.82 lower)	⊕⊕○○ LOW	
Length of Hospital Stay												
1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	44	46	--	MD 3.09 days fewer (5.06 fewer to 1.12 fewer)	⊕⊕○○ LOW	
Need for MV												
1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	8/44 (18.2%)	18/46 (39.1%)	RR 0.48 (0.23 to 1.00)	203 fewer per 1,000 (from 301 fewer to 0 fewer)	⊕⊕○○ LOW	

CI: Confidence interval; MD: mean difference

Explanations

- a. The study used adult subjects.
- b. The subject population was small.

Appendix 3C. GRADE Evidence Profile: Dexamethasone 6 mg OD vs. 12 mg OD

Authors: Grazielle S. Verzosa, MD, DPPS; Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS; Ma. Lucila M. Perez, MD, MSC, FPPS

Question: Should Dexamethasone 6 mg OD or Dexamethasone 12 mg OD be used in the treatment of children with COVID-19 infection?

Setting: In-patient

Bibliography:

Munch MW, Russell L, Uhre KR, Lindgaard AL, Degn JF, Wetterslev M, et al. Effect of 12 mg vs 6 mg of dexamethasone on the number of days alive without life support in adults with COVID-19 and severe hypoxemia. JAMA. 2021 Nov 9;326(18).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	180/478 (37.7%)	157/490 (32.0%)	RR 1.18 (0.99 to 1.40)	58 more per 1,000 (from 3 fewer to 128 more)	⊕⊕○○ LOW	
Life Support-free Days												
1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	478	489	--	MD 2.8 days fewer (5.8 fewer to 0.2 more)	⊕⊕○○ LOW	
Ventilator-free Days												
1	randomized trials	not serious	not serious	serious ^a	not serious	none	480	491	--	MD 1 days fewer (1.79 fewer to 0.21 fewer)	⊕⊕⊕○ MODERATE	
Cardiovascular Support-free Days												
1	randomized trials	not serious	not serious	serious ^a	not serious	none	480	491	--	MD 1.5 days fewer (2.12 fewer to 0.88 fewer)	⊕⊕⊕○ MODERATE	
Renal Replacement Therapy-free Days												
1	randomized trials	not serious	not serious	serious ^a	not serious	none	480	491	-	MD 1.1 days fewer (1.54 fewer to 0.66 fewer)	⊕⊕⊕○ MODERATE	
Adverse Events												

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	65/485 (13.4%)	56/497 (11.3%)	RR 1.19 (0.85 to 1.66)	21 more per 1,000 (from 17 fewer to 74 more)	⊕⊕○○ LOW	
Septic Shock												
1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	50/485 (10.3%)	42/497 (8.5%)	RR 1.22 (0.83 to 1.80)	19 more per 1,000 (from 14 fewer to 68 more)	⊕⊕○○ LOW	
Invasive Fungal Infection												
1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	21/485 (4.3%)	15/497 (3.0%)	RR 1.43 (0.75 to 2.75)	13 more per 1,000 (from 8 fewer to 53 more)	⊕⊕○○ LOW	
Gastrointestinal Bleeding												
1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	5/485 (1.0%)	9/497 (1.8%)	RR 0.57 (0.19 to 1.69)	8 fewer per 1,000 (from 15 fewer to 12 more)	⊕⊕○○ LOW	

CI: Confidence interval; MD: mean difference; RR: relative risk

Explanations

- a. The study used adult subjects.
- b. CI crossed the null value.

Appendix 3D. GRADE Evidence Profile: Dexamethasone 8 mg OD vs. 8 mg BID

Authors: Grazielle S. Verzosa, MD, DPPS; Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS; Ma. Lucila M. Perez, MD, MSc, FPPS

Question: Should Dexamethasone 8 mg OD or Dexamethasone 8 mg BID be used in the treatment of children with COVID-19 infection?

Setting: In-patient

Bibliography:

Toroghi N, Abbasian L, Nourian A, Davoudi-Monfared E, Khalili H, Hasannezhad M, et al. Comparing efficacy and safety of different doses of dexamethasone in the treatment of COVID-19: A three-arm randomized clinical trial. Pharmacological Reports. 2021;

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	8/47 (17.0%)	12/40 (30.0%)	RR 0.57 (0.26 to 1.25)	129 fewer per 1,000 (from 222 fewer to 75 more)	⊕⊕○○ LOW	
Time to Clinical Response (Days)												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	47	40	--	MD 1 days fewer (1.82 fewer to 0.18 fewer)	⊕⊕○○ LOW	
Need for Mechanical Ventilation												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	3/47 (6.4%)	5/40 (12.5%)	RR 0.51 (0.13 to 2.01)	61 fewer per 1,000 (from 109 fewer to 126 more)	⊕⊕○○ LOW	
Duration of Mechanical Ventilation (Days)												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	47	40	--	MD 0 days (0.84 fewer to 0.84 more)	⊕⊕○○ LOW	
Length of Hospital Stay (Days)												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	47	40	--	MD 0.8 days fewer (2.16 fewer to 0.46 more)	⊕⊕○○ LOW	
ICU Admission Rate												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	5/47 (10.6%)	5/40 (12.5%)	RR 0.85 (0.27 to 2.73)	19 fewer per 1,000 (from 91 fewer to 216 more)	⊕⊕○○ LOW	
Length of ICU-stay (Days)												

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious	serious ^a	serious ^{b,c}	none	47	40	--	MD 0.2 days fewer (0.79 fewer to 0.39 more)	⊕⊕○○ LOW	
Hospital Readmission												
1	randomized trials	not serious	not serious	serious ^a	serious ^{b,c}	none	1/47 (2.1%)	1/40 (2.5%)	RR 0.85 (0.05 to 13.17)	4 fewer per 1,000 (from 24 fewer to 304 more)	⊕⊕○○ LOW	
Acute Kidney Injury												
1	randomized trials	not serious	not serious	serious ^a	serious ^{b,c}	none	3/47 (6.4%)	0/40 (0.0%)	RR 5.98 (0.32 to 112.39)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	
Acute Hepatic Injury												
1	randomized trials	not serious	not serious	serious ^a	serious ^{b,c}	none	5/47 (10.6%)	3/40 (7.5%)	RR 1.42 (0.36 to 5.57)	31 more per 1,000 (from 48 fewer to 343 more)	⊕⊕○○ LOW	
Arrhythmia												
1	randomized trials	not serious	not serious	serious ^a	serious ^{b,c}	none	5/47 (10.6%)	3/40 (7.5%)	RR 1.42 (0.36 to 5.57)	31 more per 1,000 (from 48 fewer to 343 more)	⊕⊕○○ LOW	
Myocardial Infarction												
1	randomized trials	not serious	not serious	serious ^a	serious ^{b,c}	none	2/47 (4.3%)	0/40 (0.0%)	RR 4.27 (0.21 to 86.44)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	
Hyperglycemia												
1	randomized trials	not serious	not serious	serious ^a	serious ^{b,c}	none	14/47 (29.8%)	15/40 (37.5%)	RR 0.79 (0.44 to 1.44)	79 fewer per 1,000 (from 210 fewer to 165 more)	⊕⊕○○ LOW	
Secondary infection												

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	1/47 (2.1%)	1/40 (2.5%)	RR 0.85 (0.05 to 13.17)	4 fewer per 1,000 (from 24 fewer to 304 more)	⊕⊕○○ LOW	

CI: Confidence interval; MD: mean difference; RR: relative risk

Explanations

- a. The study used adult subjects.
- b. The subject population was small.
- c. CI crossed the null value.

Appendix 3E. GRADE Evidence Profile: Dexamethasone 8 mg OD vs. 8 mg TID

Authors: Grazielle S. Verzosa, MD, DPPS; Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS; Ma. Lucila M. Perez, MD, MSC, FPPS

Question: Should Dexamethasone 8 mg OD or Dexamethasone 8 mg TID be used in the treatment of children with COVID-19 infection?

Setting: In-patient

Bibliography:

Toroghi N, Abbasian L, Nourian A, Davoudi-Monfared E, Khalili H, Hasannezhad M, et al. Comparing efficacy and safety of different doses of dexamethasone in the treatment of COVID-19: A three-arm randomized clinical trial. Pharmacological Reports. 2021;

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	8/47 (17.0%)	19/46 (41.3%)	RR 0.41 (0.20 to 0.85)	244 fewer per 1,000 (from 330 fewer to 62 fewer)	⊕⊕○○ LOW	
Time to Clinical Response (Days)												
1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	47	46	--	MD 1.8 days fewer (2.9 fewer to 0.7 fewer)	⊕⊕○○ LOW	
Need for Mechanical Ventilation												
1	randomized trials	not serious	not serious	serious ^a	serious ^{b,c}	none	3/47 (6.4%)	6/46 (13.0%)	RR 0.49 (0.13 to 1.84)	67 fewer per 1,000 (from 113 fewer to 110 more)	⊕⊕○○ LOW	
Duration of Mechanical Ventilation (Days)												
1	randomized trials	not serious	not serious	serious ^a	serious ^{b,c}	none	47	46	--	MD 1 days fewer (2.04 fewer to 0.04 more)	⊕⊕○○ LOW	
Length of Hospital Stay (Days)												
1	randomized trials	not serious	not serious	serious ^a	serious ^{b,c}	none	47	46	--	MD 1.3 days fewer (2.65 fewer to 0.05 more)	⊕⊕○○ LOW	
ICU Admission Rate												

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	5/47 (10.6%)	9/46 (19.6%)	RR 0.54 (0.20 to 1.50)	90 fewer per 1,000 (from 157 fewer to 98 more)	⊕⊕○○ LOW	
Length of ICU-stay (Days)												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	47	46	--	MD 2 days fewer (3.07 fewer to 0.93 fewer)	⊕⊕○○ LOW	
Hospital Readmission												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	1/47 (2.1%)	1/46 (2.2%)	RR 0.98 (0.06 to 15.19)	0 fewer per 1,000 (from 20 fewer to 308 more)	⊕⊕○○ LOW	
Acute Kidney Injury												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	3/47 (6.4%)	1/46 (2.2%)	RR 2.94 (0.32 to 27.21)	42 more per 1,000 (from 15 fewer to 570 more)	⊕⊕○○ LOW	
Acute Hepatic Injury												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	5/47 (10.6%)	4/46 (8.7%)	RR 1.22 (0.35 to 4.27)	19 more per 1,000 (from 57 fewer to 284 more)	⊕⊕○○ LOW	
Arrhythmia												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	6/47 (12.8%)	11/46 (23.9%)	RR 0.53 (0.22 to 1.32)	112 fewer per 1,000 (from 187 fewer to 77 more)	⊕⊕○○ LOW	
Myocardial Infarction												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	2/47 (4.3%)	1/46 (2.2%)	RR 1.96 (0.18 to 20.85)	21 more per 1,000 (from 18 fewer to 432 more)	⊕⊕○○ LOW	
Hyperglycemia												

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious	serious ^a	serious ^{b,c}	none	14/47 (29.8%)	22/46 (47.8%)	RR 0.62 (0.37 to 1.06)	182 fewer per 1,000 (from 301 fewer to 29 more)	⊕⊕○○ LOW	

Secondary infection

1	randomized trials	not serious	not serious	serious ^a	serious ^{b,c}	none	1/47 (2.1%)	4/46 (8.7%)	RR 0.24 (0.03 to 2.11)	66 fewer per 1,000 (from 84 fewer to 97 more)	⊕⊕○○ LOW	
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CI: Confidence interval; MD: mean difference; RR: relative risk

Explanations

- a. The study used adult subjects.
- b. The subject population was small.
- c. CI crossed the null value

Appendix 3F. GRADE Evidence Profile: Dexamethasone low-dose vs. high-dose

Authors: Grazielle S. Verzosa, MD, DPPS; María Teresa S. Tolosa, MD, D Clin Epi, FPDS; Ma. Lucila M. Pérez, MD, MSc, FPPS

Question: Should Low-Dose or High-Dose Dexamethasone be used in the treatment of children with COVID-19 infection?

Setting: In-patient

Bibliography:

Taboada M, Rodríguez N, Varela PM, Rodríguez MT, Abelleira R, González A, et al. Effect of high versus low dose of dexamethasone on clinical worsening in patients hospitalised with moderate or severe COVID-19 pneumonia: An open-label, Randomised Clinical Trial. European Respiratory Journal. 2021Dec16;

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	6/102 (5.9%)	4/98 (4.1%)	RR 1.00 (0.98 to 1.02)	0 fewer per 1,000 (from 1 fewer to 1 more)	⊕⊕○○ LOW	
Clinical Worsening within 11 days												
1	randomized trials	serious ^c	not serious	serious ^a	not serious	none	32/102 (31.4%)	16/98 (16.3%)	RR 1.92 (1.13 to 3.27)	150 more per 1,000 (from 21 more to 371 more)	⊕⊕○○ LOW	
Time to Recovery (Days)												
1	randomized trials	serious ^c	not serious	serious ^a	serious ^b	none	102	98	--	MD 0.05 days fewer (0.54 fewer to 0.44 more)	⊕○○○ VERY LOW	
ICU Admission Rate												
1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	13/102 (12.7%)	15/98 (15.3%)	RR 1.00 (0.98 to 1.02)	0 fewer per 1,000 (from 3 fewer to 3 more)	⊕⊕○○ LOW	
Length of ICU Stay (Days)												
1	randomized trials	serious ^c	not serious	serious ^a	not serious	none	102	98	--	MD 1.63 days more (1 more to 2.26 more)	⊕⊕○○ LOW	
Need for Mechanical Ventilation												
1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	9/102 (8.8%)	10/98 (10.2%)	RR 1.00 (0.98 to 1.02)	0 fewer per 1,000 (from 2 fewer to 2 more)	⊕⊕○○ LOW	
Duration of Mechanical Ventilation (Days)												

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	serious ^c	not serious	serious ^a	not serious	none	102	98	--	MD 4.02 days more (3.44 more to 4.6 more)	⊕⊕○○ LOW	

Length of Hospital Stay (Days)

1	randomized trials	serious ^c	not serious	serious ^a	not serious	none	102	98	--	MD 0.63 days fewer (1.21 fewer to 0.05 fewer)	⊕⊕○○ LOW	
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Nosocomial Infection

1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	10/102 (9.8%)	10/98 (10.2%)	RR 1.08 (0.43 to 2.75)	8 more per 1,000 (from 58 fewer to 179 more)	⊕⊕○○ LOW	
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Need for Insulin

1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	49/102 (48.0%)	47/98 (48.0%)	RR 1.00 (0.57 to 1.74)	0 fewer per 1,000 (from 206 fewer to 355 more)	⊕⊕○○ LOW	
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Thrombosis

1	randomized trials	not serious	not serious	serious ^a	serious ^b	none	6/102 (5.9%)	1/98 (1.0%)	RR 0.17 (0.02 to 1.43)	8 fewer per 1,000 (from 10 fewer to 4 more)	⊕⊕○○ LOW	
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CI: Confidence interval; MD: mean difference; RR: relative risk

Explanations

- a. The study used adult subjects.
- b. CI crossed the null value.
- c. The study was open-label.

Appendix 3G. GRADE Evidence Profile: Inhaled plus intranasal ciclesonide vs. placebo

Authors: Grazielle S. Verzosa, MD, DPPS; Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS; Ma. Lucila M. Perez, MD, MSc, FPPS

Question: Should Inhaled plus Intranasal Ciclesonide be used in the treatment of children with COVID-19 infection?

Setting: Out-patient

Bibliography:

Ezer N, Belga S, Daneman N, Chan A, Smith BM, Daniels S-A, et al. Inhaled and intranasal ciclesonide for the treatment of covid-19 in adult outpatients: Contain phase ii randomised controlled trial. BMJ. 2021;

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Respiratory Symptom Resolution (Day 7)												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	34/98 (34.7%)	42/105 (40.0%)	RR 0.87 (0.61 to 1.24)	52 fewer per 1,000 (from 156 fewer to 96 more)	⊕⊕○○ LOW	
Respiratory Symptom Resolution (Day 14)												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	57/98 (58.2%)	69/105 (65.7%)	RR 0.89 (0.71 to 1.10)	72 fewer per 1,000 (from 191 fewer to 66 more)	⊕⊕○○ LOW	
Overall Feeling of Improvement (Day 7)												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	74/98 (75.5%)	77/105 (73.3%)	RR 1.03 (0.88 to 1.21)	22 more per 1,000 (from 88 fewer to 154 more)	⊕⊕○○ LOW	
Overall Feeling of Improvement (Day 14)												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	91/98 (92.9%)	95/105 (90.5%)	RR 1.03 (0.94 to 1.11)	27 more per 1,000 (from 54 fewer to 100 more)	⊕⊕○○ LOW	
Symptom Resolution (Day 7)												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	22/98 (22.4%)	25/105 (23.8%)	RR 0.94 (0.57 to 1.56)	14 fewer per 1,000 (from 102 fewer to 133 more)	⊕⊕○○ LOW	
Symptom Resolution (Day 14)												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	44/98 (44.9%)	57/105 (54.3%)	RR 0.83 (0.62 to 1.10)	92 fewer per 1,000 (from 206 fewer to 54 more)	⊕⊕○○ LOW	
Hospital Admission (Day 14)												

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	3/98 (3.1%)	6/105 (5.7%)	RR 0.54 (0.14 to 2.08)	26 fewer per 1,000 (from 49 fewer to 62 more)	⊕⊕○○ LOW	
Mortality												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	0/98 (0.0%)	0/105 (0.0%)	not estimable	--	⊕⊕○○ LOW	
Improvement in Cough (Day 7)												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	54/86 (62.8%)	57/89 (64.0%)	RR 0.98 (0.78 to 1.23)	13 fewer per 1,000 (from 141 fewer to 147 more)	⊕⊕○○ LOW	
Improvement in Cough (Day 14)												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	72/86 (83.7%)	74/89 (83.1%)	RR 1.01 (0.88 to 1.15)	8 more per 1,000 (from 100 fewer to 125 more)	⊕⊕○○ LOW	
Resolution of Dyspnea (Day 7)												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	27/49 (55.1%)	38/53 (71.7%)	RR 0.77 (0.57 to 1.04)	165 fewer per 1,000 (from 308 fewer to 29 more)	⊕⊕○○ LOW	
Resolution of Dyspnea (Day 14)												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	40/49 (81.6%)	45/53 (84.9%)	RR 0.96 (0.81 to 1.14)	34 fewer per 1,000 (from 161 fewer to 119 more)	⊕⊕○○ LOW	
Adverse Events												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	15/98 (15.3%)	23/105 (21.9%)	RR 0.70 (0.39 to 1.26)	66 fewer per 1,000 (from 134 fewer to 57 more)	⊕⊕○○ LOW	

Appendix 4. Forest Plots

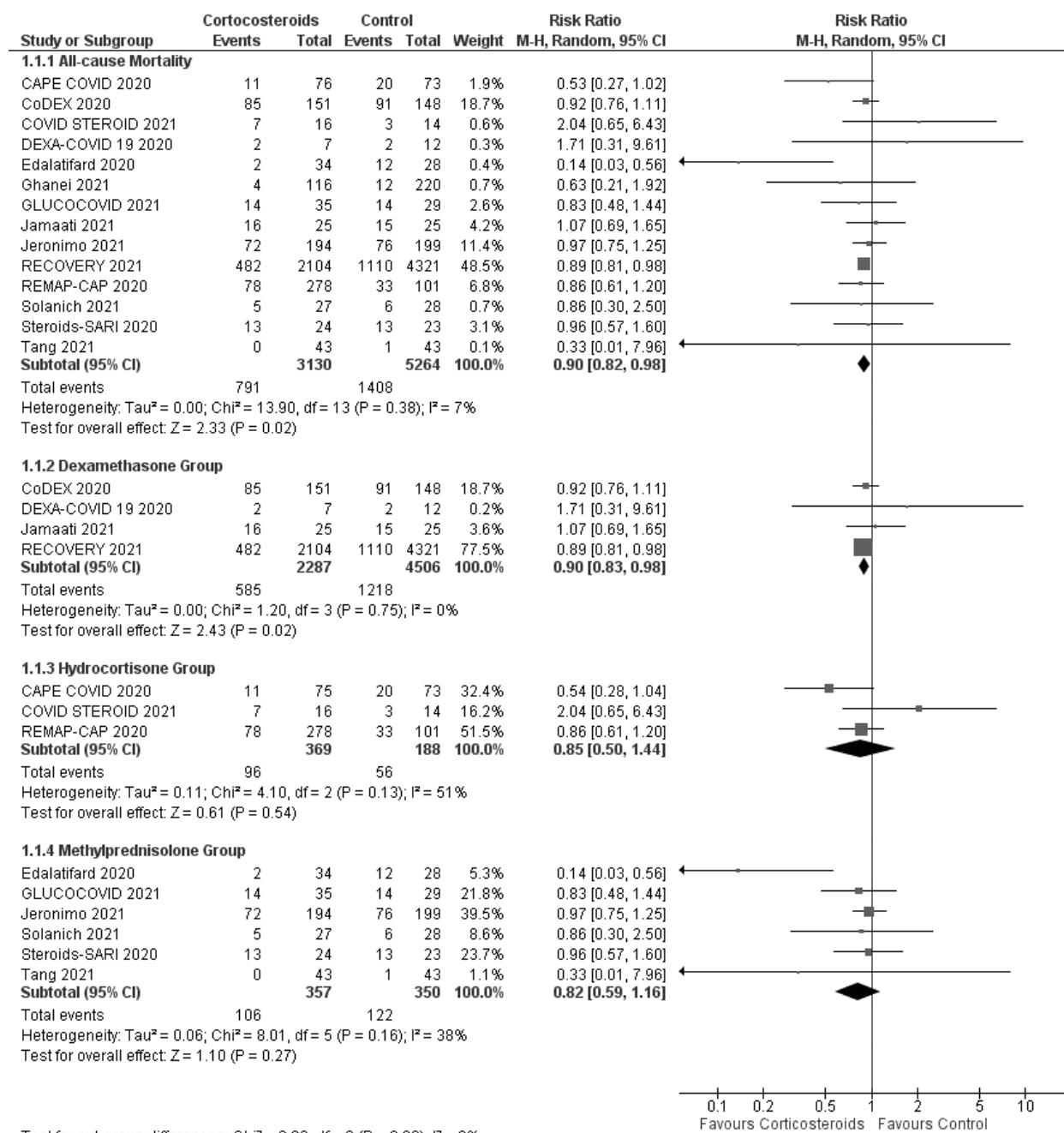


Figure 1. All-Cause Mortality

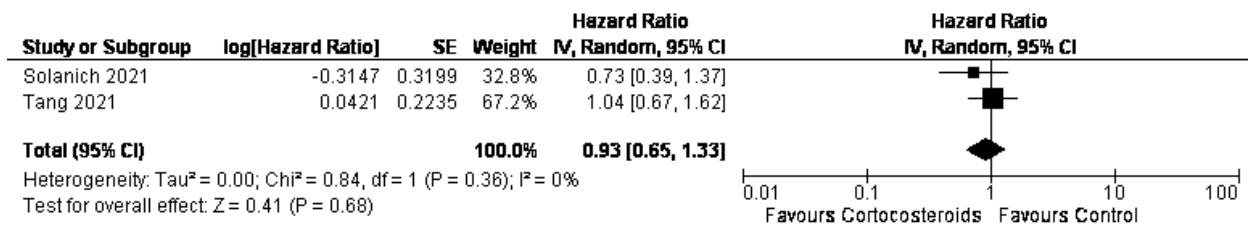


Figure 2. Time to Clinical Improvement

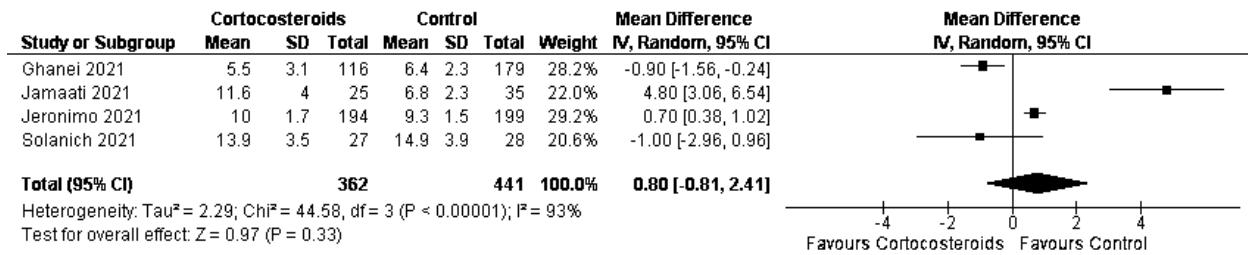


Figure 3. Length of Hospital Stay

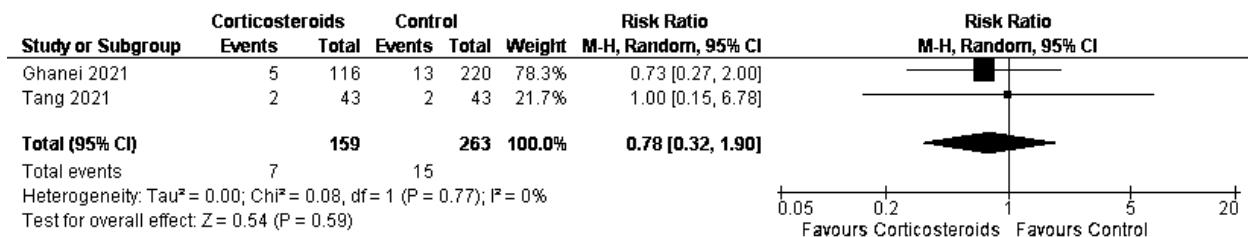


Figure 4. ICU Admission

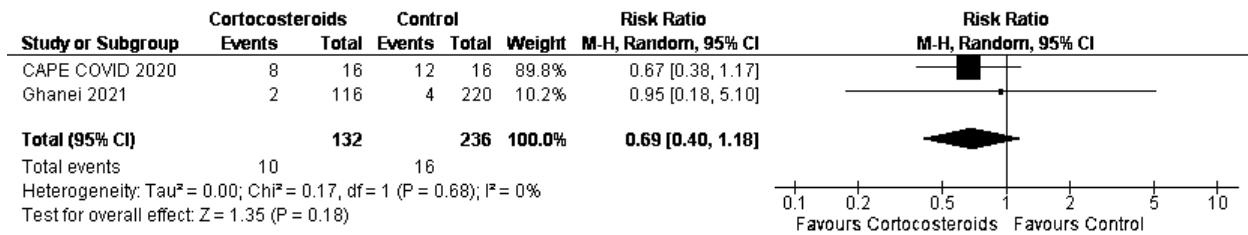


Figure 5. Intubation Rate

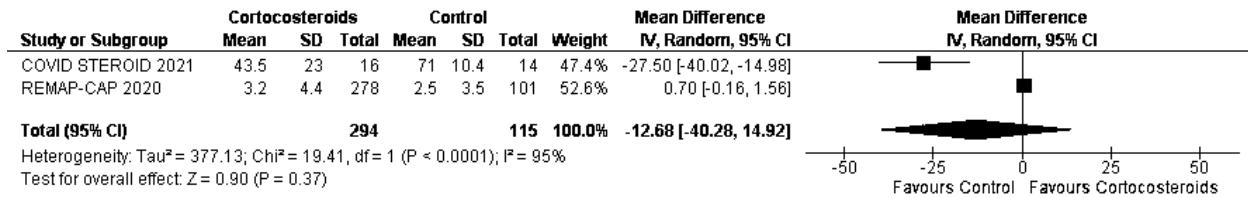


Figure 6. Life Support-free Days

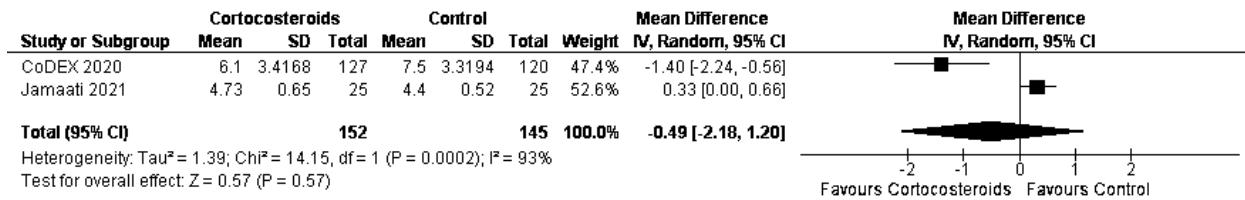


Figure 7. SOFA Score

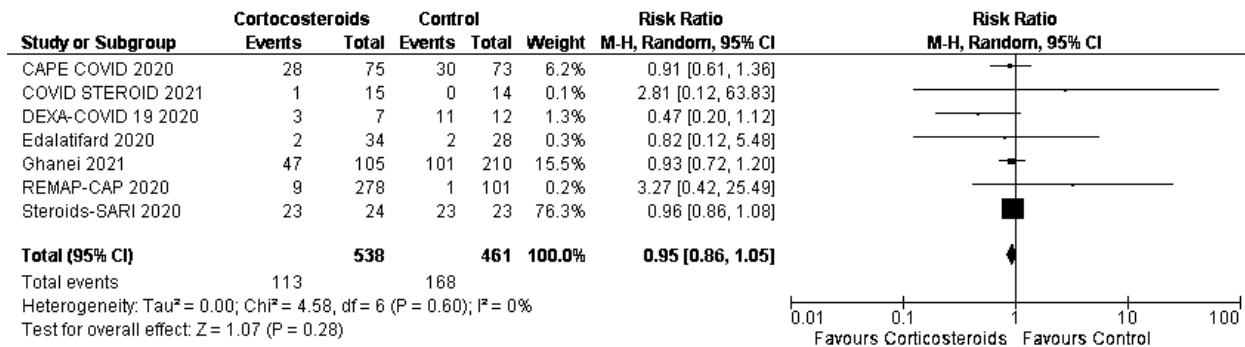


Figure 8. Adverse Events

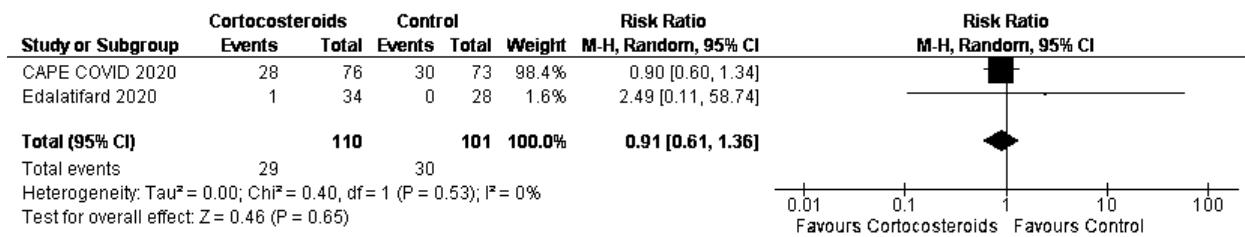


Figure 9. Nosocomial Infection

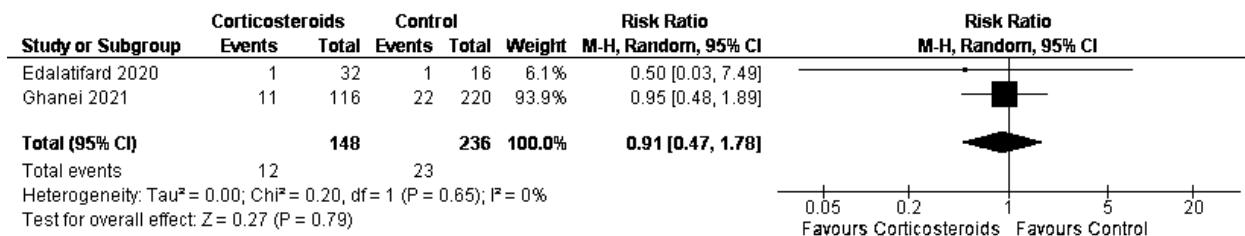


Figure 10. Gastrointestinal Symptoms

Appendix 5. Table of Ongoing Studies

Title (IRCT/NCT Number)	Interventions	Characteristics	Population	Dates/ Location(s)
Comparison between Intravenous Dexamethasone and Methylprednisolone in the Treatment of Hospitalized Patients with COVID-19 (IRCT20210223050466N1)	Dexamethasone Methylprednisolone	Single-center Randomized Single-blind Trial	15 to 80 years old with RT-PCR-confirmed COVID-19	April 26, 2021 – ongoing recruitment Iran
Dexamethasone vs. Methylprednisolone for the Treatment of Patients with ARDS Caused by COVID-19 (NCT04499313)	Dexamethasone Methylprednisolone	Multicenter Randomized Open-label Trial	20 to 80 years old with moderate to severe COVID-19 requiring hospitalization	August 5, 2020 – ongoing recruitment Bangladesh
Methylprednisolone vs. Dexamethasone in COVID-19 Pneumonia (MEDEAS RCT) (NCT04636671)	Methylprednisolone Dexamethasone	Single-center Randomized Open-label Trial	18 years and older with COVID-19 on oxygen support, CPAP, or NPPV	April 14, 2021 – ongoing recruitment Italy
Comparison Between Prednisolone and Dexamethasone on Mortality in Patients on Oxygen Therapy, With CoViD-19 (COPreDex) (NCT04765371)	Dexamethasone Prednisolone	Multicenter Randomized Open-label Trial	18 years and older with COVID-19 requiring oxygen therapy	March 3, 2021 – October 2023 France
Glucocorticoid Therapy in Coronavirus Disease COVID-19 Patients (NCT04780581)	Dexamethasone Methylprednisolone	Multicenter Randomized Open-label Trial	18 years and older with CT-confirmed COVID-19 requiring oxygen therapy	February 1, 2021 – December 31, 2021 Spain
RCT on the Efficacy of Dexamethasone Versus Methyl Prednisolone in Covid-19 Infected Patients with High Oxygen Flow (NCT05062681)	Dexamethasone Methylprednisolone	Single-center Randomized Single-blind Trial	18 years and older with COVID-19 on high oxygen flow therapy or positive pressure ventilation	September 15, 2021 – March 15, 2022 Egypt
Effect of Two Different Doses of Dexamethasone in Patients with ARDS and COVID-19 (REMED) (NCT04663555)	Dexamethasone (20 or 6 mg/day)	Phase II Single-center Randomized Open-label Trial	18 years and older with moderate or severe COVID-19	February 2, 2021 – March 31, 2023 Czech Republic
Higher vs. Lower Doses of Dexamethasone for COVID-19 and Severe	Dexamethasone (12 or 6 mg/day)	Multicenter Randomized	18 years and older COVID-19	August 27, 2020 –

Hypoxia (COVIDSTEROID2) (NCT04509973)		Quadruple-blind Trial	patients with severe hypoxia	November 17, 2021 Denmark India Sweden Switzerland
Randomized Open Investigation Determining Steroid Dose (ROIDS-Dose) (NCT04834375)	Dexamethasone (0.2 mg/kg/day or 6 mg/day)	Single-center Randomized Open-label Trial	18 years and older COVID-19 patients with hypoxemia	March 19, 2021 – April 19, 2022 USA
The Efficacy of Different Hormone Doses in 2019-nCoV Severe Pneumonia (NCT04263402)	Methylprednisolone (< 40 or 40-80 mg/day)	Single-center Randomized Single-blind Trial	18 years and older COVID-19 patients with severe pneumonia	February 1, 2020 – ongoing recruitment China
Efficacy of DEXamethasone in Patients with Acute Hypoxemic REspiratory Failure Caused by INFections (DEXA-REFINE) (NCT04545242)	Dexamethasone (6 mg/day or 20 mg/day x 5 days + 10 mg/day x 5 days)	Phase IV Multicenter Randomized Open-label Trial	18 years and older intubated and mechanically ventilated COVID-19 patients	February 8, 2021 – December 30, 2023 Spain
Timing of Corticosteroids in COVID-19 (NCT04530409)	Early-Dexamethasone Late-Dexamethasone	Phase IV Single-center Randomized Open-label Trial	18 years and older with mild or moderate severity COVID-19	February 10, 2021 – ongoing recruitment Egypt
DEXamethasone EARLY Administration in Hospitalized Patients with Covid-19 Pneumonia (EARLYDEXCoV2) (NCT04836780)	Early-Dexamethasone Late-Dexamethasone	Multicenter Randomized Open-label Trial	18 years and older COVID-19 patients with infiltrates on chest radiography or CT	June 10, 2021 – March 30, 2022 Spain
Evaluation of the Efficacy of High Doses of Methylprednisolone in SARS-CoV2 (COVID-19) Pneumonia Patients (NCT04673162)	Methylprednisolone + Dexamethasone Dexamethasone	Multicenter Randomized Quadruple-blind Trial	18 years and older with COVID-19 on non-invasive oxygen support	December 2020 (not yet recruiting) Italy
Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP)	Hydrocortisone (fixed duration vs. shock-dependent)	Multicenter Randomized Open-label Trial	18 years and older COVID-19 patients admitted to an ICU for severe community	October 12, 2020 – December 2023 USA

(NCT02735707)			acquired pneumonia	Australia Belgium Canada Croatia Germany Hungary Ireland Netherlands New Zealand Portugal Romania Spain UK
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Appendix 6. Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 11)

FACTORS		JUDGEMENT (N = 11)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS			
Problem	No	Yes (11)		Varies		Uncertain					
Benefits	Large (6)	Moderate (5)	Small	Trivial	Varies	Uncertain		<ul style="list-style-type: none"> Dexamethasone significantly decreased all-cause mortality in COVID-19 patients. 			
Harm	Large	Moderate (1)	Small (8)	Trivial (1)	Varies	Uncertain (1)		<ul style="list-style-type: none"> Adverse events are comparable between the intervention and control groups and among the different doses of dexamethasone. 			
Certainty of evidence	High	Moderate		Low (2)		Very low (9)					
Balance of effects	Favors drug (5)	Probably favors drug (6)	Does not favor drug or no drug	Probably favors no drug	Favors no drug	Varies	Uncertain				
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (3)		Probably no important uncertainty or variability (6)		No important uncertainty or variability (1)					
Resources required	Uncertain	Varies	Large costs	Moderate costs (6)	Negligible costs or savings (4)	Moderate savings (1)	Large savings				
Certainty of evidence of resources required	No included studies		Very low (1)	Low (5)	Moderate (5)	High					
Cost-effectiveness	No included studies	Varies	Favors the comparison (2)	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention (2)	Favors the intervention (7)	<ul style="list-style-type: none"> Cost-effectiveness study done in South Africa using local currency converted to US dollars favors the addition of dexamethasone to standard of care. 			
Equity	Uncertain	Varies (1)	Reduced (1)	Probably reduced (2)	Probably no impact (2)	Probably increased (4)	Increased (1)				
Acceptability	Uncertain (5)	Varies	No (1)	Probably no (1)	Probably yes (4)	Yes (1)					
Feasibility	Uncertain (5)	Varies	No	Probably no	Probably yes (3)	Yes (3)					

Additional Comments

- More randomized controlled trials on the use of corticosteroids in children is needed.
- Supply may be limited in far-flung areas but the drug is relatively inexpensive.

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.

Evidence Summary

Key Findings

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 tocilizumab. 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.

Introduction

Some patients with COVID-19 develop a hyperinflammatory syndrome that is characterized by elevations in proinflammatory cytokines and multiorgan dysfunction also known as the immunopathology of SARS-CoV-2 infection. [2,3] Tocilizumab, a monoclonal anti-IL-6-receptor blocking antibody, has been proposed as a therapeutic agent to mitigate hyperinflammation associated with COVID-19. It has been utilized in children with cytokine release syndrome associated with CAR T-cell therapy including systemic and polyarticular juvenile idiopathic arthritis. [2,4]

FDA issued an emergency use authorization (EUA) for tocilizumab for the treatment of hospitalized adults and pediatric patients 2 years of age and older with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). [1,2] This review looks into the effectiveness of tocilizumab in the treatment of children with COVID-19 and MIS-C.

Review Methods

A systematic literature search was performed to identify relevant studies in PubMed, Cochrane Library, WHO trial Registry, ClinicalTrial.gov and Covid-19 NMA databases among others up to January 10, 2022. A preprint search was also done in medRxiv, chinaXiv and bioRxiv. The search strategy combined concepts related to tocilizumab, COVID-19, pediatrics, and children. MeSH and free text search were done using the following terms: Covid 19 (Coronavirus 19, SARS-CoV 2,); tocilizumab (Actemra, IL-6 receptor inhibitor, IL-6 receptor antagonist); Children (Pediatrics); Observational Studies, Meta-Analysis, and Randomized Clinical Trial. References listed in each identified study was manually searched for related articles to identify all eligible studies and minimize any potential publication bias. No language or journal type restriction was applied (Appendix 1). The inclusion criteria for this review were as follows:

Table 1. PICO criteria for tocilizumab and COVID-19.

Population	Children with COVID-19
Intervention/Exposure	Tocilizumab
Comparison	Usual care, standard of care, placebo, any active control
Outcomes	Mortality, need for ventilation or ICU stay, clinical improvement, adverse effects

Results

There were no observational or randomized controlled trial (RCT) retrieved on the effectiveness of tocilizumab for the treatment of acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C). In the absence of adequate data on children with acute COVID-19, outcome and safety data for adult patients were reviewed as indirect evidence. The Adult COVID-19 Living Clinical Practice Guidelines Phase II (Philippines) which was reviewed to be of good quality using AGREE II served as primary reference and was then supplemented with data from the Covid-19 NMA initiative (Appendix 3).

Two (2) new RCTS were added to the existing data from the Adult LCPG Phase II, both of which were evaluated to have low risk of bias using Cochrane ROB 2. Results were pooled and subgroup analyses on the effect of tocilizumab on mortality stratified according to oxygen requirement and co-administration of steroids were done.

Characteristics of Study Population, Interventions, and Comparators

Indirect evidence coming from 17 RCTs among adult patients were multicenter studies [5-21]. All of the trials reviewed were also included in the COVID-NMA Living Data [22]. Four (4) of the 17 trials were preprints [18-21]. Overall, a total of 9,649 patients were included in this meta-analysis, in which 5,319 and 4,330 patients were assigned to the tocilizumab and control groups, respectively. The population, drugs used, and methodology process were comparable in all included studies.

The study participants in all trials were 18 years old and above with clinically suspected or laboratory confirmed SARS-CoV-2 infection, with presence of pulmonary infiltrates,

and with oxygen saturation of <94% on room air. Patients were excluded if the treating physician determined that death was imminent and inevitable within 24 hours or if they had active tuberculosis or a bacterial, fungal, or viral infection other than SARS-CoV-2. Four (4) trials included elevated laboratory markers such as C-reactive protein (CRP), d-dimer and ferritin in their inclusion criteria [10-12,19]. Seven (7) trials excluded patients on mechanical ventilation at the start of the trial [7,9-11,16,18,19], while two (2) trials enrolled critical patients admitted in the intensive care unit who were receiving respiratory or cardiovascular organ support [9,18].

Patients allocated to the intervention group received tocilizumab as a single intravenous infusion over 60 minutes. The dose of tocilizumab was 8mg/kg/dose with a maximum dose of 800mg. A second dose could be given 12–24 hours later if, in the opinion of the attending clinician, the patient's condition had not improved or if fever persists after 24hours from the initial dose. The standard of care was used as comparator, and these were based on local practice and may or may not include the administration of low-dose glucocorticoids, anticoagulants, or anti-viral drugs (e.g., dexamethasone, aspirin, lopinavir/ritonavir, remdesivir, and hydroxychloroquine) on top of other supportive measures (Appendix 3).

Overall Quality of Evidence

The overall quality of evidence was rated very low. The population of all included studies are adults (>18 years old) and only serves as indirect evidence for our pediatric population. Other compounding reasons are the presence of serious risk of bias and imprecision. The included studies had serious risk of bias due to issues on performance bias, detection bias, and reporting bias. Blinding was only present in five out of the 17 included studies [7,11,17,19,21]. Moreover, there were noted differences in the administration of steroids, antivirals, and other supplementary medications used in the control group for some of the included studies (Appendix 2).

Efficacy Outcomes

Mortality Outcomes

Based on the pooled results of the 16 out of the 17 RCTs included, tocilizumab significantly reduced all-cause mortality at day 14 to day 90 follow-up compared to standard of care among adults ($RR = 0.88$, 95% CI 0.82-0.94; Low Certainty). Tocilizumab significantly reduced all-cause mortality at day 28 ($RR 0.87$, 95% CI 0.81-0.94; Low Certainty) but had no significant effect on mortality at day 90 ($RR 0.89$, 95% CI 0.76-1.02; Very Low Certainty). All results had low heterogeneity and low certainty of evidence except for 90-day mortality which has a very low certainty of evidence.

Subgroup analysis of mortality outcome according to oxygen requirement type did not show significant benefit across groups. These included those requiring oxygen supplementation ($RR 0.88$, 95% CI 0.75-1.04; Low Certainty); those requiring non-invasive ventilation ($RR 0.89$, 95% CI 0.79-1.00; Low Certainty); and those requiring invasive mechanical ventilation ($RR 0.97$, 95% CI 0.82-1.15; Very Low Certainty).

Subgroup analysis (n=6 studies) by co-administration of steroids demonstrated significant reduction in mortality (RR 0.80, 95% CI 0.66-0.97; Low Certainty). There was no observed benefit among patients who were not given steroids (RR 1.09, 95% CI 0.91-1.29).

Clinical Improvement

Pooled results (n=8 studies) showed no significant difference both in clinical improvement at day 28 (RR 1.06, 95% CI 0.99-1.12; Low Certainty) and in the time to clinical improvement (HR 1.11, 95% CI 0.99-1.25) among adult patients given tocilizumab compared to those who received standard of care. Clinical improvement was evaluated by the patients' clinical, general, and laboratory conditions and were determined by good consciousness, ameliorated dyspnea, stopped fever for 3 days, O₂ saturation greater than 93%, normal range of urinary output, tolerated oral regimen (PO), blood pressure more than 10 millimeters of mercury (mmHg), respiratory rate and heart rate within normal limits and reduced CRP amount.

Need for Mechanical Ventilation

Pooled results of nine studies showed significant reduction in the need for mechanical ventilation among adult patients given tocilizumab compared to standard of care (RR 0.78, 95% CI 0.68-0.89; Low Certainty).

Length of ICU Stay and Hospital Stay

There was no observed difference in the length of ICU stay (n=3) (MD -1.94 days, 95% CI -6.8 to 2.91; Very Low Certainty) and hospital stay (n=2) (MD -2.5 days, 95% CI -6.8 to 1.80; Very Low Certainty) in those given tocilizumab compared to that of standard of care.

Time to Negative Conversion

Wang et.al presented data regarding time to negative conversion which showed no significant difference between those given tocilizumab and those who only received standard of care with a median of 17 days (IQR: 12-20 days) and 16 days (IQR: 12-21.5 days) respectively [12]. This is similar with the results in the study done by Rosas 2021 (REMDACTA Trial) which showed an equivocal result [17].

Cure Rate

Cure followed the definition by the "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (5th or updated version)": (1) fever attenuated continuously for 7 days, (2) twice negative SARS-CoV-2 nucleic acid detections, (3) CT scan demonstrating chest effusion improved more than 50% when the patient is discharged from the hospital [12]. The study by Wang et.al. (2020) showed that the cure rate of the tocilizumab group tended to be higher than that of the control group (94.12% vs. 87.10%), but the difference between the two groups was not statistically significant [RD 0.07 (95% CI 7.19% to -21.23%)] [12]. This is similar with the findings of Talaschian et.al [19].

Safety Outcomes

Adverse Events and Serious Adverse Events

Tocilizumab did not significantly increase the risk for adverse events (RR 1.03 95% CI 0.97-1.11; Very Low Certainty) and serious adverse events among adult patients (RR 0.92, 95% CI 0.77-1.08; Very Low Certainty). Common adverse events noted with tocilizumab were neutropenia, leukopenia, anxiety, arrhythmia, insomnia, stroke, and constipation. Serious adverse events observed were pneumothorax, intracranial bleeding, and pulmonary embolism among others.

Other Considerations (Evidence to Decision)

Tocilizumab, a recombinant humanized anti-IL-6 receptor monoclonal antibody that inhibits the binding of IL-6 to both membrane and soluble IL-6 receptors, is being used as compassionate drug in the Philippines for various cancers and arthritis. Administration of this drug is through intravenous infusion for one dose with a maximum of two doses. The Presidential Executive Order 104 regulates the price of tocilizumab 200mg/10 ml, 10ml vial to P10,392.98 for wholesale price and P28,830.82 for retail price. Tocilizumab 400mg/20ml, 20ml vial is regulated at P20,581.45 for wholesale price and P28,830.84 for retail price. [23] Assuming the maximum dose of 800mg, the total drug regimen cost per patient per treatment course would be P57,661.68 (retail price) or a little lower in price in children since the recommended dosage are as follows: <30kg: 12mg/kg/dose and for > or = 30kgs: 8mg/kg/dose.

There are currently no local feasibility studies for this drug and no studies assessing patients' values or acceptability of the drug

Recommendations from Other Groups

As of November 2021, US-NIH states that there are no pediatric data from placebo-controlled randomized clinical trials and limited data from observational studies to inform the development of pediatric-specific recommendations for the treatment of COVID-19 in children. Hence, there is insufficient evidence for the Panel to recommend either for or against the use of tocilizumab for hospitalized children with COVID-19 or MIS-C. If used, tocilizumab should be used in combination with dexamethasone. This is based on outcome and safety data for adult patients and the child's risk of disease progression [1].

The CPG Australian Guidelines for the Clinical Care of Patients with Covid-19 (2021) suggest to consider using tocilizumab for the treatment of COVID-19 in children and adolescents who require supplemental oxygen, particularly where there is evidence of systemic inflammation. (Conditional Recommendation) [24].

For local recommendation, the Pediatric Infectious Disease Society of the Philippines released a guide as of January 2022 wherein they suggest the use of tocilizumab plus systemic steroids in patients showing rapid respiratory deterioration and/or requiring high doses of oxygen associated with elevated markers of inflammation [25].

Research Gaps

As of February 2, 2022, there is one ongoing trial specific on the effect of tocilizumab on the pediatric population and is currently in the process of recruitment with an estimated completion date on January 2023.

The data specific for the use of tocilizumab in children with Covid-19 are limited, derived mainly from clinical experiential accounts. A randomized clinical trial, if possible, is needed to further assess and evaluate optimal components of care in this particular patient population. Though their condition is similar to adult patients with Covid-19, the differences in other processes might affect the final outcome when studied strictly among the pediatric population.

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Evidence Summary Appendices

Appendix 1. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	("tocilizumab" [Supplementary Concept] OR "tocilizumab" [All Fields]) AND ("covid 19"[All Fields] OR "covid 19" [MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy" [Supplementary Concept] OR "covid 19 nucleic acid testing" [All Fields] OR "covid 19 nucleic acid testing" [MeSH Terms] OR "covid 19 serological testing" [All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2" [All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov" [All Fields] OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields])) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("child" [MeSH Terms] OR "child" [All Fields] OR "children"[All Fields] OR "child s" [All Fields] OR "children s"[All Fields] OR "childrens" [All Fields] OR "childs"[All Fields])	01/02/22 10:03AM	19	15
CENTRAL	tocilizumab: "tocilizumab"[Supplementary Concept] OR "tocilizumab" [All Fields] covid 19: ("COVID-19" OR "COVID-19" [MeSH Terms] OR "COVID-19 Vaccines" OR "COVID-19 Vaccines" [MeSH Terms] OR "COVID-19 serotherapy" OR "COVID-19 serotherapy" [Supplementary Concept] OR "COVID-19 Nucleic Acid Testing" OR "covid-19 nucleic acid testing" [MeSH Terms] OR "COVID-19 Serological Testing" OR "covid-19 serological testing" [MeSH Terms] OR "COVID-19 Testing" OR "covid-19 testing"[MeSH Terms] OR "SARS-CoV-2" OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR ("coronavirus"[MeSH Terms] OR "coronavirus" OR "COV") AND 2019/11/01[PDAT] : 3000/12/31[PDAT])) children: "child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child's"[All Fields] OR "children's"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]	01/02/22 2:13PM	24	12
COVID-NMA Initiative	Tocilizumab	01/02/22 6:30PM	17	17
Google Scholar	Tocilizumab AND COVID AND randomized trial AND Children	01/02/22 12:18PM	13	10
ClinicalTrials.gov	COVID-19, Investigational Trials, Tocilizumab With or without Children or Pediatrics *For ongoing studies	01/01/22 7:30PM	96	2
Chinese Clinical Trial Registry	COVID Tocilizumab	01/01/22 8:00AM	3	0
EU Clinical Trials Register	COVID Tocilizumab	01/01/22 10:32AM	6	4
Japan Primary Registries Network/	COVID Tocilizumab	01/01/22 2:30PM	0	0

NIPH Clinical Trials Search				
chinaxiv.org	COVID Tocilizumab	01/01/22 9:45AM	1	0
Medrxiv.org	COVID Tocilizumab	01/01/22 11:50AM	5	5
Biorxiv.org	COVID Tocilizumab	01/01/22 12:42PM	0	0

Appendix 2. Characteristics of Included Studies

Title/Author	Study design	Country	Population	Intervention Group(s)	Control	Outcomes
Horby 2021 RECOVERY N=4116	Open label RCT	Multicenter; United Kingdom	Adult patients >18 years old with suspected or confirmed Covid.	Tocilizumab 8mg/kg	Standard of care	-All-cause mortality at day 28 -Time to discharge -Receipt of invasive mechanical ventilation -Use of non-invasive respiratory support -Time to successful cessation of invasive mechanical ventilation -Use of renal dialysis/hemofiltration -Major cardiac arrhythmia -Serious adverse events
Gordon 2020 REMAP-CAP N=755	Adaptive RCT	Multicenter; United Kingdom, France, the Netherlands, Australia	ICU admitted critical Covid-19 patients AND receiving respiratory or cardiovascular organ support	Group 1: Tocilizumab 8 mg/kg Group 2: Sarilumab	Standard of care	-Respiratory and cardiovascular organ support-free days -Survival -Time to ICU discharge -Time to hospital discharge -WHO scale at day 14 -Progression to invasive mechanical ventilation, ECMO or death -Serious adverse events
Hermine 2020 N= 131	Open label RCT	Multicenter; France	Moderate, severe or critical Covid-19 patients with O2 levels of 3 L/min or higher but without noninvasive ventilation (NIV) or mechanical ventilation (MV).	Tocilizumab 8 mg/kg	Standard of care	-Mortality on day 4 and day 14 -Mechanical ventilation on day 4 and day 14 -Clinical status (WHO CPS) at day 7 and day 14 -Overall survival -Time to discharge -Time to oxygen supply independency -C-reactive protein levels -Adverse events
Rosas 2020 COVACTA N=452	Double-blind, placebo controlled RCT	Canada, Denmark, France, Germany, Italy, Netherland, Spain, UK, USA	Severe Covid-19 patients	Tocilizumab 8mg/kg	Placebo	-Clinical status at day 28 -Mortality -Ventilator free days -Time to improvement -Time to hospital discharge -Adverse events

Salama 2020 N=388	Double-blind, placebo controlled RCT	USA, Mexico, Kenya, South Africa, Peru, Brazil	Hospitalized Covid-19 pneumonia patients not on continuous positive airway pressure, bilevel positive airway pressure, or mechanical ventilation.	Tocilizumab 8mg/kg	Placebo	-Invasive mechanical ventilation or ECMO -Mortality -Time to hospital discharge or readiness for discharge -Time to at least a two-category improvement in clinical status -Time to clinical failure
Salvarani 2020 N=126	Open-label RCT	Italy	Non-ICU Covid-19 patients.	Tocilizumab 8mg/kg	Standard of care	-Clinical worsening at day 14 -Admission to ICU with mechanical ventilation -Death from any cause -PaO ₂ /FIO ₂ ratio less than 150 mm Hg
Stone 2020 N=243	Double-blind, placebo controlled RCT	USA	Confirmed Covid-19 patients not on O ₂ above 10 L/minute	Tocilizumab 8mg/kg	Placebo	-Mortality -Mechanical ventilation -Clinical worsening -Time to improvement -Time to death -Duration of supplemental O ₂ -Admission to ICU
Wang 2020 N=65	Open-label RCT	China	Moderate or severe Covid-19 patients with elevated IL-6.	Tocilizumab	Standard of care	-Cure rate -Recovery rate of hypoxia over 14 days, -Worsening rate of hypoxia during hospitalization, -Duration of hospital stay, -Time to negative virus load.
Veiga 2021 N=129	Open-label RCT	Brazil	Severe or critical Covid-19 patients	Tocilizumab 8mg/kg	Standard of care	-Clinical status at Day 15 -All cause mortality -In-hospital mortality -Sequential organ failure assessment score -Clinical status at day 8 and day 29 -Ventilator-free days within 29 days -Time to independence from supplemental oxygen -Duration of hospital stay

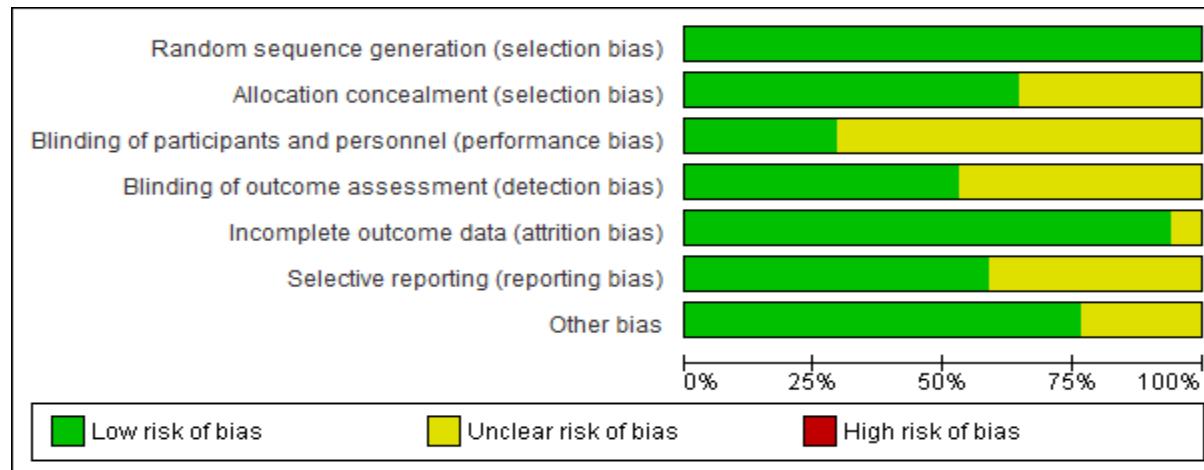
Soin 2021 (COVINTOC) N= 183	Open-label RCT	India	Moderate to severe Covid-19 patients Moderate – RR 15-30 AND SpO2 90-94% Severe- RR>30 OR SpO2 <90% OR ARDS OR septic shock	Tocilizumab 6 mg/ kg	Standard of care	-Clinical progression -Mortality -Clinical improvement -Time to clinical improvement -Ventilator free days -Organ failure-free days -ICU admission -Time to hospital discharge -Time to negative result on RT-PCR -Adverse events -Serious adverse events
Rutgers* 2021 N= 354	Open label RCT	The Netherlands	Hospitalized COVID 19 patients with the following conditions: Need for supplemental Oxygen Ferritin >2000 ug/l or doubling serum ferritin in 20-48 hours	Tocilizumab 8 mg/kg	Standard of care	-30-day mortality -Duration of hospital stay -ICU admission -Duration of ICU stay -Duration of mechanical ventilation -Time to mechanical ventilation -Time to death
Talaschian 2021 N= 40	Double blind RCT	Iran	COVID-19 patients with the following conditions: Elevated CRP (>10 mg/L)/ IL 6 (> 18 pg/ml) / Lymphopenia (WBC< 1100/MCL) O2 sat <93% or RR >24 Not connected to mechanical ventilator Not responding to standard COVID-19 treatment	Tocilizumab 8 mg/kg	Standard of care	-Clinical improvement -28-day mortality -Time to improvement

Derde 2021 N=2274	Open label, Adaptive RCT	US, Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, UK	ICU admitted critical Covid-19 patient AND receiving respiratory or cardiovascular organ support	Group 1: Tocilizumab 8 mg/kg Group 2: Sarilumab Group 3: Anakinra Group 4: Interferon B1a	Standard of care	-Respiratory and cardiovascular organ support-free days -Survival -In-hospital mortality 90 days -Time to ICU discharge -Time to hospital discharge
Hamed 2021 N=76	Open label RCT	Dubai	Hospitalized covid 19 patient AND Lung infiltrates >50% of lung fields within 48 hrs admission, O ₂ saturation <93% at rest on room air	Group 1: Methylprednisolone Group 2: Methylprednisolone and Tocilizumab	Historical control group	-All-cause mortality day 45 -Admission to ICU -Length of ICU stay -Invasive ventilation -Days on ventilation -Length of hospital stay
Hermine 2021 (CORIMUNO- TOCI-DEX) N= 453	Open label RCT	France	Moderate to severe COVID-19 requiring oxygen but without ventilation support, high flow or mech vent, WHO class 5	Tocilizumab 8mg/kg at Day 1 PLUS Dexamethasone 10mg/d for 5 days and tapering up to 10 days	Dexameth asone 10mg/d for 5 days and tapering up to 10 days	-Survival without mechanical ventilation at day 14 -WHO-CPS progression -Time to oxygen supply independency -Time to hospital discharge adverse events
Rosas 2021 (REMDECTA) N=649	Double blind RCT	Multicenter:Ca nada, Denmark, France, Germany, Italy, Netherlands, Spain, UK, USA	included patients hospitalized with severe COVID-19 pneumonia requiring>6 L/min supplemental oxygen.	Tocilizumab 8 mg/kg + Remdesivir	Standard of care with Remdesev ir only	-Time from randomization to hospital discharge or "ready for discharge" to day 28.

Declerq 2021 (COV-AID) N=153	Open label RCT	Multicenter: Belgium	-Older than 18 years -Laboratory proven diagnosis of COVID-19 with symptoms between 6 and 16 days -Ratio of the partial pressure of oxygen (PaO ₂) to the fraction of inspired oxygen (FiO ₂ ; P:F ratio) of less than 350 mm Hg on room air or less than 280 mm Hg on supplemental oxygen and bilateral pulmonary infiltrates.	Tocilizumab 8 mg/kg	Standard of care	-Time to clinical improvement
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Appendix 3. Risk of Bias Summary

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Declerq 2021	+	+	+	+	+	+	+
Derde 2021	+	+	?	?	+	?	?
Gordon 2021	+	+	?	?	+	+	?
Hamed 2021	+	?	?	+	+	?	+
Hermine 2020	+	+	?	?	+	+	?
Hermine 2021	+	?	?	?	+	?	+
Horby 2021	+	+	?	?	+	+	+
Rosas 2020	+	+	+	+	+	+	+
Rosas 2021	+	?	?	+	+	?	?
Rutgers 2021	+	?	?	+	+	?	+
Salama 2020	+	+	+	+	+	+	+
Salvarani 2020	+	+	?	+	+	?	+
Soin 2021	+	+	?	?	+	+	+
Stone 2020	+	+	+	+	+	+	+
Talaschian 2021	+	?	+	+	?	?	?
Veiga 2021	+	+	?	?	+	+	+
Wang 2020	+	?	?	?	+	+	+



Appendix 4: GRADE Evidence Profile

Author(s): Jofermarie O. Pineda, MD; María Teresa S. Tolosa, MD, FPDS, DipCE; Ma. Lucila M. Perez, MD, MSc, FPPS

Question: Tocilizumab compared to Standard of Care for Children with Covid-19

Setting: Hospital

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Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tocilizumab	Standard of Care	Relative (95% CI)	Absolute (95% CI)		
All Cause Mortality (follow-up range 14 days to 90 days)												
16	randomised trials N=9,584	serious ^a	not serious	serious ^b	not serious	none	1321/5286 (25.0%)	1228/4298 (28.6%)	RR 0.88 (0.82 to 0.94)	34 fewer per 1,000 (from 51 fewer to 17 fewer)	⊕⊕○○ Low	CRITICAL
Mortality Outcome on Day 28												
13	randomised trials N=8,027	serious ^a	not serious	serious ^b	not serious	none	992/4236 (23.4%)	1064/3791 (28.1%)	RR 0.87 (0.81 to 0.94)	36 fewer per 1,000 (from 53 fewer to 17 fewer)	⊕⊕○○ Low	CRITICAL
Mortality Outcome on Day 90												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tocilizumab	Standard of Care	Relative (95% CI)	Absolute (95% CI)		
6	randomised trials N=2,526	serious ^a	not serious	serious ^b	serious ^d	none	383/1597 (24.0%)	214/929 (23.0%)	RR 0.89 (0.78 to 1.03)	25 fewer per 1,000 (from 51 fewer to 7 more)	⊕○○○ Very low	CRITICAL
Clinical Improvement at Day 28												
8	randomised trials N=5,625	serious ^a	not serious	serious ^b	not serious	none	1778/2952 (60.2%)	1434/2673 (53.6%)	RR 1.06 (0.99 to 1.12)	32 more per 1,000 (from 5 fewer to 64 more)	⊕⊕○○ Low	CRITICAL
Need for Mechanical Ventilation												
9	randomised trials N=5,365	serious ^a	not serious	serious ^b	not serious	none	342/2741 (12.5%)	408/2624 (15.5%)	RR 0.78 (0.68 to 0.89)	34 fewer per 1,000 (from 50 fewer to 17 fewer)	⊕⊕○○ Low	CRITICAL
Length of Hospital Stay												
2	randomised trials N=182	serious ^a	not serious	serious ^b	serious ^c	none	91	91	-	MD 1.94 lower (6.8 lower to 2.91 higher)	⊕○○○ Very low	CRITICAL
Length of ICU Stay												
3	randomised trials N=670	serious ^a	not serious	serious ^b	serious ^c	none	411	259	-	MD 2.5 lower (6.8 lower to 1.8 higher)	⊕○○○ Very low	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tocilizumab	Standard of Care	Relative (95% CI)	Absolute (95% CI)		
Adverse Events												
9	randomised trials N=2,323	serious ^a	not serious	serious ^b	serious ^c	none	844/1447 (58.3%)	439/876 (50.1%)	RR 1.03 (0.97 to 1.11)	15 more per 1,000 (from 15 fewer to 55 more)	⊕○○○ Very low	CRITICAL
Serious Adverse Event												
10	randomised trials N=2,532	serious ^a	not serious	serious ^b	serious ^c	none	241/1419 (17.0%)	164/1113 (14.7%)	RR 0.92 (0.77 to 1.08)	12 fewer per 1,000 (from 34 fewer to 12 more)	⊕○○○ Very low	CRITICAL
Mortality Outcome when co-administered with steroids												
6	randomised trials N=4,407	serious ^a	not serious	serious ^b	not serious	none	534/2230 (23.9%)	664/2177 (30.5%)	RR 0.80 (0.66 to 0.97)	61 fewer per 1,000 (from 104 fewer to 9 fewer)	⊕⊕○○ Low	CRITICAL
Pooled effect of tocilizumab on mortality according to oxygen: Requiring Oxygen Supplementation												
8	randomised trials N=3,381	serious ^a	not serious	serious ^b	not serious	none	245/1807 (13.6%)	256/1574 (16.3%)	RR 0.88 (0.75 to 1.04)	20 fewer per 1,000 (from 41 fewer to 7 more)	⊕⊕○○ Low	CRITICAL
Pooled effect of tocilizumab on mortality according to oxygen: Requiring Non invasive Mechanical Ventilation												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tocilizumab	Standard of Care	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials N=1,819	serious ^a	not serious	serious ^b	not serious	none	309/913 (33.8%)	358/906 (39.5%)	RR 0.89 (0.79 to 1.00)	43 fewer per 1,000 (from 83 fewer to 0 fewer)	⊕⊕○○ Low	CRITICAL
Pooled effect of tocilizumab on mortality according to oxygen: Requiring Invasive Mechanical Ventilation												
2	randomised trials N=730	serious ^a	not serious	serious ^b	serious ^c	none	145/381 (38.1%)	151/349 (43.3%)	RR 0.97 (0.82 to 1.15)	13 fewer per 1,000 (from 78 fewer to 65 more)	⊕○○○ Very low	CRITICAL

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

- a. Some concerns with regards to the imbalance in the administration of antivirals and steroids as well as other supplemental medications. Other than this, some of the included studies have moderate risk of bias upon appraisal.
- b. The population in all of the studies are adults.
- c. Wide confidence interval with possibility for benefit and harm
- d. Crosses 1

Appendix 5: Forest Plots

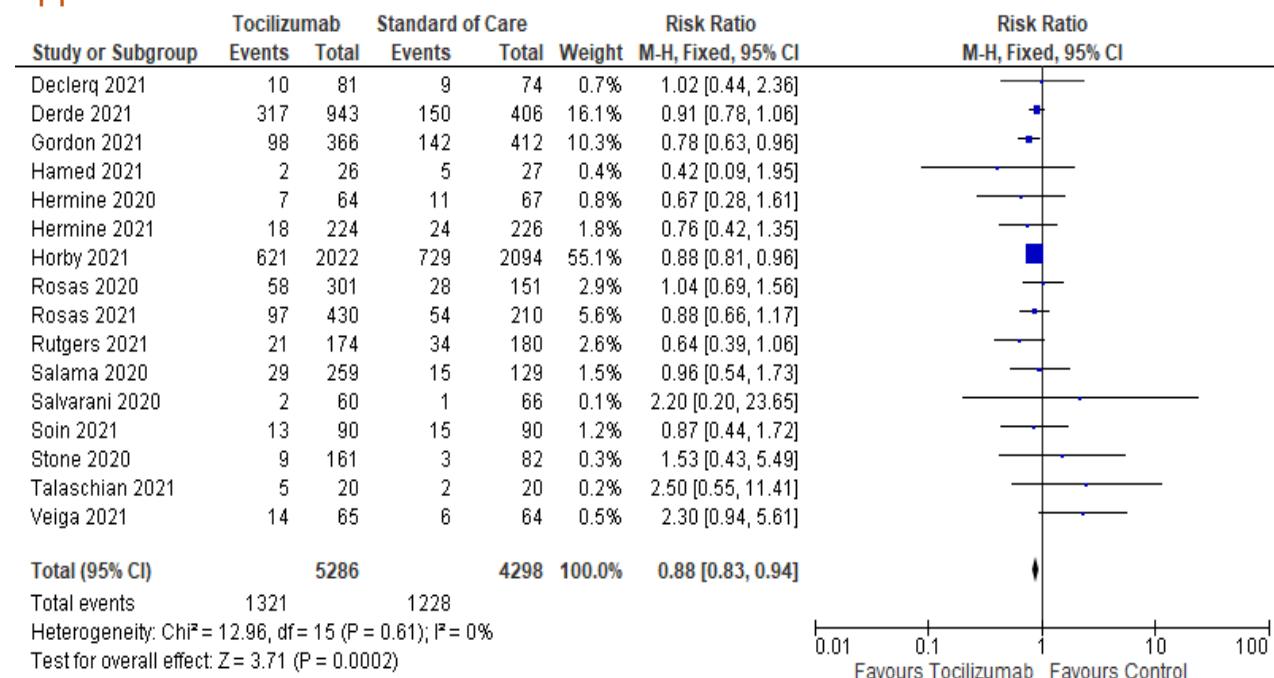


Figure 1. Pooled effect of Tocilizumab on all-cause mortality (d14 to d90)

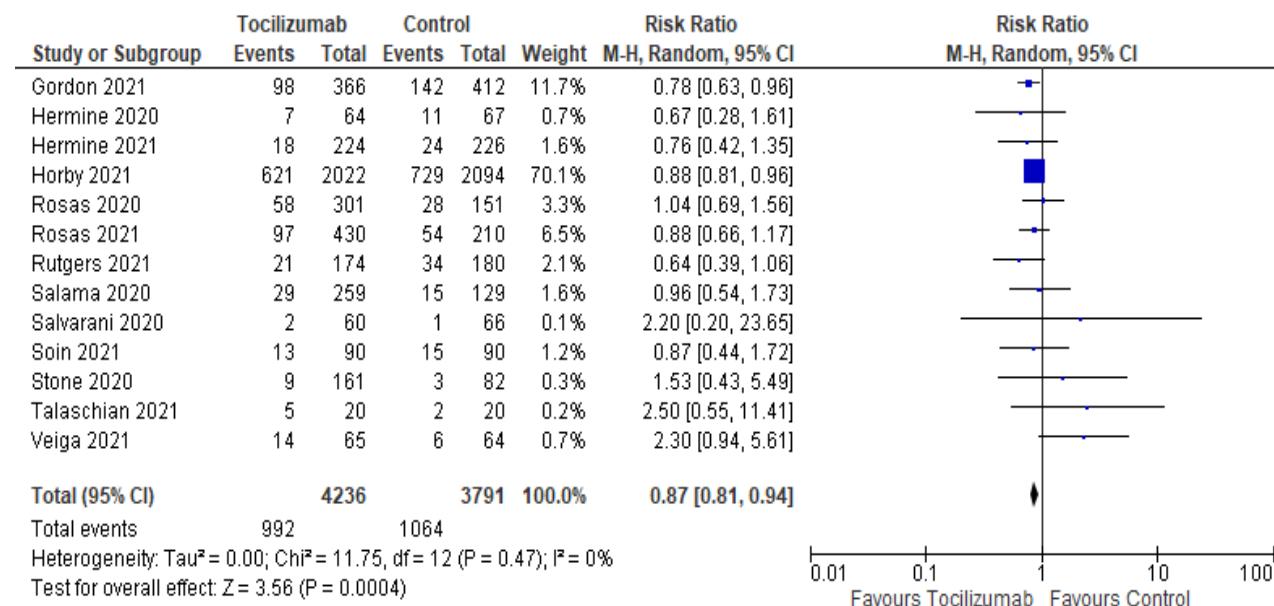


Figure 2. Mortality at 28 days

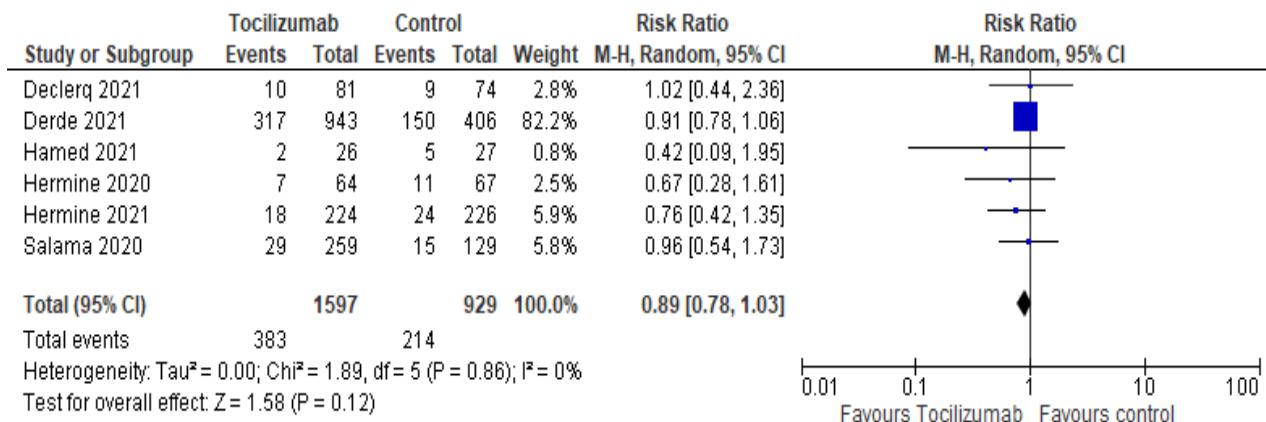


Figure 3. Mortality at 90days

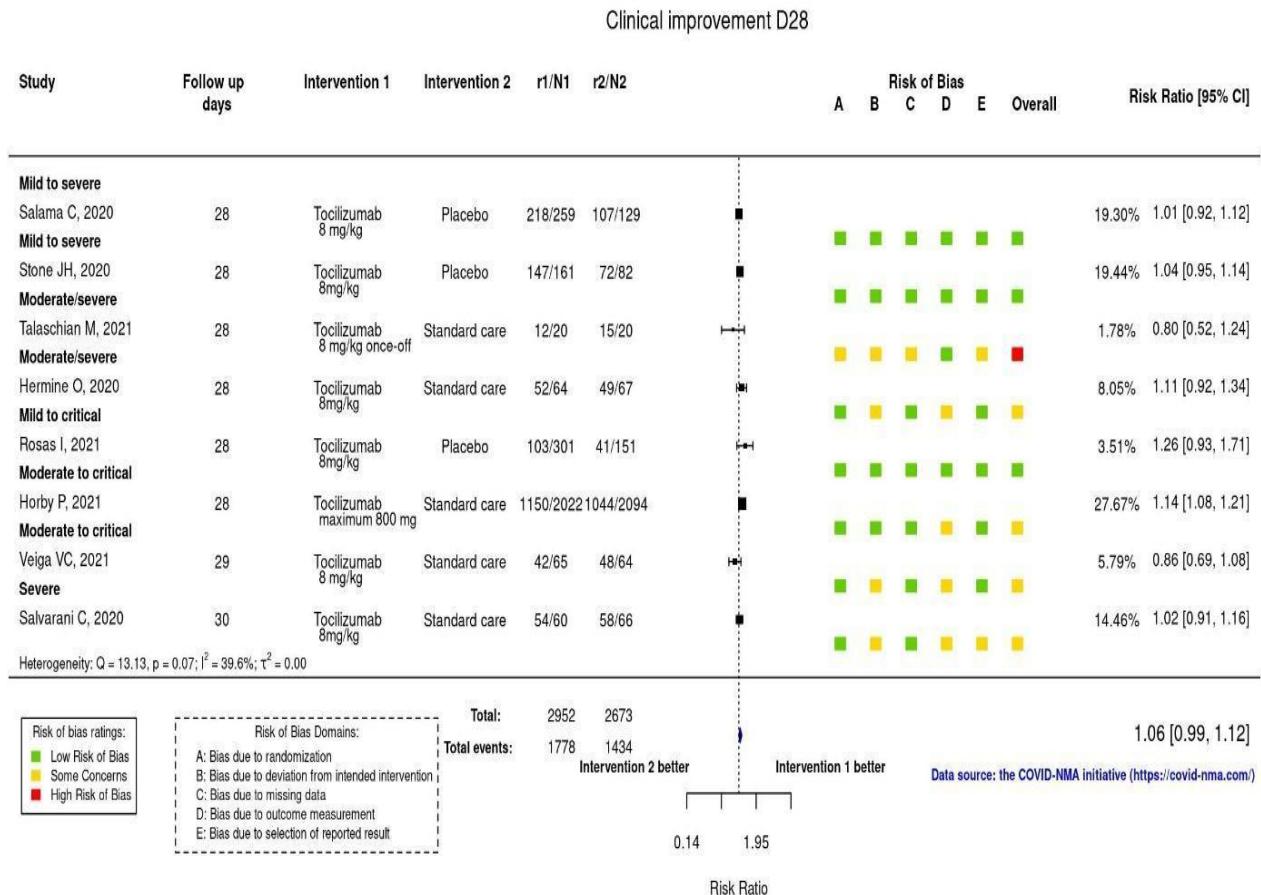


Figure 4. Clinical Improvement at 28days. Source: covid-nma.com

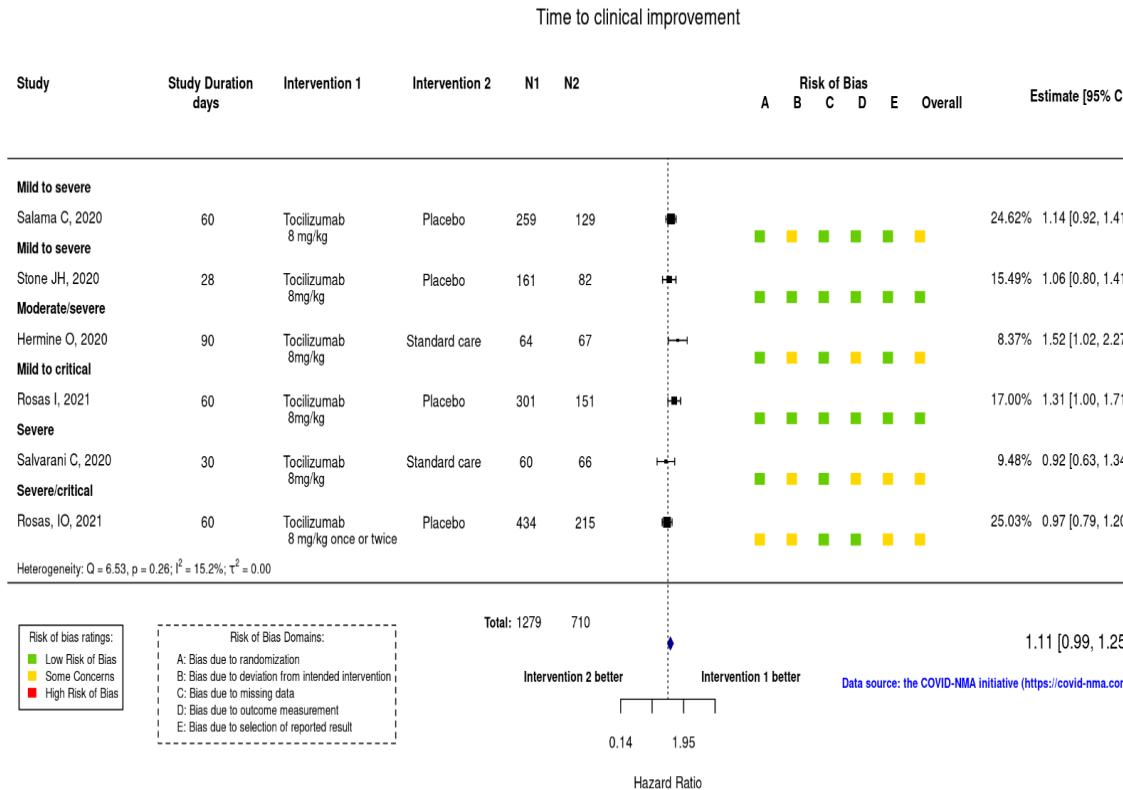


Figure 5. Effect of tocilizumab on time to clinical improvement (Hazard ratio). Source: covid-nma.com

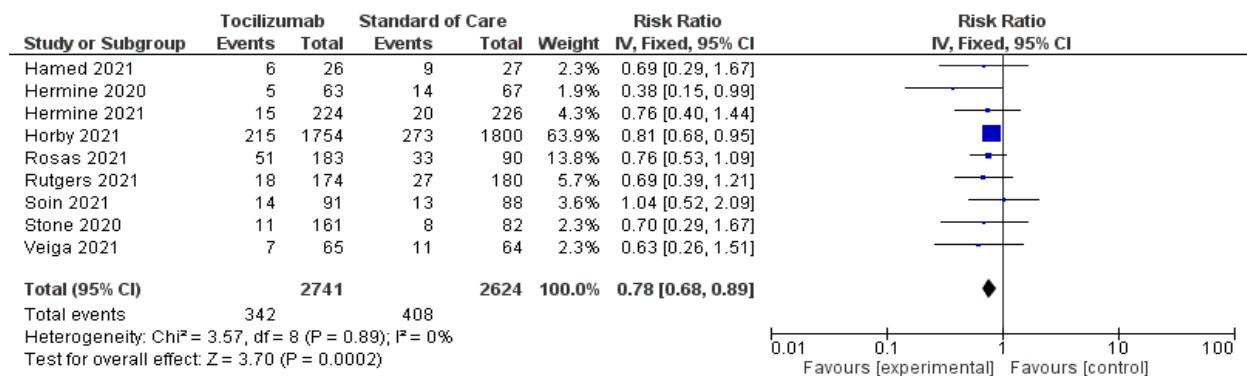


Figure 6. Pooled effect of tocilizumab on initiation of mechanical ventilation

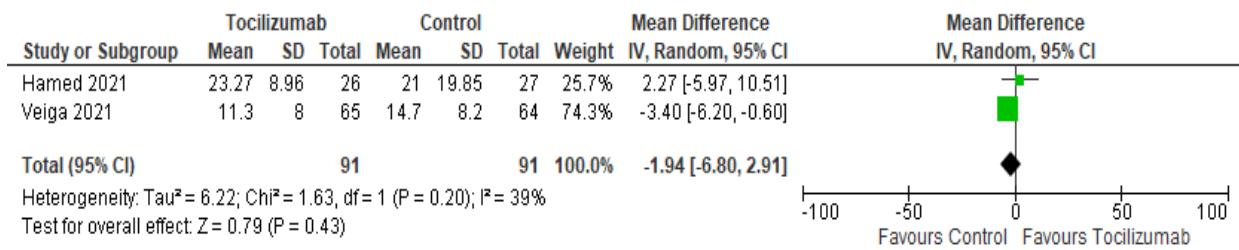


Figure 7. Length of Hospital Stay

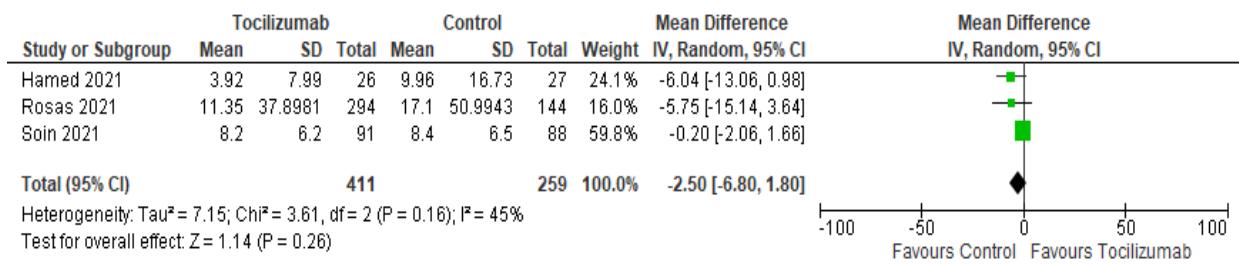


Figure 8. Length of ICU Stay

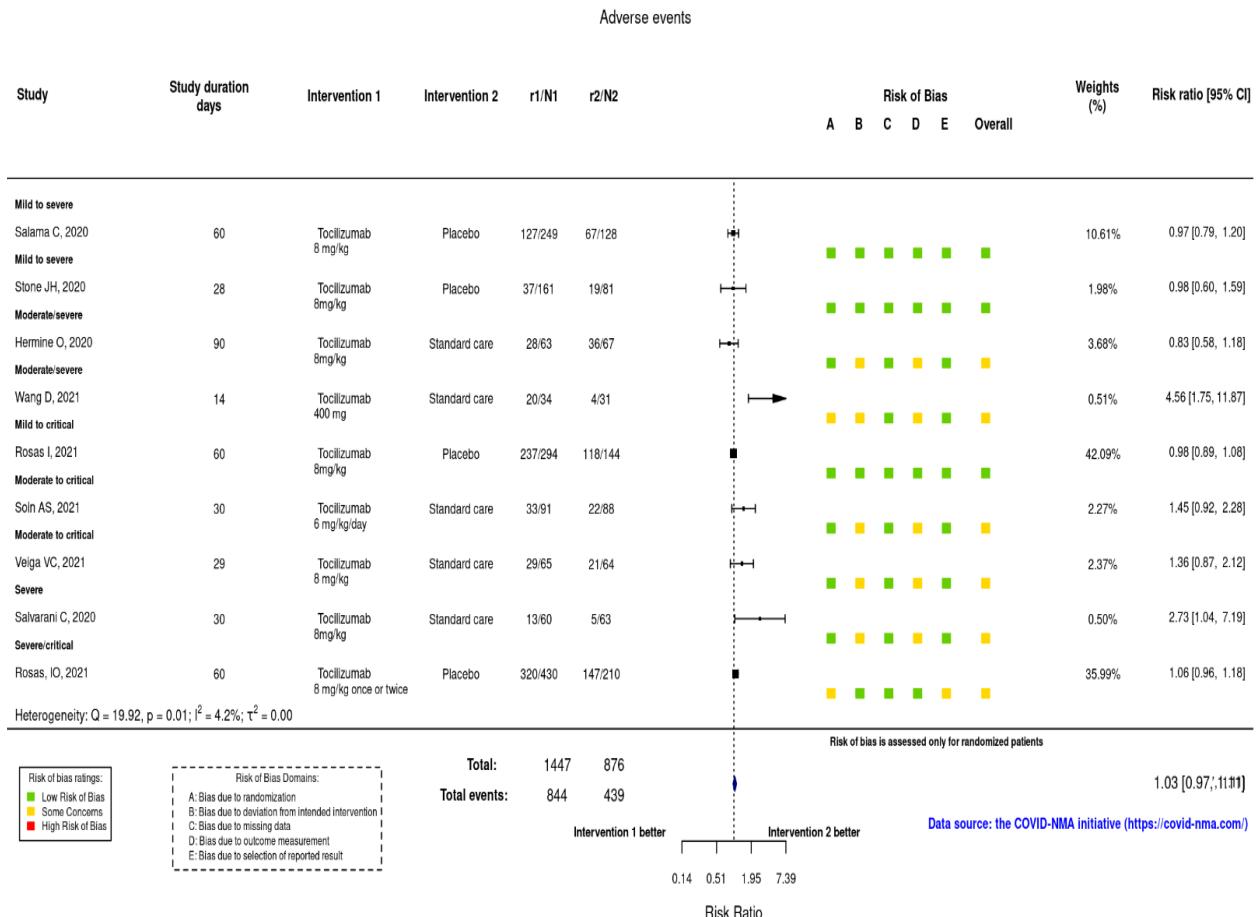


Figure 9. Pooled effect of tocilizumab on the incidence adverse event. Source: covid-nma.com

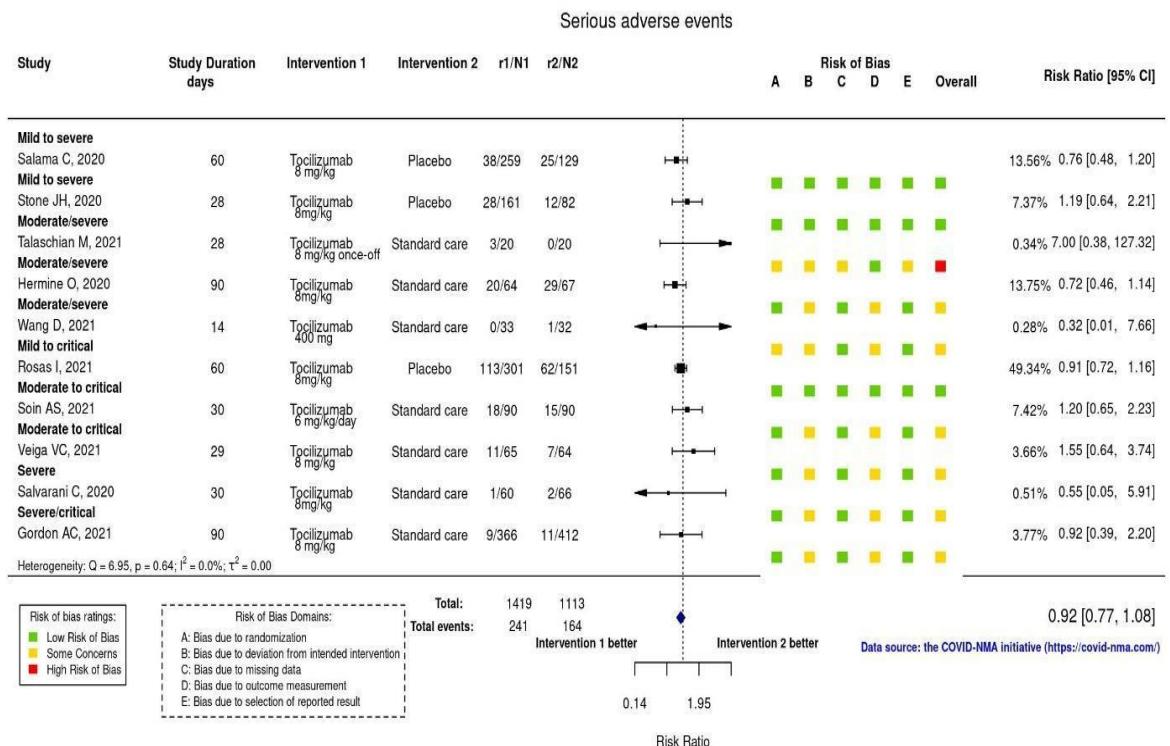


Figure 10. Pooled effect of tocilizumab on the incidence of serious adverse events. Source: covid-nma.com

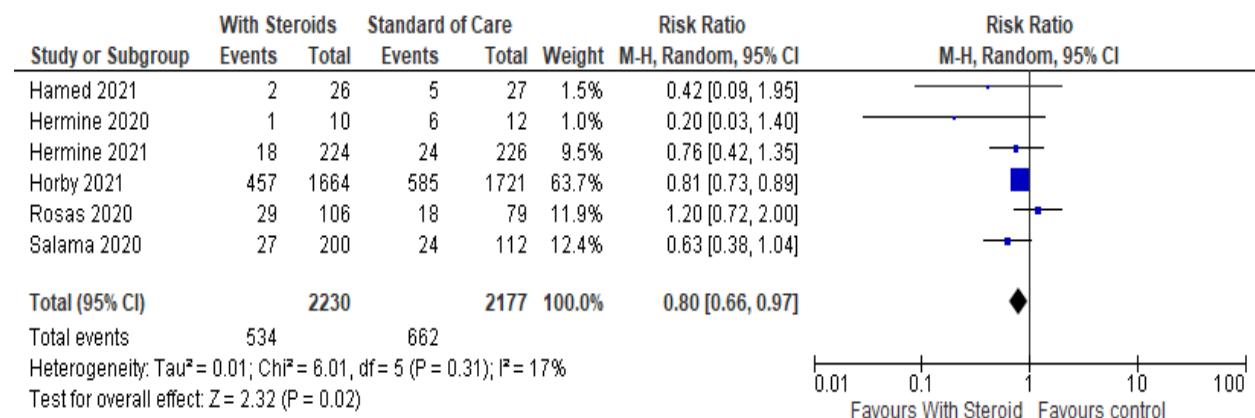


Figure 11. Pooled effect of tocilizumab on mortality with co-administration of steroids

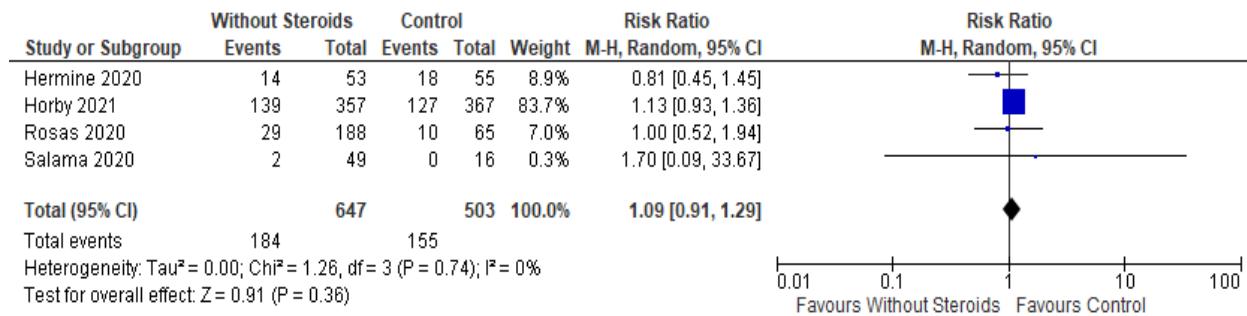


Figure 12. Pooled effect of tocilizumab on mortality without co-administration of steroids

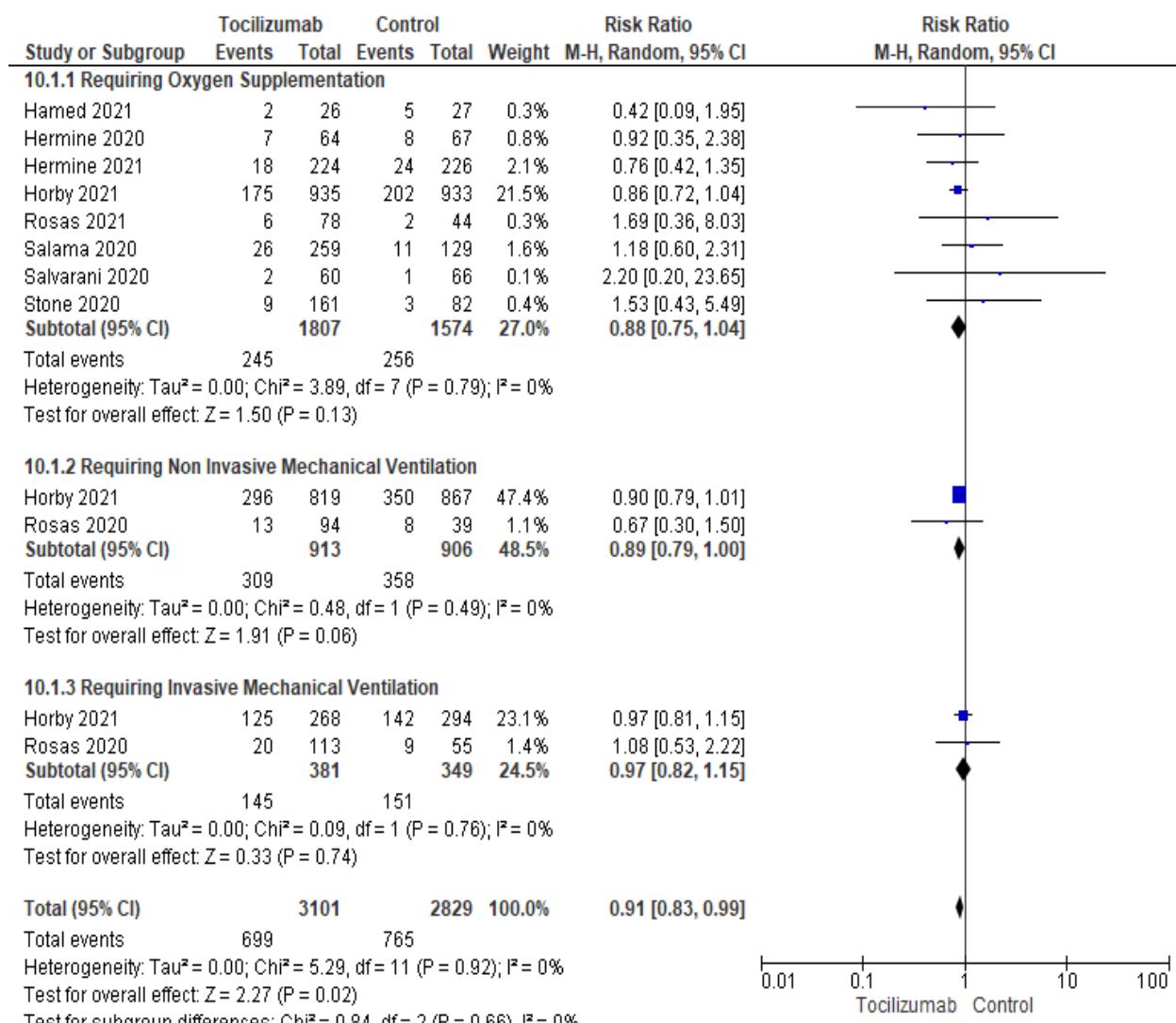


Figure 13. Pooled effect of tocilizumab on mortality according to oxygen requirement

Appendix 6: Characteristics of Ongoing Studies

Title/Identifier Expected Completion Date	Study Desig	Interventions	Patients/Population Recruited	Outcomes
<p>NCT05164133</p> <p>A Study Evaluating Tocilizumab in Pediatric Patients with Covid 19</p> <p>Recruiting</p> <p>Study Start: January 15, 2022</p> <p>Completion date: January 2, 2023</p>	<ul style="list-style-type: none"> Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment 	<p>Intervention: Tocilizumab</p> <p>Control: Standard of Care</p>	<p>-Up to 17 years old</p> <p>-With COVID-19 disease</p>	<ul style="list-style-type: none"> Serum concentration of TCZ Maximum serum concentration (C max) of TCZ Area under the curve from Days 0-28 (AUC days 0-28) of TCZ Serum concentration on Day 28 (C day 28) of TCZ Clearance (CL) of TCZ Volume of distribution of TCZ Duration of 90% saturation of sIL-6R Concentration of IL-6 Concentration of sIL-6R Concentration of C-reactive protein Percentage of participants with adverse events Percentage of participants with severe adverse events

Appendix 7: Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 11)

FACTORS		JUDGEMENT (N = 11)					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS	
Problem	No	Yes (11)		Varies		Uncertain		
Benefits	Large (1)	Moderate (10)	Small (1)	Trivial	Varies (1)	Uncertain		• Reduces all-cause mortality
Harm	Large	Moderate	Small (9)	Trivial (2)	Varies	Uncertain		• No significant difference in adverse events and serious adverse events between intervention and control groups
Certainty of evidence	High	Moderate		Low (1)		Very low (10)		• Rated very low due to serious risk of bias, indirectness and imprecision
Balance of effects	Favors drug (3)	Probably favors drug (8)	Does not favor drug or no drug	Probably favors no drug	Favors no drug	Varies	Uncertain	
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (5)		Probably no important uncertainty or variability (5)		No important uncertainty or variability		
Resources required	Uncertain	Varies	Large costs (11)	Moderate costs	Negligible costs or savings	Moderate savings	Large savings	• Php 28,830.84 per patient for retail price of 400mg/20mL vial
Certainty of evidence of resources required	No included studies (2)		Very low	Low	Moderate (8)	High (1)		
Cost-effectiveness	No included studies (1)	Varies	Favors the comparison (1)	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention (6)	Favors the intervention (3)	• Tocilizumab in combination with dexamethasone in adults was shown to be cost-effective in reducing COVID-related deaths in the severely ill.
Equity	Uncertain (4)	Varies (1)	Reduced (2)	Probably reduced (1)	Probably no impact	Probably increased (3)	Increased	
Acceptability	Uncertain (4)	Varies	No (1)	Probably no	Probably yes (6)	Yes (1)		
Feasibility	Uncertain (5)	Varies (1)	No	Probably no	Probably yes (3)	Yes (2)		

Additional Comments

- Because of the cost of the drug, accessibility and affordability may be a concern.

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

RECOMMENDATION
We suggest the use of remdesivir in hospitalized children with severe COVID-19 infection. (Very low certainty of evidence; Weak recommendation)

Consensus Issues

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).

RECOMMENDATION
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.*

Consensus Issues

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.

Evidence Summary

Key Findings

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.

Introduction

Remdesivir is an antiviral drug administered intravenously that has been shown to inhibit viral replication. This was initially developed for the Ebola virus and is currently being evaluated as a potential treatment for COVID-19 infection [1].

Previously published RCTs on the use of remdesivir for adult patients with moderate to severe COVID-19 had shorter time to recovery and a lower risk of progression to more severe respiratory disease, safety profiles were similar to placebo and may have greater efficacy when initiated early. Pediatric approval by the US FDA for its use on those 12 years old and above or and weighing $\geq 40\text{kg}$ was extrapolated from adult trials with pharmacokinetic modeling and safety profile expected to be comparable to adults [2].

Review Methods

A systematic search was done until January 20, 2022 using free text and MeSH terms for coronavirus, SARS-COV-2, COVID-19 in children and remdesivir. The inclusion criteria for this review may be found in Table 1. Only RCTs and observational analytic studies were included. Pubmed, Cochrane Library, Google scholar and COVID-NMA were sought. Preprints were also checked in the medRxiv database. Ongoing studies were also searched in NIH clinicaltrials.gov. Relevant cited references were also manually searched.

Table 1. PICO criteria for remdesivir and COVID-19.

Population	Children with COVID-19
Intervention/Exposure	Remdesivir
Comparison	Usual care, standard of care, placebo, any active control
Outcomes	Hospitalization, mortality, recovery, clinical improvement, need for mechanical ventilation, duration of hospital or ICU stay, adverse events, time to negative viral conversion

Since few to no studies were seen in children on remdesivir, the Philippine COVID-19 Living Clinical Practice Guidelines (LCPG) Phase 1 on adults was also reviewed as indirect evidence. To update the LCPG, newer clinical trials on the use of remdesivir in adult patients were also included. Available meta-analysis from the COVID-NMA was incorporated in this review. The observational analytic study was appraised using the Newcastle-Ottawa Scale (NOS), Cochrane RoB II for RCTs and AGREE II tool for CPGs. Sub-group analysis by age, dose and severity were done.

Results

The only study on children was a multi-center cohort done in various countries (United States, Spain, United Kingdom, Italy, France and Germany) which included 77 pediatric patients with severe COVID-19 infection who all received remdesivir through a compassionate use program. There was no control group. The median age was 14 years old (range <2 months to 17 years [IQR 7-16]), 51% (39/77) were on invasive ventilation and 79% (61/77) had at least 1 co-morbid medical condition. A 10-day course was recommended with the following dosing regimen:

- >40kg: Loading dose of 200mg intravenously then 100mg intravenously subsequent days.
- < 40kg: Loading dose of 5mg/kg intravenously on day 1 then 2.5mg/kg/intravenously on subsequent days

Only 62% (48/77) received all 10 doses of remdesivir in this study. Concomitant medications (hydroxychloroquine, methylprednisolone, anakinra, tocilizumab, hydrocortisone and dexamethasone) were also given to some of the study participants. The study was assessed to be of fair quality using the Newcastle Ottawa Scale.

In 83% (64/77) of patients, there was recovery after 28 days of follow-up. Subgroup analysis by requirement for invasive mechanical ventilation at baseline and age (≤ 12 and > 12 years) were done. Those on invasive ventilation at baseline had significantly longer time to recovery (HR 0.47, 95% CI 0.28-0.78) than those without. The patients aged ≤ 12 years old also showed significantly longer time to recovery (HR 0.54, 95% CI 0.33-0.89 compared to older cases.

Of 77 patients, 32% experienced at least 1 adverse event. Risk for adverse events was comparable regardless if they were on non-invasive ventilation or not. Adverse events reported were elevated ALT and AST level and anemia. Serious adverse events were elevations in transaminase levels (grade 3 and 4 elevations) and renal adverse events (hematuria, elevations in creatinine levels, toxic nephropathy and renal impairment). Four deaths (4/77, 5%) were reported in this study, all of whom received 9-10 days of remdesivir.

The Philippine COVID-19 LCPG Phase 1 on adults had a favorable assessment using AGREE Scale. The trials were further updated with 6 new trials resulting in a total of ten (10) RCTs done in adults included in this review (N=10,454) [4-13]. Remdesivir was compared to placebo in three trials [8-9,12] and local standard of care in seven [4-7,10-11,13]. Some treatment interventions used for standard of care included corticosteroids [5-7,10-11,13], anti-coagulation [5,10], antivirals [11] and immunomodulators [5,11]. Nine trials recruited patients with COVID-19 that required hospitalization while one trial focused on non-hospitalized COVID-19 patients [9]. The studies with hospitalized patients included those with mild to critical COVID. Eight RCTs used a 10-day course of Remdesivir while two studies used a 5-day course [10-11]. The study on out-patient use used a 3-day course. The primary outcome of the studies was all-cause mortality, with duration of follow up ranging from 24 to 90 days. Other outcomes reported were time to

clinical improvement, need for mechanical ventilation, need for ICU admission, adverse events and serious adverse events. Appendix 2 shows the characteristics of all the included studies.

The overall certainty of evidence was rated to be very low due to serious risk of bias, inconsistency, indirectness and imprecision. The serious risk of bias was mostly due to performance bias, as most of the trials were open label/unblinded as well as detection bias and attrition bias. See risk of bias summary and GRADE evidence summary in Appendix 3-5.

Hospitalized patients

Mortality

Pooled results among nine RCTs (N=9,891) showed that remdesivir had no effect on all-cause mortality at day 28 (RR 0.91, 95 % CI 0.82-1.01) among adult patients.

Subgroup analysis among adult patients with mild-moderate disease (no oxygen support requirement) at baseline had inconclusive results (RR 0.86, 95% CI 0.55-1.36). Patients with severe disease (those on low flow oxygen support) also did not show significant benefit (RR 0.69, 95% CI 0.41-1.13. I²=55%). There was no effect among patients with critical disease (those on high flow oxygen support, NIV, mechanical ventilation or ECMO) (RR 1.00, 95% CI 0.87-1.14).

Sub group analysis by treatment duration showed inconclusive effect on mortality for those on the 5-day treatment regimen (RR 0.98, 95% CI 0.37, 2.56; I²=0%) and no effect for those given the 10-day treatment regimen (RR 0.92, 95% CI 0.83, 1.03; I²=0%).

Clinical Improvement

Pooled results in four RCTs on adult cases showed that the rate of clinical improvement up to day 28 among those given remdesivir was comparable to those given placebo or standard treatment (RR 1.07, 95% CI 1.01, 1.13). There was no significant effect seen on time to clinical improvement (RR 1.07, 95% CI 0.91, 1.27; I²=50.7%) as well. However, a decreased risk for clinical deterioration as measured by the WHO progression scale (RR 0.75, 95% CI 0.62,0.89) was reported.

Remdesivir has also shown a reduction in the risk for mechanical ventilation which was not statistically significant and had considerable heterogeneity (RR 0.75, 95% CI 0.56, 1.02; I²=82%). There is an inconclusive risk for ICU admission (RR 0.98, 95% CI 0.43, 2.22; 1 RCT, n=181).

Non-hospitalized patients

One double-blind placebo-controlled RCT involved 562 non-hospitalized adult patients 12 years old and above with COVID-19, with symptom onset in the previous 7 days and had at least one risk factor for disease progression]. Risk factors included 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. [7] A 3-day course of Remdesivir was given

in the intervention group (200mg on Day 1 and 100 mg on day 2 and 3). Overall certainty of evidence for this study was low due to serious indirectness and imprecision. Remdesivir showed a significant benefit in preventing COVID-19 related hospitalization or death from any cause (RR 0.13, 95% CI 0.03, 0.6).

There were eight pediatric patients included in the RCT (3 on remdesivir and 5 on placebo group). Subgroup analysis on these children showed inconclusive results for COVID-19 related hospitalization or death from any cause (RR 1.5, 95% 0.03, 61.3) and safety with mild-moderate COVID-19 (RR 0.58, 95% 0.03-11.2). Only one pediatric patient (placebo group) reported mild fatigue. There were no COVID-19 related hospitalization or death from any cause by Day 28.

Negative Viral Conversion

Remdesivir showed no benefit for negative viral conversion by Day 7 of illness (RR 1.02, 95% 0.76-1.38; 1 RCT n = 196).

Safety

Remdesivir showed no significant risk for adverse events (RR 0.99, 95% CI 0.92, 1.08; I²=31%) and serious adverse events (RR 0.84, 95% CI 0.67, 1.04; I²=49%) in hospitalized patients. In the out-patient study, there was also no significant risk for adverse events (RR 0.91, 95% CI 0.75,1.1) but it showed a significant decreased risk for serious adverse events (RR 0.26 95%CI 0.10,0.70). The most common adverse events reported were nausea, headache, cough, diarrhea, dyspnea, fatigue, pyrexia, increased creatinine level, decreased glomerular filtration rate, hypersensitivity reactions and elevation in hepatic enzymes. Serious adverse events included respiratory failure, cardiopulmonary failure and renal failure necessitating kidney replacement therapy.

Other Considerations (Evidence to Decision)

Remdesivir is available locally as 100mg of lyophilized powder for reconstitution in a single-use vial, under a compassionate special permit (CSP) for use in the treatment of COVID-19 [14]. The suggested retail price specified in a DOH memorandum is up to Php 8,200 per 100mg vial [15]. Following the recommended dosing of 200mg IV on Day 1 and 100mg IV on Days 2 to 10 for a 10-day course, the total cost per patient (at the SRP) is Php 90,200.00. For outpatient therapy, the total cost per patient is Php 32,800 for the recommended 3-day course. Cost effectiveness and cost utility analysis in the United States showed that remdesivir is more costly and less effective for the treatment of severe COVID-19 compared to Dexamethasone, while in South Africa and Turkey it saved costs by reducing the number of ICU days with higher QALYs [16-18].

Remdesivir has been granted emergency use authorization by the US FDA for the treatment of COVID-19 in adults and children more than 12 years old and weighing at least 40kg. The US NIH recommendations noted that administering IV infusions of remdesivir for up to 5 consecutive days can be difficult in the outpatient setting.

Recommendations from Other Groups

Table 2. Summary of recommendations from other groups

Society/ Regulatory Agency	Recommendation
US NIH • February 1, 2022 • February 24, 2022	<p>Recommended for:</p> <ul style="list-style-type: none"> Non-hospitalized children aged ≥ 12 years and weighing ≥ 40 kg at high risk of disease progression, initiate treatment as soon as possible and within 7 days of symptom onset; Hospitalized children aged ≥ 12 years with COVID-19 who have risk factors for severe disease and have an emergent or increasing need for supplemental oxygen Hospitalized children aged ≥ 16 years with COVID-19 who have an emergent or increasing need for supplemental oxygen regardless of whether they have risk factors for severe disease <p>In consultation with a pediatric infectious disease specialist, remdesivir can be considered for hospitalized children of all ages with COVID-19 who have an emergent or increasing need for supplemental oxygen</p>
Pediatric Infectious Disease Society – USA (September 12, 2020)	<p>Outpatients and hospitalized patients with asymptomatic, mild, or moderate COVID-19 should be managed with supportive care only. Remdesivir should be used only within the context of a clinical trial in these populations.</p> <p>Remdesivir is <u>suggested</u> for children with severe COVID-19.</p> <p>Remdesivir should be considered for children with critical COVID-19, unless there are contraindications.</p> <ul style="list-style-type: none"> Severe COVID-19: recommended duration of up to 5 days of remdesivir therapy for children. If used for children with critical COVID-19, a duration of 5–10 days is suggested; consider on a case-by-case basis for children not improving after 5 days of therapy.
National COVID-19 Clinical Evidence Taskforce – Australia October 24, 2021	Use of remdesivir for children or adolescents with COVID-19 outside a trial setting should not be routinely considered (Low certainty of evidence, Conditional)
Philippine COVID Living CPG (March 2021)	<p>We suggest:</p> <ul style="list-style-type: none"> against the use of remdesivir in patients with COVID-19 infection who have O2 saturation $>94\%$ and do not

	<p>require oxygen supplementation*; also in patients with COVID-19 infection who are already on invasive mechanical ventilation*.</p> <p>For addition of remdesivir to dexamethasone in patients with COVID-19 infection who have O2 saturation \leq 94% and/or requiring oxygen supplementation*.</p> <p>* All low certainty of evidence, conditional recommendation</p>
WHO November 20, 2020	Recommend against remdesivir in COVID-19 hospitalized patients. There is no evidence showing improvement in survival or other outcomes.

Research Gaps

Current clinical recommendations on the use of remdesivir have been based on efficacy and safety profiles in trials done among adult patients. There is one ongoing randomized controlled trial that is currently ongoing on the pharmacokinetics and safety of its use in the pediatric population. An update of this review will be done once the results are available.

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Evidence Summary Appendices

Appendix 1. Search Yield and Results

Date of Last Search: January 20, 2022

Database	Search Terms	YIELD	ELIGIBL E
Pubmed	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (remdesivir)	2148	9 (2 pediatric)
Cochrane	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (remdesivir)	198	8 (1 pedia)
Google Scholar	Remdesivir AND COVID-19 AND pediatric	3,200	2
COVID-NMA initiative	Remdesivir	13	9
ONGOING TRIALS			
ClinicalTrials.gov https://clinicaltrials.gov/	covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (remdesivir) AND children	30	1
PRE PRINT			
Medrxiv	covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (remdesivir)	1075 4	0

Appendix 2. Table of Included Studies

Title/Author	Patients (n) and Duration of Follow up	Intervention	Control	Outcome	Method
Pediatric (1)					
Compassionate Use of Remdesivir in Children with Severe COVID-19 Goldman, et al (May 2021)	N = 77 Hospitalized patients <18 years old with confirmed COVID-19 infection Follow up: 28 days	Remdesivir course for 10 days	N/A	Mortality Oxygen support requirement Need for invasive ventilation Length of hospital stay Adverse events	Observational (Cohort)
Adult (10)					
Early Remdesivir to prevent progression to severe COVID-19 in outpatients Gottlieb, et al (Dec 2021)	N = 562 (8 pediatric patients) Non-hospitalized patients with COVID-19 with symptom onset within 7 days and one risk factor for disease progression Follow up: 28 days	Remdesivir for 3 day course	Placebo	COVID-19 related hospitalization All cause mortality COVID-19 related medical visit COVID-19 related death Adverse events	Randomized, double blind placebo controlled trial
Remdesivir Efficacy in COVID-19 Treatment: A Randomized Controlled Trial Abd-Elsalam, et al (2021)	N=209 (200 analyzed) Hospitalized Mild to moderate symptoms Age: 18 to 80 years old	Remdesivir 200mg on D1 then 100mg D2-10 (10 day course)	Standard of care (Zinc, NAC, Lactoferrin, Vitamin C)	Duration of hospital stay Need for mechanical ventilation Adverse Events	Randomized controlled open label

Remdesivir plus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy) Ader, et al (Feb 2022, published online Sept 2021)	N= 857 (832 analyzed) Age: \geq 18 years old Hospitalized patients requiring oxygen support Follow up: 90 days	Remdesivir 200mg on D1 then 100mg D2-10 (10 day course) + Standard of Care	Standard of Care only (dexamethasone, anticoagulants)	Clinical Status on Day 15 (WHO ordinal scale) Time to Improvement Change from baselines Time to hospital discharge and duration of hospitalization Time to mech ventilation Mortality Oxygenation and ventilator free days until Day 29 Adverse events	Phase 3 open label RCT
Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a RCT Ali, et al (Jan 2022)	N = 1282 (1267 analyzed) Hospitalized adults Follow up: 28 days	Remdesivir 200mg on D1 then 100mg D2-10 (10 day course) + Standard of Care	Standard of care	Mortality Change in clinical severity Oxygen and ventilator free days Incidence of new oxygen or mechanical ventilation use Adverse events	Open label RCT
Evaluation of the Effects of Remdesivir and Hydroxychloroquine on Viral Clearance in COVID-19 Barratt, et al (2021)	N = 185 (101 assigned to remdesivir subgroup, 83 analyzed) Age: \geq 18 years old Admitted in the hospital or ICU Follow up: 90 days	Remdesivir 200mg on D1 then 100mg D2-10 (10 day course) + Standard of Care Additional arm: HCQ	Standard of care	All cause in hospital mortality Need for mechanical ventilation Duration of mechanical ventilation Need for ICU admission Adverse events	Open label RCT

Remdesivir for the Treatment of COVID-19 Beigel, et al (2020)	N=1062 (1048 analyzed) Severe COVID-19 patients	Remdesivir 200mg on D1 then 100mg D2-10 (10 day course)	Placebo	Time to recovery Clinical status Time to discharge Number of days with supplemental oxygen, NIV or high flow and mechanical ventilation Adverse events	Double blind, randomized placebo controlled
Clinical outcomes of using remdesivir in patients with moderate to severe COVID-19: a prospective randomized study Mahajan, et al (2021)	N= 82 (70 analyzed) Age: 18-60 years old Admitted in the hospital Moderate to severe COVID	Remdesivir 200mg on D1 then 100mg D2-4 (5 day course)	Standard of care	Clinical status on Day 12 Mortality Safety Outcomes	Randomized controlled trial
Effect of Remdesivir vs Standard of Care on Clinical Status at 11 days in patients with Moderate COVID-19 Spinner, et al (2020)	N = 596 (584 analyzed) Hospitalized patients with moderateCOVID	Remdesivir 200mg on D1 then 100mg on subsequent days (5 or 10 day course)	Standard of care	Clinical status on day 11 (7-point ordinal scale) Clinical improvement (2-category change from baseline) Time to recovery Adverse events	Double blind Randomized controlled trial

Remdesivir in adults with severe COVID-19: a randomized, double blind placebo controlled multicentre trial Wang (2020)	N = 237 (226 analyzed) Age \geq 18 years old Severe COVID patients Follow up: 28 days	Remdesivir 200mg on D1 then 100mg D2-10 (10 day course)	Placebo	Clinical status (6-point ordinal scale) Clinical improvement (2 points reduction from baseline, or discharge from hospital) Time to clinical improvement Viral load Mortality Adverse events	Double blind Randomized controlled trial
Repurposed Antiviral Drugs for COVID-19 – Interim WHO Solidarity Trial Results WHO (2021)	N = 11,330 (5,025 Remdesivir and control)	Remdesivir 200mg on D1 then 100mg D2-10 (10 day course)	Standard of Care	Mortality Need for mechanical ventilation Duration of hospitalization	

Appendix 3. Study Appraisal

Goldman et al (May 2021) – **Fair Quality**

Table 1. Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Selection

- 1) Representativeness of the exposed cohort
 - a) Truly representative (**one star**) *
 - b) Somewhat representative (**one star**)
 - c) Selected group
 - d) No description of the derivation of the cohort
- 2) Selection of the non-exposed cohort
 - a) Drawn from the same community as the exposed cohort *
 - b) Drawn from a different source
 - c) No description of the derivation of the non exposed cohort
- 3) Ascertainment of exposure
 - a) Secure record (e.g., surgical record)
 - b) Structured interview (**one star**)
 - c) Written self report
 - d) No description
 - e) Other
- 4) Demonstration that outcome of interest was not present at start of study
 - a) Yes (**one star**)
 - b) No

Comparability

- 1) Comparability of cohorts on the basis of the design or analysis controlled for confounders
 - a) The study controls for age, sex and marital status (**one star**) *
 - b) Study controls for other factors (list) _____ (**one star**)
 - c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

- 1) Assessment of outcome
 - a) Independent blind assessment (**one star**)
 - b) Record linkage (**one star**)
 - c) Self report
 - d) No description
 - e) Other
- 2) Was follow-up long enough for outcomes to occur
 - a) Yes (**one star**) *
 - b) No

Indicate the median duration of follow-up and a brief rationale for the assessment above: 28 day follow up

- 3) Adequacy of follow-up of cohorts
 - a) Complete follow up- all subject accounted for (**one star**) *
 - b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (**one star**)
 - c) Follow up rate less than 80% and no description of those lost
 - d) No statement

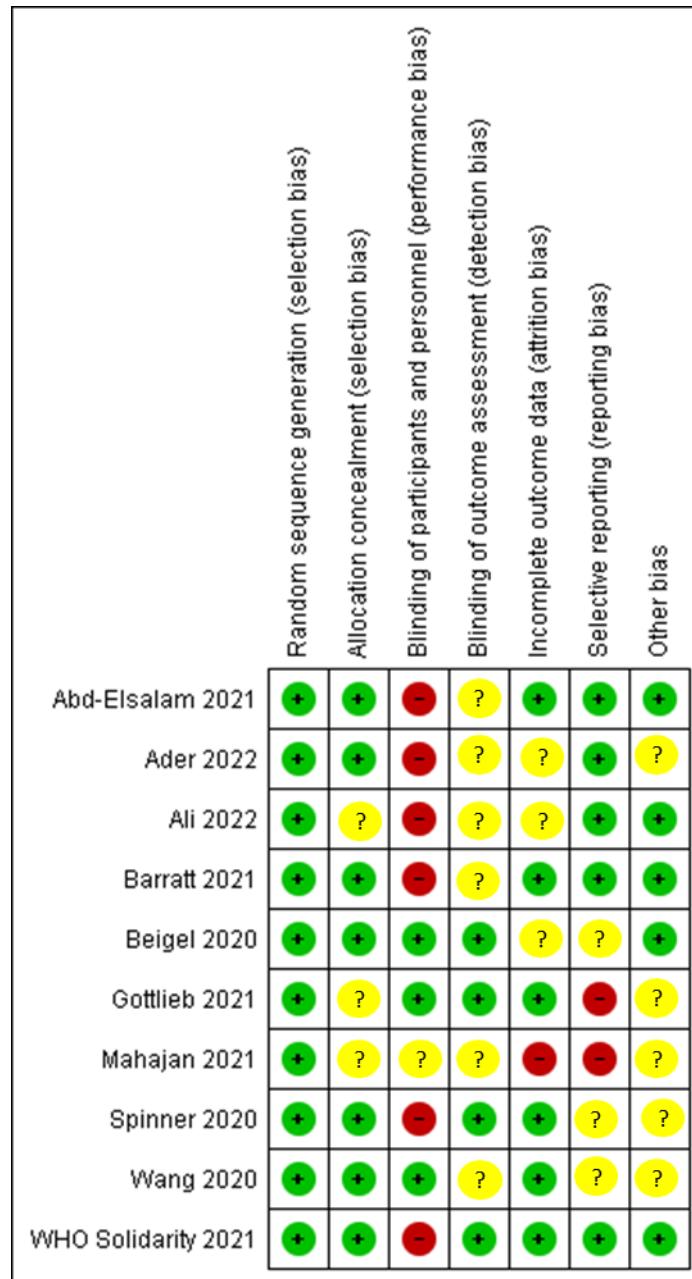


Figure 1. Risk of Bias Summary of Randomized Controlled trials (Adult)

Appendix 4A. GRADE Evidence Profile: Hospitalized Patients

Author(s): Melissa A. Dator, MD, Maria Teresa S. Tolosa, MD, FPDS, DipCE; Ma. Lucila M. Perez, MD, MSc, FPPS

Bibliography: (1) Abd-Elsalam S, et al. 2021 ; (2) Ader F, et al. 2022 (3) Ali K, et al. 2022 (4) Barratt-Due et al 2021 (5) Beigel J et al 2020 (6) Mahajan L. 2021. (7) Spinner C 2020. (8) Wang Y. 2021. (9) WHO Solidarity Trial 2021

Question: Should remdesivir compared to placebo or standard of care be used in the treatment for COVID-19 hospitalized patients?

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	Placebo or Standard of Care	Relative (95% CI)	Absolute (95% CI)		
Mortality (Day 28)												
9	randomised trials	serious ^a	not serious	serious ^b	not serious	none	554/5092 (10.9%)	591/4799 (12.3%)	RR 0.91 (0.82 to 1.01)	11 fewer per 1,000 (from 22 fewer to 1 more)		Critical
Mortality (Day 28) - 5 day Remdesivir												
2	randomised trials	serious ^a	not serious	serious ^b	serious ^c	none	8/232 (3.4%)	7/141 (5.0%)	RR 0.98 (0.37 to 2.56)	1 fewer per 1,000 (from 31 fewer to 77 more)		Critical
Mortality (Day 28) - 10 day Remdesivir												
8	randomised trials	serious ^a	not serious	serious ^b	not serious	none	546/4848 (11.3%)	575/4658 (12.3%)	RR 0.92 (0.83 to 1.03)	10 fewer per 1,000 (from 21 fewer to 4 more)		Critical
Clinical Improvement												
4	randomised trials	serious ^a	not serious	serious ^b	not serious	none	715/1024 (69.8%)	455/748 (60.8%)	RR 1.07 (1.01 to 1.13)	43 more per 1,000 (from 6 more to 79 more)		Critical
Clinical Deterioration (WHO Progression Score)												
5	randomised trials	serious ^d	not serious	serious ^b	not serious	none	189/1565 (12.1%)	229/1269 (18.0%)	RR 0.75 (0.62 to 0.89)	45 fewer per 1,000 (from 69 fewer to 20 fewer)		Important
Need for Mechanical Ventilation												
5	randomised trials	serious ^a	serious ^a	serious ^b	serious ^c	none	516/4271 (12.1%)	614/4196 (14.6%)	RR 0.75 (0.56 to 1.02)	37 fewer per 1,000 (from 64 fewer to 3 more)		Critical
Negative Viral Conversion												
1	randomised trials	serious ^f	not serious	serious ^b	serious ^c	none	66/131 (50.4%)	32/65 (49.2%)	RR 1.02 (0.76 to 1.38)	10 more per 1,000 (from 118 fewer to 187 more)		Important

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	Placebo or Standard of Care	Relative (95% CI)	Absolute (95% CI)		
Serious Adverse Events												
5	randomised trials	serious ^g	not serious	serious ^b	serious ^c	none	329/2158 (15.2%)	346/1875 (18.5%)	RR 0.84 (0.67 to 1.04)	30 fewer per 1,000 (from 61 fewer to 7 more)	 Very low	Critical
Adverse Events												
5	randomised trials	serious ^g	not serious	serious ^b	not serious	none	941/2158 (43.6%)	790/1875 (42.1%)	RR 0.99 (0.92 to 1.08)	4 fewer per 1,000 (from 34 fewer to 34 more)	 Low	Critical

CI: confidence interval; RR: risk ratio

Explanations

- a. Some trials with issues on randomization, missing outcome data, performance bias and detection bias
- b. Trials done on adult patients only. No pediatric patients enrolled
- c. Wide confidence interval
- d. 1 study assessed to have overall high risk of bias
- e. Considerable heterogeneity ($I^2= 82\%$)
- f. Missing outcome data
- g. Studies had deviations from intended intervention, missing outcome data and reporting bias

Appendix 4B. GRADE Evidence Profile: Non-hospitalized Patients

Author(s): Melissa A. Dator, MD, Maria Teresa S. Tolosa, MD, FPDS, DipCE; Ma. Lucila M. Perez, MD, MSc, FPPS

Question: Should remdesivir compared to placebo or standard of care be used in the treatment for COVID-19 non- hospitalized patients?

Bibliography: Gottlieb R, 2022

№ of studies	Study design	Certainty assessment					№ of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	Placebo	Relative (95% CI)	Absolute (95% CI)		
COVID-19 related hospitalization or death from any cause - Day 28												
1 (N=568)	randomised trials	not serious	not serious	serious ^a	serious ^c	none	2/279 (0.7%)	15/283 (5.3%)	RR 0.13 (0.03 to 0.60)	46 fewer per 1,000 (from 51 fewer to 21 fewer)	⊕⊕○○ Low	Critical
Adverse events												
1 (N=568)	randomised trials	not serious	not serious	serious ^a	serious ^c	none	118/279 (42.3%)	131/283 (46.3%)	RR 0.91 (0.75 to 1.10)	42 fewer per 1,000 (from 116 fewer to 46 more)	⊕⊕○○ Low	Critical
Serious adverse events												
1 (N=568)	randomised trials	not serious	not serious	serious ^a	serious ^c	none	5/279 (1.8%)	19/283 (6.7%)	RR 0.26 (0.10 to 0.70)	50 fewer per 1,000 (from 60 fewer to 20 fewer)	⊕⊕○○ Low	Critical
COVID-19 related hospitalization or death from any cause - Pediatric only												
1 (N=8)	randomised trials	not serious	not serious	not serious	very serious ^b	none	0/3 (0.0%)	0/5 (0.0%)	RR 1.50 (0.03 to 61.30)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ Low	Critical

Adverse Event - Pediatric only												
1 (N=8)	randomised trials	not serious	not serious	not serious	serious ^b	none	0/3 (0.0%)	1/5 (20.0%)	RR 0.58 (0.03 to 11.20)	84 fewer per 1,000 (from 194 fewer to 1,000 more)	 Moderate	Critical

CI: confidence interval; RR: risk ratio

Explanations

- a. Majority of the population in the study were adults. Only 8 patients were below 18 years old.
- b. Wide confidence interval
- c. Target sample size of 1264 not met

Appendix 5. Forest Plots

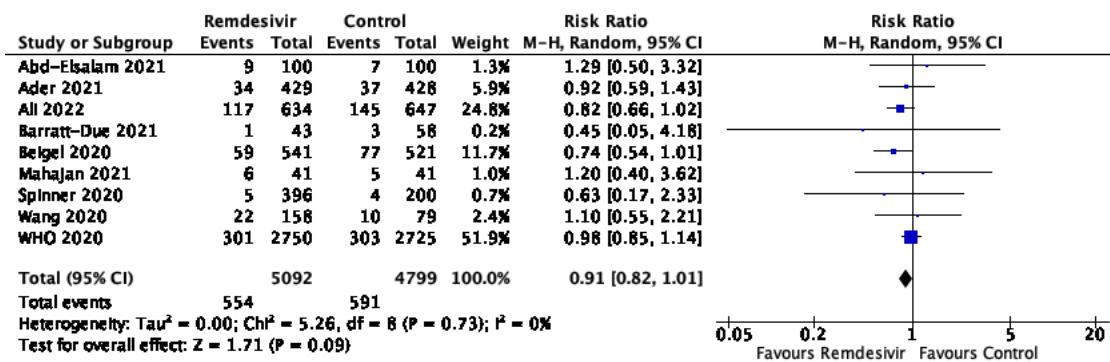


Figure 1. Pooled effect of remdesivir on all-cause mortality at Day 28 among hospitalized patients

(Source: Tan-Lim, Philippine COVID-19 Living CPG)

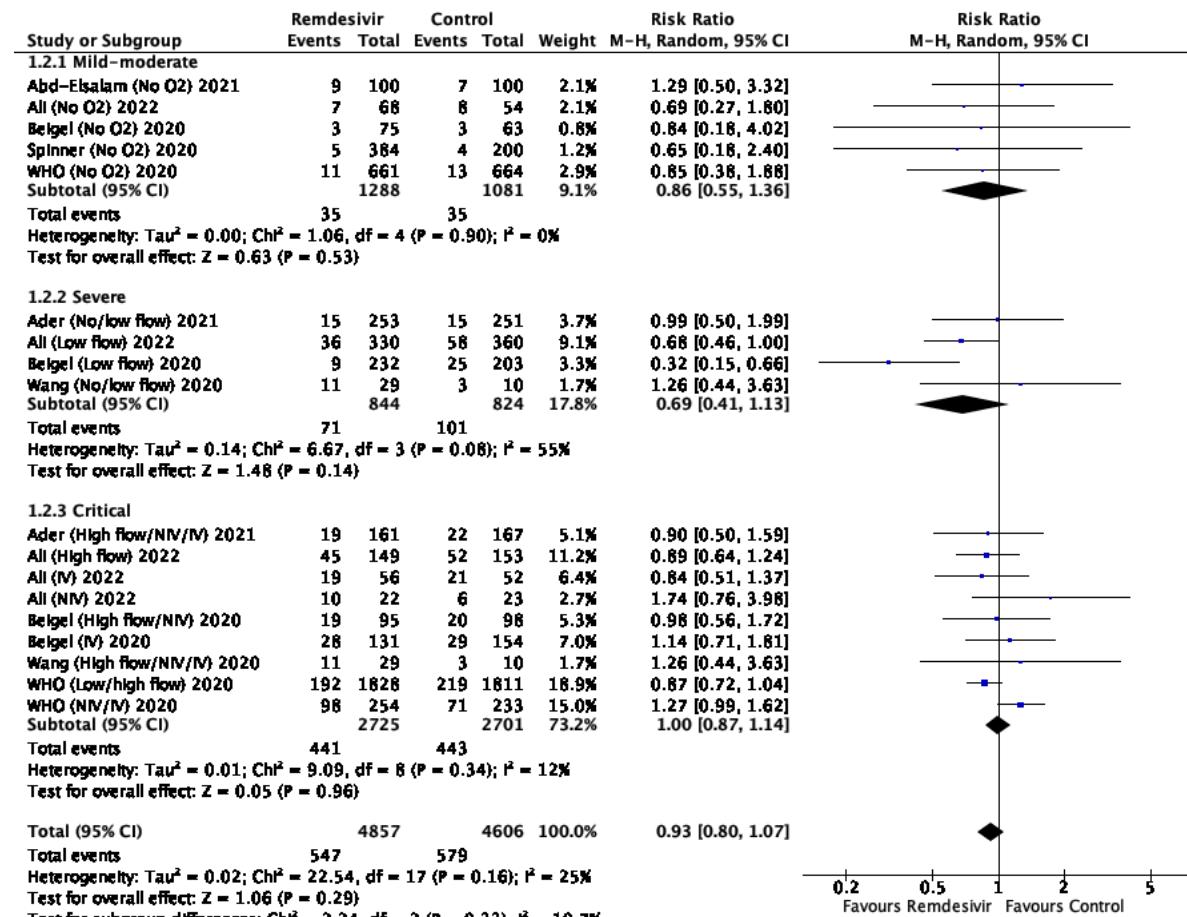


Figure 2. Subgroup analysis for mortality by disease severity

(Source: Tan-Lim, Philippine COVID-19 Living CPG)

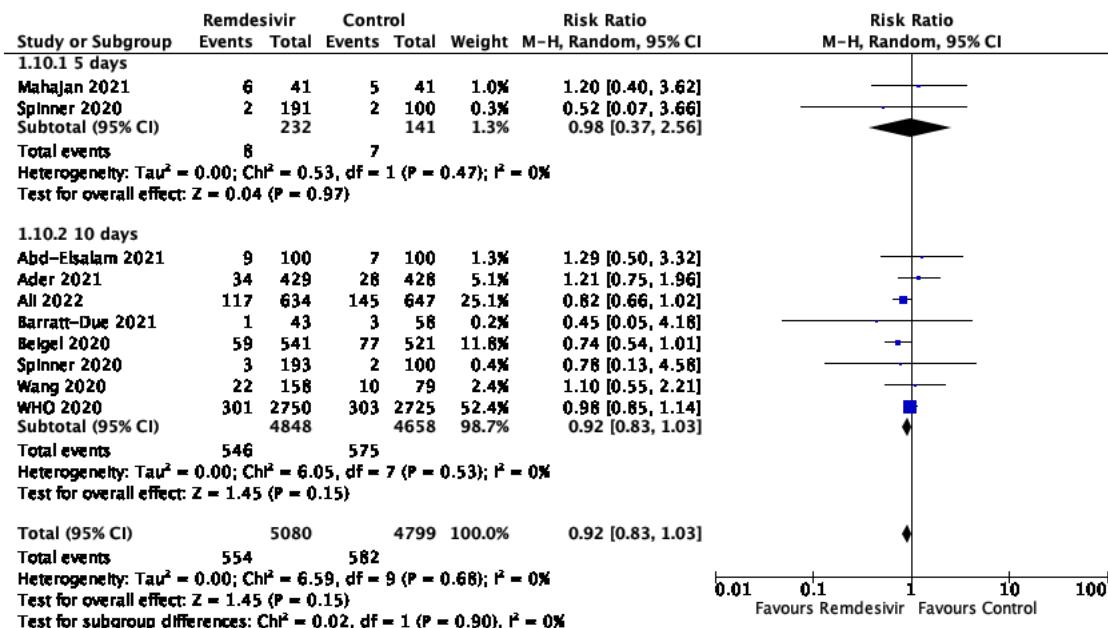


Figure 3. Subgroup analysis for mortality by treatment duration
(Source: Tan-Lim, Philippine COVID-19 Living CPG)

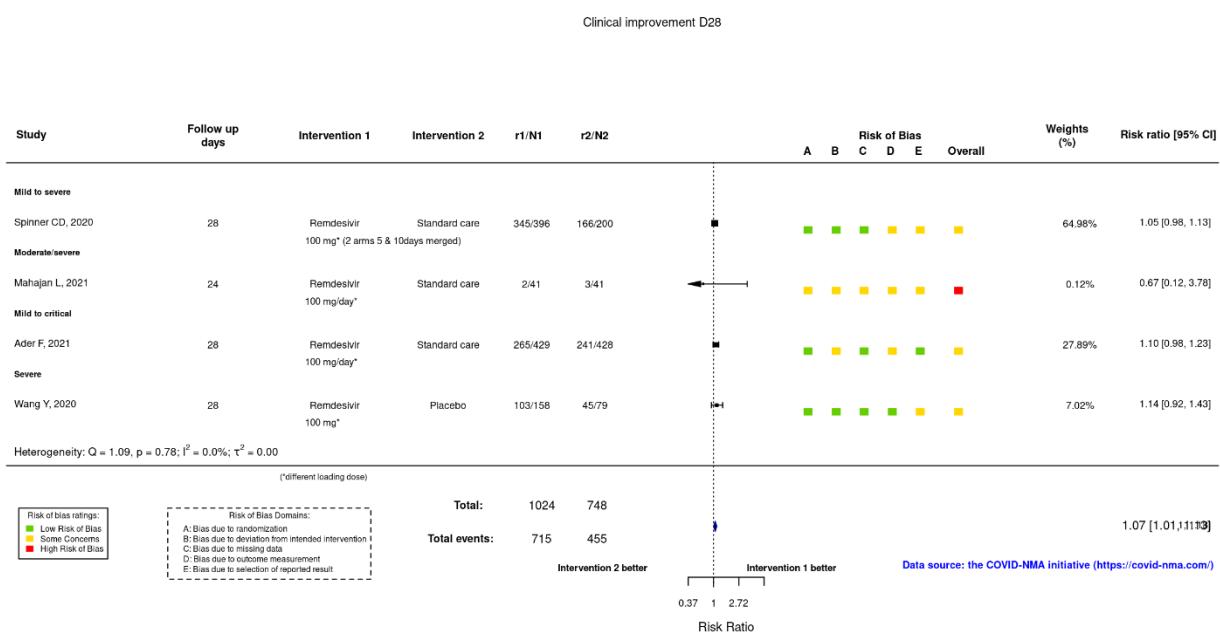


Figure 4. Pooled effect of remdesivir on clinical improvement among hospitalized patients
(Source: www.covid-nma.com)

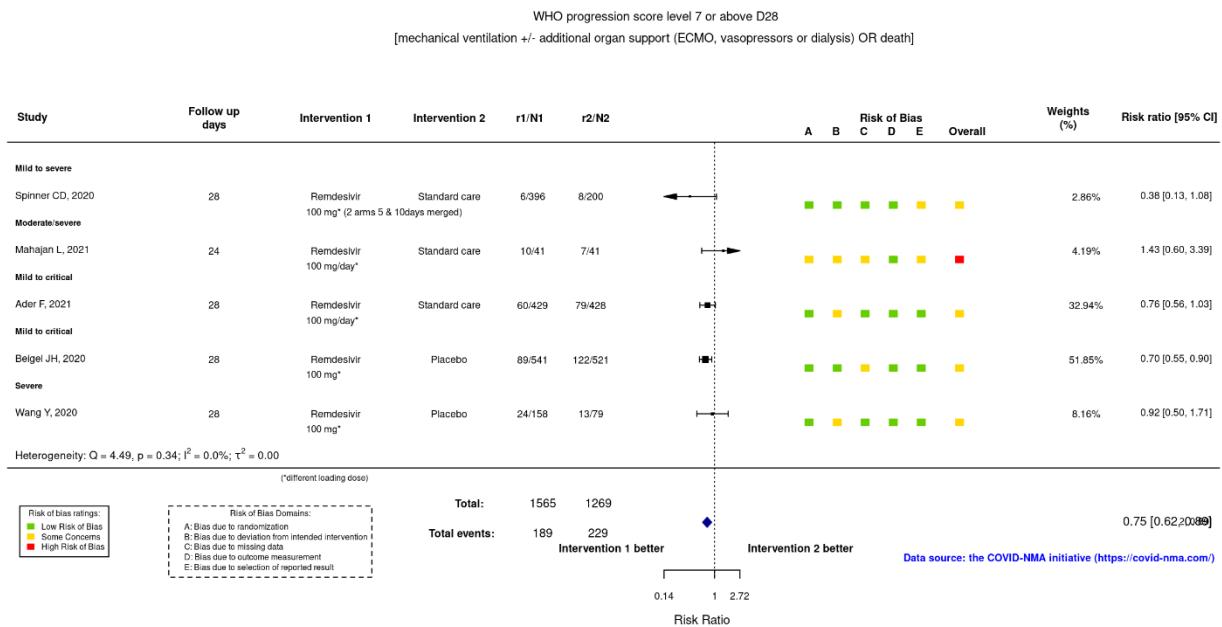


Figure 5. Pooled effect of remdesivir on clinical deterioration using the WHO progression score among hospitalized patients (Source: www.covid-nma.com)

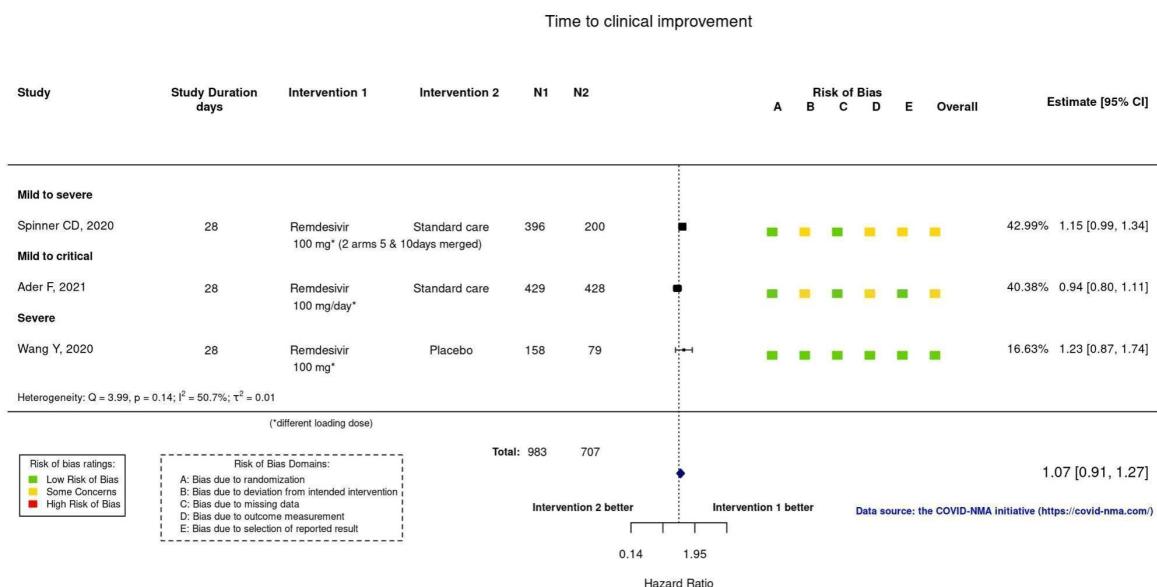


Figure 6. Pooled effect of remdesivir on time to clinical improvement among hospitalized patients (Source: <https://www.covid-nma.com>)

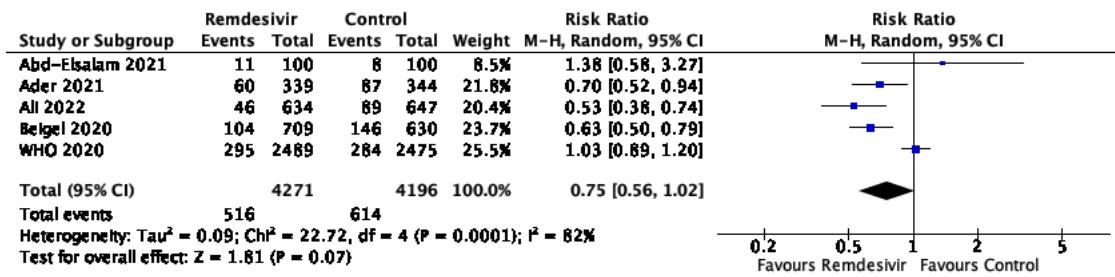


Figure 7. Pooled effect of remdesivir on need for mechanical ventilation among hospitalized patients
(Source: Tan-Lim, Philippine COVID-19 Living CPG)

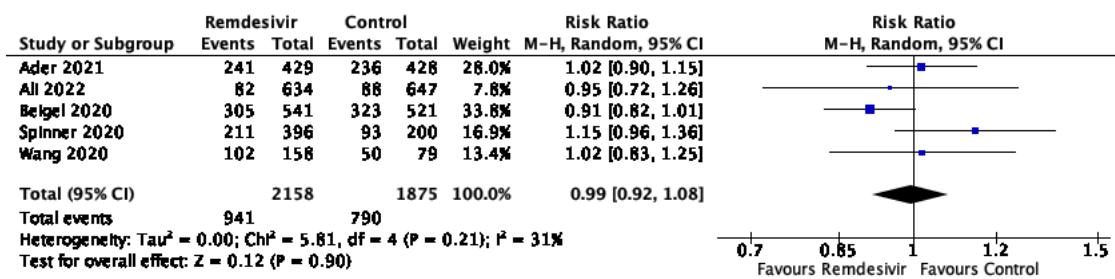


Figure 8. Pooled effect of remdesivir on adverse events among hospitalized patients
(Source: Tan-Lim, Philippine COVID-19 Living CPG)

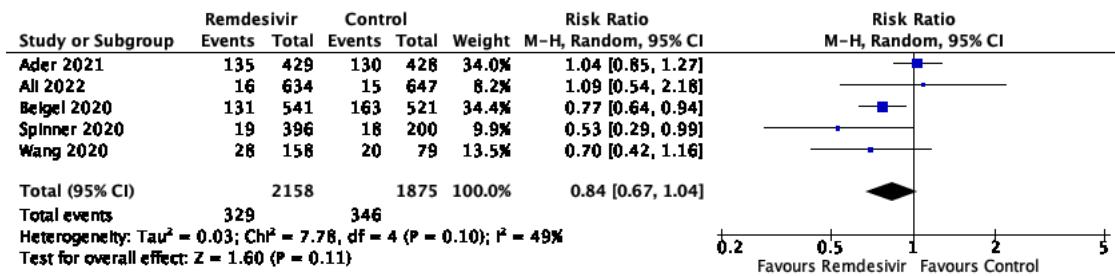


Figure 9. Pooled effect of remdesivir on serious adverse events among hospitalized patients
(Source: Tan-Lim, Philippine COVID-19 Living CPG)

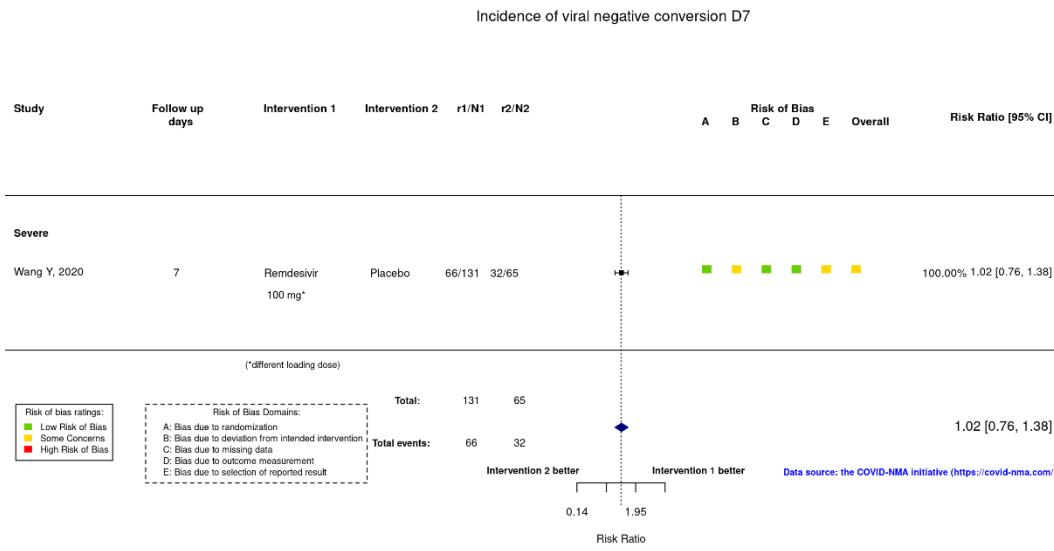


Figure 10. Incidence of viral negative conversion by Day 7 (Source: www.covid-nma.com)

Appendix 6. Table of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
<p>Status to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of Remdesivir in Participants From Birth to < 18 Years of Age with COVID-19 (CARAVAN)</p> <p>NCT04431453</p> <p><i>Status:</i> Recruiting</p> <p><i>Estimated completion:</i> Feb 2022</p>	<p>Pediatric patients 0 days to <18 years old, to include term and preterm neonates (8 cohorts) with COVID-19 (N = 52)</p>	<p>Remdesivir for 10 days Dose depending on cohorts</p>	<p><i>Primary:</i> Adverse events Laboratory Abnormalities Plasma Concentration of Remdesivir</p> <p><i>Secondary:</i> Oxygenation Use Use of Mechanical Ventilator or ECMO Clinical improvement Time to hospital discharge Days to confirmed RT PCR negative Change to severe COVID Bilirubin concentration in <14 days old Clinical improvements based on PEWS scale Plasma concentrations SBECD Use of other medications other than RDV</p>	<p>Open label Phase 2/3 RCT</p>

Appendix 7: Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 11)

FACTORS		JUDGEMENT (N = 11)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (11)		Varies		Uncertain		
Benefits	Large	Moderate (2)	Small (6)	Trivial (2)	Varies	Uncertain (1)		Hospitalized <ul style="list-style-type: none"> • No significant benefit on all-cause mortality day 28, time to clinical improvement • Significant benefit in reducing risk of clinical deterioration • Non-statistically significant benefit in reducing MV use Non-hospitalized <ul style="list-style-type: none"> • Significant benefit in reducing COVID-19 related hospitalization or all-cause mortality
Harm	Large	Moderate	Small (6)	Trivial (4)	Varies	Uncertain (1)		<ul style="list-style-type: none"> • No significant difference in adverse events and serious adverse events between intervention and control groups
Certainty of evidence	High	Moderate		Low		Very low (11)		<ul style="list-style-type: none"> • Rated very low due to serious risk of bias, indirectness and imprecision
Balance of effects	Favors drug	Probably favors drug (6)	Does not favor drug or no drug (1)	Probably favors no drug (1)	Favors no drug	Varies	Uncertain (3)	
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (4)		Probably no important uncertainty or variability (5)		No important uncertainty or variability (1)		
Resources required	Uncertain	Varies	Large costs (9)	Moderate costs (2)	Negligible costs or savings	Moderate savings	Large savings	<ul style="list-style-type: none"> • Php 32,800.00 for 3-day OPD course • Php 90,200.00 for in-patient course
Certainty of evidence of resources required	No included studies (4)		Very low	Low (1)	Moderate (5)	High (1)		
Cost-effectiveness	No included studies (1)	Varies (3)	Favors the comparison (1)	Probably favors the comparison (2)	Does not favor the comparison or the intervention	Probably favors the intervention (4)	Favors the intervention	
Equity	Uncertain (4)	Varies (1)	Reduced	Probably reduced (4)	Probably no impact (1)	Probably increased (1)	Increased	
Acceptability	Uncertain (6)	Varies	No	Probably no (1)	Probably yes (3)	Yes (1)		
Feasibility	Uncertain (5)	Varies (3)	No (1)	Probably no	Probably yes (1)	Yes (1)		

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)
<i>Consensus Issues</i> 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.

Evidence Summary

Key Findings

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.

Introduction

COVID-19 infection in adults has exhibited the predisposition to thrombotic coagulopathies speculated to be caused by an inflammatory-driven endothelial dysfunction and a hypercoagulable state. There is a reported incidence of 21-31% for venous thromboembolism in adults with COVID-19, with many patients having elevated levels of D-dimer, fibrinogen, and mild prolongation of prothrombin time. In contrast, the reported rate of thrombotic events in hospitalized children with COVID-19 and MIS-C is 2.1%, and 6.5% respectively compared to 0.7% in those who are asymptomatic. In a particular retrospective review by Whitworth et al, thrombotic events in adolescents is higher at 6.8% with a mortality rate of 28%. [1,2]

The Philippine COVID Adult Living CPG suggests the use of prophylactic anticoagulation based on a very low certainty of evidence. While a handful of other guidelines have suggested the use of anticoagulation in adults with COVID-19, there is still very limited data for thromboprophylaxis in children.

Review Methods

An electronic search for published and pre-print studies (PubMed, Cochrane Library, Herdin, MedRxiv) and ongoing trials (Clinicaltrials.gov Registry, International Clinical Trials Registry Platform) was conducted. The inclusion criteria are stated in Table 1. Free text and MeSH terms were used for the search which lasted until January 17, 2021. Appraisal of cohort studies was done using Newcastle Ottawa Scale (NOS). Subgroup analysis for COVID severity classification, age group, kind of anticoagulant, prophylactic versus therapeutic dosing and duration was planned however was not possible due to unavailability of data. (Appendices 2,3).

Table 1. PICO criteria for anticoagulation and COVID-19.

Population	Children with COVID-19
Intervention/Exposure	Anticoagulation, thromboprophylaxis
Comparison	Usual care, standard of care, placebo, any active control
Outcomes	Bleeding, thrombosis, adverse effects

Results

Two cohort studies on children were identified (Del Borello 2020, Whitworth 2021). Cases with COVID-19 infection requiring hospitalization across all severity were enrolled, including MIS-C. Primary anticoagulants used were enoxaparin and unfractionated heparin in both studies. Results could not be pooled due to differences in anticoagulation regimen and reported outcomes.

The prospective cohort study by Del Borello et. Al (2020) enrolled 35 pediatric patients with SARS-CoV-2 infection requiring hospitalization in a tertiary care center in Italy. Risk for thrombosis was appraised using the International Society on Thrombosis and Hemostasis (ISTH)-endorsed recommendations to determine which patients underwent prophylactic anticoagulation. Only a total of six patients (moderate – 1, severe – 1, critical – 2, MIS-C – 2) were given prophylactic anticoagulation using Enoxaparin (100 U/kg) every 24 hours or unfractionated heparin (10 U/kg/hr). All patients on anticoagulation had preexisting conditions: obesity, cystic fibrosis, leukemia, sickle cell disease. Outcomes documented were mortality, thrombotic/bleeding events. However, data on comparison was not available, only adverse events were reported. [1] (Appendix 3)

The retrospective cohort by Whitworth et al. conducted in 7 pediatric hospitals in the U.S. reviewed the rate of thrombosis in 564 pediatric patients (0 to <21 years of age) hospitalized for either COVID or MIS-C. Of these, 128 of 426 (30%) of COVID-19, and 80 of 138 (58.0%) MIS-C admissions were given thromboprophylaxis with varying regimens and dosing. The most commonly used anticoagulant was enoxaparin (89%), followed by unfractionated heparin (6.8%). Dosing regimen for prophylactic anticoagulation using enoxaparin varied depending on physician prescription either once or twice a day at approximately 0.5mg/kg. Dosing used for heparin and duration of treatment for both anticoagulants were not available. Post hoc analysis was done to determine effect on preventing thrombotic events and risk of bleeding while on prophylactic anticoagulation. [2] (Appendix 5)

Summary of Certainty of Evidence

Certainty of evidence was deemed very low for both studies due to high risk of bias, a very small sample size (Borello et al. 2020), heterogeneity in intervention, low event rate and wide confidence intervals (Whitworth et al. 2021). Assessment of outcomes was not mentioned and follow up was not defined in the study by Borello et al. (Appendix 4)

Mortality

There was no reported mortality in the six patients that received prophylactic coagulation in the study by Borello et al. On the other hand, Whitworth et al did not identify the number of deaths specific to the group that was given anticoagulation therapy.

Thrombosis

Data from Whitworth revealed no significant benefit for prophylactic anticoagulation over no anticoagulation in preventing thrombotic events for hospitalized children with COVID-19 and MIS-C. (RR 2.14, 95% CI 0.86 – 5.34, n= 564). On subgroup analysis, likewise there was no significant benefit for hospitalized children regardless of diagnosis of COVID-19 (n = 426) or MIS-C (n = 138) with RR 1.16 (95% CI 0.29 – 4.57) and RR 2.41 (95% CI 0.52 – 11.22), respectively. There was no thrombotic event in any of the six patients that received prophylactic coagulation in the study by Borello et al.

Bleeding

Post hoc analysis of data from Whitworth et. Al. showed inconclusive results in terms of the risk of bleeding while on prophylactic anticoagulation, for both COVID and MIS-C pediatric patients. (RR 0.35, 95% CI 0.04 – 2.94, n = 564). Subgroup analysis for bleeding in COVID patients only and in MIS-C were also inconclusive with RR 0.47, 95% CI 0.06 – 4.00 (n = 426) and RR 0.73, 95% CI 0.01 – 36.19 (n = 138), respectively. In contrast, no bleeding events were identified by Del Borello et al. among patients given anticoagulation.

Other Considerations (Evidence to Decision)

Table 2. Evidence to Decision Considerations

Cost [3] ^{a,b}	No evidence was found on the cost-effectivity of anticoagulation therapy in COVID-19 patients. <i>Enoxaparin 100 mg/ml, 0.4 mL pre-filled syringe: Php 179.89 – 398.00 Enoxaparin 100 mg/mL, 0.6 mL pre-filled syringe: Php 195.00 – 465.00 Heparin (as sodium) 1000 IU/mL, 5 mL vial: Php 42.23 – 134.22 Heparin (as sodium) 5000 IU/mL, 5 mL vial: Php 140 – 180</i>
Availability	Enoxaparin and heparin are included in the Philippine National Formulary. [3]
Patient's Values or Preferences; Social Impact	No available evidence.
Factors to Impact Acceptability or Compliance	Fernando et al. demonstrated that in critically ill, non-COVID adult patients, anticoagulation-associated bleeding led to higher mortality, prolonged hospital stay, and subsequent higher hospitalization cost. Around 15% of patients maintained on anticoagulation experienced major bleeding episodes throughout their hospital or ICU admission. [4]

^aHealth facilities may have a price variation up to 10% above DPRI to account for inflation

^bDosing regimen is dependent on the weight of the child, and duration is variable.

The Philippine Drug Price Reference Index (DPRI) of the Department of Health (DOH) [3]

Recommendations from Other Groups

Locally, the Philippine Pediatric Society (PPS) and the Pediatric Infectious Disease Society of the Philippines (PIDSP) suggest the use of prophylactic anticoagulation for high risk hospitalized COVID-19 pediatric patients. Only one other society was identified to provide a statement on the use of anticoagulation in children with COVID-19: The Australian Living CPG (Clinical Practice Guidelines), updated last December 2021, which acknowledges the lack of available data of the intervention in the pediatric population.

The Philippine COVID Living CPG conditionally suggests the use of prophylactic anticoagulation in admitted adult patients based on a very low certainty of evidence. Recommendations from other societies and associations are detailed in the table below. Most recommend the use of thromboprophylaxis in adults with COVID-19 that require hospitalization.

Table 3. Summary of Recommendations from other Groups

Association/ Institution (Date last updated)	Recommendation/s
PPS-PIDSP Interim COVID Guidelines (01/08/2022) [5]	Prophylactic anticoagulation may be started (in consultation with Hematology) for hospitalized COVID-19 patients with D-dimer levels more than 5 times the upper limit of normal values or if with presence of at least 1 clinical risk factor for VTE.
Australian Living CPG (12/2021) [6]	<ul style="list-style-type: none"> There is insufficient evidence in children and adolescents to recommend a modified thromboprophylaxis regimen. Consider known risk factors for initiating thromboprophylaxis in children and adolescents. <i>Certainty of the Evidence (CoE):</i> currently no direct evidence comparing the effectiveness of VTE prophylaxis regimens in children and adolescents with COVID-19.
Philippine COVID Living CPG (10/2021) [7]	<p>Among admitted patients with COVID-19 infection, the use of prophylactic anticoagulation is suggested, unless with contraindications. (<i>Very low certainty of evidence, Conditional recommendation</i>)</p> <p>The use of prophylactic over therapeutic dose anticoagulation is recommended among hospitalized patients with moderate, severe or critical COVID-19 disease unless there are any contraindications. (<i>Low certainty of evidence; Strong recommendation</i>)</p>
American Society of Hematology (7/15/2021) [8]	<p>All hospitalized patients with COVID-19:</p> <ul style="list-style-type: none"> Prophylactic anticoagulation is recommended unless risk of bleeding outweighs risk Standard dose prophylaxis is suggested over intermediate or therapeutic dose

National Institute of Health (NIH) (2/11/2021) [9]	Non-hospitalized patients with COVID-19: Anticoagulation should not be initiated unless there are other indications or the patient is participating in a clinical trial. Hospitalized patients with COVID-19: All non-pregnant adults are recommended to receive prophylactic anticoagulation. There is insufficient evidence to support the use of higher than standard dose outside of clinical trials
World Health Organization (WHO) (1/25/21) [10]	Hospitalized patients with COVID-19: Standard dose prophylactic anticoagulation rather than higher prophylactic dose or therapeutic dose is suggested unless there is a warranted indication. (<i>Conditional recommendation</i>)

Research Gaps

One ongoing randomized controlled trial (RCT) in children was identified (Appendix 7). The COVID-19 Anticoagulation in Children – Thromboprophylaxis or COVAC-TP Trial is a multicenter single arm trial in children less than 18 years of age with COVID using Enoxaparin as the intervention. Outcomes expected are safety and efficacy. The trial concluded recruitment in June 2021.

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10. World Health Organization. Therapeutics and COVID-19: living guideline [Internet]. [cited 2022 Jan 05]. Available from: <https://www.who.int/publications/item/WHO-2019-nCoV-therapeutics-2021.3>

Evidence Summary Appendices

Appendix 1. Search Yield and Results

Search terms:

#1 COVID-19 OR SARS-COV2

#2 anti-coagulation OR thrombolysis OR thromboprophylaxis

#3 children OR pediatric age group

#4 - #1 AND #2

#5 - #3 AND #4

Search: #1 AND #2	791
(“covid 19”[All Fields] OR “covid 19”[MeSH Terms] OR “covid 19 vaccines”[All Fields] OR “covid 19 vaccines”[MeSH Terms] OR “covid 19 serotherapy”[All Fields] OR “covid 19 serotherapy”[Supplementary Concept] OR “covid 19 nucleic acid testing”[All Fields] OR “covid 19 nucleic acid testing”[MeSH Terms] OR “covid 19 serological testing”[All Fields] OR “covid 19 serological testing”[MeSH Terms] OR “covid 19 testing”[All Fields] OR “covid 19 testing”[MeSH Terms] OR “sars cov 2”[All Fields] OR “sars cov 2”[MeSH Terms] OR “severe acute respiratory syndrome coronavirus 2”[All Fields] OR “ncov”[All Fields] OR “2019 ncov”[All Fields] OR ((“coronavirus”[MeSH Terms] OR “coronavirus”[All Fields] OR “cov”[All Fields]) AND 2019/11/01:3000/12/31[Date – Publication]) OR (“sars cov 2”[MeSH Terms] OR “sars cov 2”[All Fields] OR “sars cov 2”[All Fields])) AND (“anti-coagulation”[All Fields] OR “thrombolysis”[All Fields] OR “thromboprophylaxis”[All Fields]))	
Translations COVID-19: (“COVID-19” OR “COVID-19”[MeSH Terms] OR “COVID-19 Vaccines” OR “COVID-19 Vaccines”[MeSH Terms] OR “COVID-19 serotherapy” OR “COVID-19 serotherapy”[Supplementary Concept] OR “COVID-19 Nucleic Acid Testing” OR “covid-19 nucleic acid testing”[MeSH Terms] OR “COVID-19 Serological Testing” OR “covid-19 serological testing”[MeSH Terms] OR “COVID-19 Testing” OR “covid-19 testing”[MeSH Terms] OR “SARS-CoV-2” OR “sars-cov-2”[MeSH Terms] OR “Severe Acute Respiratory Syndrome Coronavirus 2” OR “NCOV” OR “2019 NCOV” OR ((“coronavirus”[MeSH Terms] OR “coronavirus” OR “COV”) AND 2019/11/01[PDAT] : 3000/12/31[PDAT])) SARS-COV 2: “sars-cov-2”[MeSH Terms] OR “sars-cov-2”[All Fields] OR “sars cov 2”[All Fields]	

syndrome coronavirus 2”[All Fields] OR “ncov”[All Fields] OR “2019 ncov”[All Fields] OR (“coronavirus”[MeSH Terms] OR “coronavirus”[All Fields] OR “cov”[All Fields]) AND 2019/11/01:3000/12/31[Date – Publication]) OR (“sars cov 2”[MeSH Terms] OR “sars cov 2”[All Fields] OR “sars cov 2”[All Fields])) AND (“anti-coagulation”[All Fields] OR “thrombolysis”[All Fields] OR “thromboprophylaxis”[All Fields]))

Translations

children: “child”[MeSH Terms] OR “child”[All Fields] OR “children”[All Fields] OR “child’s”[All Fields] OR “children’s”[All Fields] OR “childrens”[All Fields] OR “childs”[All Fields]

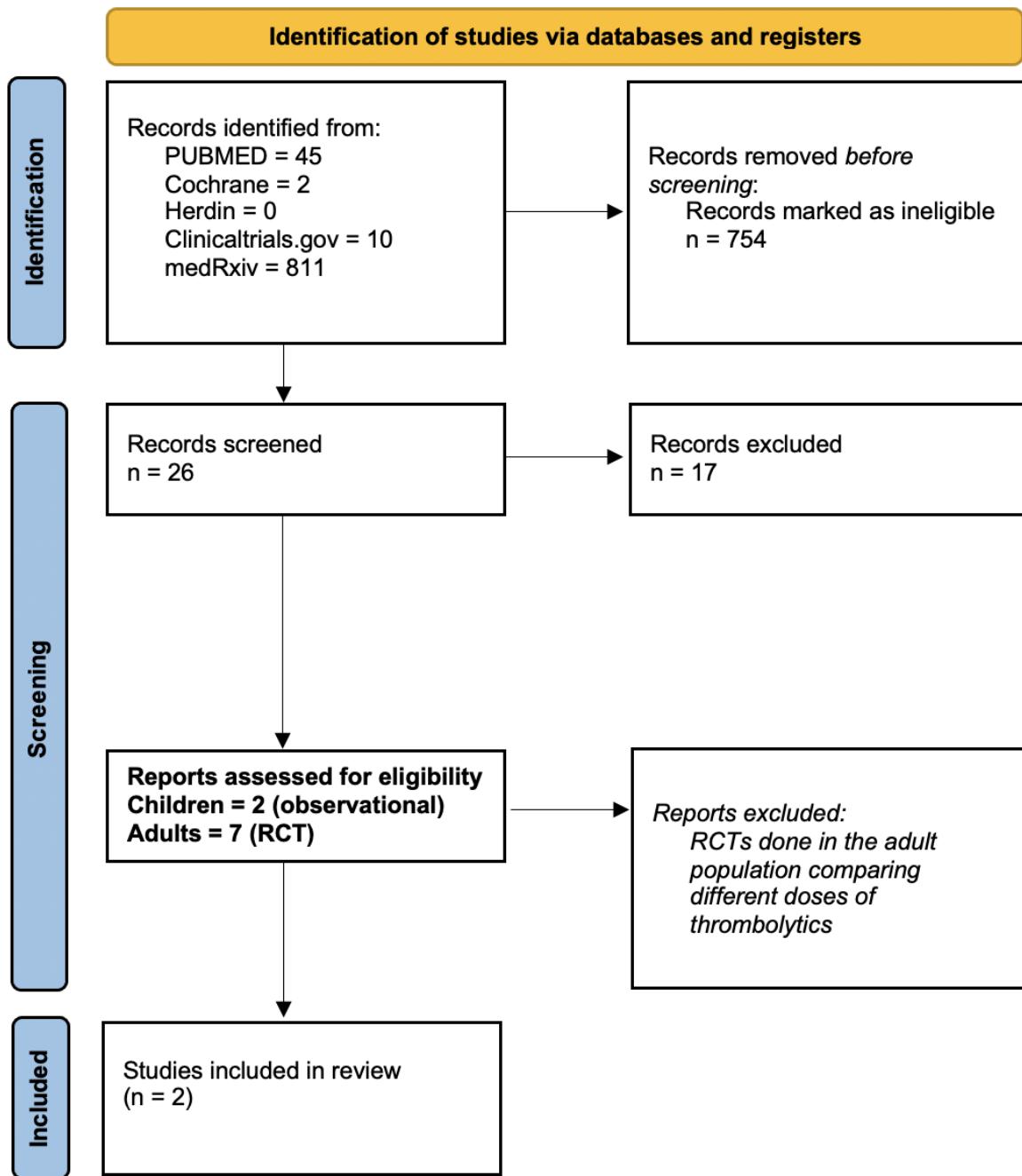
pediatric: “paediatrics”[All Fields] OR “pediatrics”[MeSH Terms] OR “pediatrics”[All Fields] OR “paediatric”[All Fields] OR “pediatric”[All Fields]

age group: “age groups”[MeSH Terms] OR (“age”[All Fields] AND “groups”[All Fields]) OR “age groups”[All Fields] OR (“age”[All Fields] AND “group”[All Fields]) OR “age group”[All Fields]

COVID-19: (“COVID-19” OR “COVID-19”[MeSH Terms] OR “COVID-19 Vaccines” OR “COVID-19 Vaccines”[MeSH Terms] OR “COVID-19 serotherapy” OR “COVID-19 serotherapy”[Supplementary Concept] OR “COVID-19 Nucleic Acid Testing” OR “covid-19 nucleic acid testing”[MeSH Terms] OR “COVID-19 Serological Testing” OR “covid-19 serological testing”[MeSH Terms] OR “COVID-19 Testing” OR “covid-19 testing”[MeSH Terms] OR “SARS-CoV-2” OR “sars-cov-2”[MeSH Terms] OR “Severe Acute Respiratory Syndrome Coronavirus 2” OR “NCOV” OR “2019 NCOV” OR ((“coronavirus”[MeSH Terms] OR “coronavirus” OR “COV”) AND 2019/11/01[PDAT] : 3000/12/31[PDAT]))

SARS-COV 2: “sars-cov-2”[MeSH Terms] OR “sars-cov-2”[All Fields] OR “sars cov 2”[All Fields]

Appendix 2. PRISMA Flow Chart



Appendix 3. Characteristics of Included Studies

Study ID	Study Design	Setting	Total population	Population	Intervention	Comparator	Outcomes
Del Borello 2020	Prospective cohort	Italy	35	0 to 21 years of age Mild to critical cases MISC	Prophylactic anticoagulation: Enoxaparin or Unfractionated Heparin	No data available for comparator group	Mortality Thrombotic events Bleeding
Whitworth 2021	Retrospective cohort	USA	564	0 to <21 years of age Hospitalized children with COVID or MIS-C	Prophylactic anticoagulation: Enoxaparin or Unfractionated Heparin	No anticoagulation	Bleeding events

Appendix 4. Risk of Bias Assessment using Newcastle Ottawa Scale (NOS)

Selection	Del Borello (2020)	Whitworth (2021)
Representativeness of the exposed cohort	Selected group	Representative
Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort *	Drawn from the same community as the exposed cohort *
Ascertainment of exposure	Secured record *	Secured record *
Demonstration of outcome of interest was not present at start of study	Yes *	No
Comparability		
Comparability of cohorts on the basis of the design or analysis controlled for confounders	Cohorts are not comparable	The study controls age and sex
Outcome		
Assessment of outcome	No description	Record linkage
Was follow-up long enough for outcomes to occur	Not mentioned	Not mentioned
Adequacy of follow-up of cohorts	No statement	No statement

ASSESSMENT: Poor quality*

***0 or 1 star (*) in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/ exposure domain**

Appendix 5A. GRADE Evidence Profile: Anticoagulation in Children with COVID (Del Borello, 2020)

Author/s: Vaneza Leah A. Espino, MD; Ma. Lucila M. Perez, MD

Question: Should anticoagulation be used in the treatment of children with COVID-19?

Setting: Italy

Bibliography: Del Borello G, et al 2020

Certainty assessment							Impact	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Mortality									
1 n = 6	observational studies	serious ^a	not serious	not serious	serious ^b	none	In the 6 patients identified to receive anticoagulation, there was no reported mortality. (0/6) No data was available for the comparator group.	⊕○○○ Very low	Critical
Thrombotic event/s									
1 n = 6	observational studies	serious ^a	not serious	not serious	serious ^b	none	In the 6 patients identified to receive anticoagulation, there were no reported thrombotic events. (0/6) No data was available for the comparator group.	⊕○○○ Very low	Critical
Bleeding event/s									
1 n = 6	observational studies	serious ^a	not serious	not serious	serious ^b	none	In the 6 patients identified to receive anticoagulation, there were no reported bleeding complications. (0/6) No data was available for the comparator group.	⊕○○○ Very low	Critical

Explanations

^a high risk of bias: no description of assessment of outcome, follow up time not mentioned

^b very small sample size

Appendix 5B. GRADE Evidence Profile: Anticoagulation in Children with COVID (Whitworth, 2021)

Author/s: Vaneza Leah A. Espino, MD; Ma. Lucila M. Perez, MD

Question: Should anticoagulation be used in the treatment of children with COVID-19?

Setting: USA

Bibliography: Whitworth H, et al.; 2021

No of studies	Study design	Risk of bias	Certainty assessment				No of patients		Effect		Certainty	Importance
			Inconsistency	Indirectness	Imprecision	Other considerations	Anticoagulation	Without anticoagulation	Relative (95% CI)	Absolute (95% CI)		
Bleeding (COVID + MIS-C)												
1 n = 564	observational studies	serious ^a	serious ^b	not serious	serious ^c	none	1/208 (0.5%)	5/356 (1.4%)	RR 0.35 (0.04 to 2.94)	9 fewer per 1,000 (from 13 fewer to 27 more)	⊕ ^{OOO} Very low	Critical
Bleeding (COVID)												
1 n = 426	observational studies	serious ^a	serious ^b	not serious	serious ^c	none	1/128 (0.8%)	5/298 (1.7%)	RR 0.47 (0.06 to 4.00)	9 fewer per 1,000 (from 16 fewer to 50 more)	⊕ ^{OOO} Very low	Critical
Bleeding (MIS-C)												
1 n = 138	observational studies	serious ^a	serious ^b	not serious	serious ^c	none	0/80 (0.0%)	0/58 (0.0%)	RR 0.73 (0.01 to 36.19)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕ ^{OOO} Very low	Critical
Thrombotic Events (COVID + MIS-C)												
1 n = 564	observational studies	serious ^a	serious ^b	not serious	serious ^c	none	10/208 (4.8%)	8/356 (2.2%)	RR 2.14 (0.86 to 5.34)	26 more per 1,000 (from 3 fewer to 98 more)	⊕ ^{OOO} Very low	Critical
Thrombotic Events: COVID												
1 n = 426	observational studies	serious ^a	serious ^b	not serious	serious ^c	none	3/128 (2.3%)	6/298 (2.0%)	RR 1.16 (0.29 to 4.57)	3 more per 1,000 (from 14 fewer to 72 more)	⊕ ^{OOO} Very low	Critical
Thrombotic Events: MIS-C												
1 n = 138	observational studies	serious ^a	serious ^b	not serious	serious ^c	none	7/80 (8.8%)	2/58 (3.4%)	RR 2.41 (0.52 to 11.22)	49 more per 1,000 (from 17 fewer to 352 more)	⊕ ^{OOO} Very low	Critical

CI: confidence interval; RR: risk ratio

Explanations

^aDowngraded due to high risk of bias

^bDowngraded due to substantial heterogeneity in intervention used among different patients in the study

^cWide confidence interval and low event rate

Appendix 6. Characteristics of Ongoing Studies

Title Identifier Expected completion date	Intervention	Comparator	Patients/population recruited	Outcome
COVID-19 Anticoagulation in Children – Thromboprophylaxis (COVAC-TP) Trial NCT04354155 June 4 2021 (no pre-print, no published results yet)	Enoxaparin Twice-daily low-dose	Single arm	Children (birth until 17 years of age)	Safety Efficacy

Appendix 7: Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 9)

FACTORS		JUDGEMENT (N = 9)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS	
Problem	No	Yes (9)		Varies		Uncertain			
Benefits	Large (1)	Moderate	Small	Trivial (2)	Varies (1)	Uncertain (5)		<ul style="list-style-type: none"> No significant benefit 	
Harm	Large	Moderate	Small (1)	Trivial (1)	Varies (1)	Uncertain (6)		<ul style="list-style-type: none"> No bleeding events 	
Certainty of evidence	High	Moderate		Low		Very low (9)		<ul style="list-style-type: none"> Rated very low due to high risk of bias, small sample size, low event rate, wide confidence intervals 	
Balance of effects	Favors drug	Probably favors drug (1)	Does not favor drug or no drug (4)	Probably favors no drug (1)	Favors no drug	Varies	Uncertain (3)		
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (4)		Probably no important uncertainty or variability (4)		No important uncertainty or variability			
Resources required	Uncertain (1)	Varies	Large costs	Moderate costs (8)	Negligible costs or savings	Moderate savings	Large savings	<ul style="list-style-type: none"> Enoxaparin 100mg/mL 0.4mL pre-filled syringe: Php 179.89-398.00 Enoxaparin 0.6mL pre-filled syringe: Php 195.00-465.00 Heparin 1000 IU/mL 5mL vial: Php 42.23-134.22 Heparin 5000 IU/mL 5mL vial: Php 140.00-180.00 	
Certainty of evidence of resources required	No included studies (8)		Very low	Low (1)	Moderate	High			
Cost-effectiveness	No included studies (9)	Varies	Favors the comparison	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention	Favors the intervention		
Equity	Uncertain (8)	Varies	Reduced	Probably reduced	Probably no impact (1)	Probably increased	Increased		
Acceptability	Uncertain (8)	Varies	No	Probably no (1)	Probably yes	Yes			
Feasibility	Uncertain (6)	Varies (1)	No	Probably no (1)	Probably yes (1)	Yes			

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

RECOMMENDATION
<p>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)</p> <p><i>*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.</i></p> <p><i>Consensus Issues</i></p> <p>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.</p>

RECOMMENDATION
<p>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)</p> <p><i>*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.</i></p> <p><i>Consensus Issues</i></p> <p>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.</p>

RECOMMENDATION
<p>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)</p> <p><i>*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.</i></p>

Consensus Issues

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.

RECOMMENDATION

There is insufficient evidence to recommend the use of sotrovimab as treatment of non-hospitalized children with COVID-19 infection. (Low certainty of evidence)

Consensus Issues

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.

RECOMMENDATION

We suggest against the use of sotrovimab as treatment of hospitalized children with COVID-19 infection. (Low certainty of evidence; Weak recommendation)

Consensus Issues

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.

RECOMMENDATION

We suggest against the use of amubarvimab plus romlusevimab as treatment of children with COVID-19 infection. (Low certainty of evidence; Weak recommendation)

Consensus Issues

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.

RECOMMENDATION

We suggest against the use of regdanvimab as treatment of children with COVID-19 infection. (Low certainty of evidence; Weak recommendation)

Consensus Issues

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.

Evidence Summary

Key Findings

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.

Introduction

Sotrovimab, regdanvimab, amubarvimab-romlusevimab, bamlanivimab-etesevimab, and casirivimab-imdevimab are monoclonal antibody therapies developed to neutralize SARS-CoV-2 virus. The SARS-CoV-2 virus enters human cells through binding of the surface spike glycoprotein of the virus with human cells [1]. Monoclonal antibodies inhibit the entry of SARS-CoV-2 into human cells by competitively binding with this glycoprotein [1]. These antibodies have same mechanism of action, but they differ based on which epitope or part of the virus they bind with. Casirivimab-imdevimab are examples of antibodies that target the ACE2 receptor binding domain of the virus [2]. With the emergence of new variants such as Delta and Omicron, some binding sites have been found to be more prone to mutations. Hence new drugs such as sotrovimab have been developed. Sotrovimab targets a highly conserved epitope of SARS-CoV-1 and SARS-

Cov-2 outside the ACE2 receptor binding domain and is hypothesized to have more efficacy against new variants [3,4]. This review aims to determine the efficacy and safety of anti-SARS-CoV-2 monoclonal antibody therapy on patients with COVID-19 infection.

Review Methods

We conducted a literature search for studies published in December 2019 to January 5, 2022. The inclusion criteria for choosing studies were: (1) laboratory confirmed COVID-19 infection diagnosed by RT-PCR or antigen test; (2) patients aged 18 years and below; (3) treatment arm was anti-SARS-CoV-2 monoclonal antibody; (4) comparator was either placebo or standard of care; (5) Phase 2 to Phase 3 randomized controlled studies; (6) outcomes studied were mortality, ICU admission, need for mechanical ventilation, length of hospital stay, days to recovery, viral load or cycle threshold, or worsening of symptoms; (7) any severity of COVID-19 infection.

Studies where the intervention arm was composed of a cocktail of drugs including anti-SARS-CoV-2 monoclonal antibody but used only placebo or standard of care as control were excluded.

Databases searched were Pubmed (MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), COVID-NMA, Epistemonikos, ChinaXiv, MedRxiv, BioRxiv, and Google Scholar. Registries for ongoing or completed clinical trials were also searched (Clinicaltrials.gov, ISRCTN registry, World Health Organization International Clinical Trials Registry Platform). A combined MeSH and free text search was done using the following terms: COVID-19, coronavirus, SARS-CoV-2, monoclonal antibody, bamlanivimab, etesevimab, casirivimab, imdevimab, sotrovimab, infant, child, children, and adolescents. References of all studies were reviewed to identify other studies. Searches were limited to human studies. Studies of any language or country were included.

Table 1. PICO criteria for monoclonal antibodies and COVID-19.

Population	Children with COVID-19
Intervention/Exposure	Monoclonal antibody therapy
Comparison	Standard of care, no control, placebo
Outcomes	Mortality, ICU admission, need for mechanical ventilation, length of hospital stay, days to recovery, viral load or cycle threshold, worsening of symptoms

After studies were identified, they were appraised using the critical appraisal tool from Dans et al. Painless Evidence-Based Medicine.. The certainty of evidence was evaluated through GRADE. Review Manager version 5.4 was used for meta-analysis of pooled studies. Pooling was planned if multiple studies are found per treatment.

Results

Of the 1516 records identified from the search, ten RCTs with a total of 21,542 participants were included in this review. The following monoclonal antibodies against SARS-CoV-2 were found: REGEN-CoV (casirivimab-imdevimab), bamlanivimab-etesevimab, sotrovimab, amubarvimab- romlusevimab, and regdanvimab. Five RCTs studied

casirivimab-imdevimab. Two RCTs studied bamlanivimab-etelevimab. Two RCTs studied sotrovimab, of which one RCT studied both sotrovimab and amubarvimab-romlusevimab. In that RCT, amubarvimab was referred to as BRII-196 and romlusevimab was referred to as BRII-198 [4]. One RCT studied regdanvimab. A new drug, tixagevimab-cilgavimab, has been approved by the US FDA for pre-exposure prophylaxis of COVID-19 but it will not be included in this review. The evidence regarding tixagevimab-cilgavimab has not yet been published or released as preprint. Only three RCTs included adolescents in the participants [1,2,5]. There were no published RCTs that studied treatment on children younger than 12 years old. The characteristics of included studies are reported in Appendix 3. The presentation of the results of the studies did not allow an analysis of the efficacy and safety of the intervention in children. The evidence presented in this review are derived from the Philippine Living COVID-19 clinical practice guidelines for adults. [6]

Casirivimab plus imdevimab (REGEN-CoV)

Hospitalized COVID-19 patients

The studies of Horby et al. and Somersan-Karakaya et al. enrolled hospitalized COVID-19 patients who were given either 1) IV casirivimab-imdevimab or 2) placebo or standard of care [2,7]. Both studies were still preprints. The study of Horby et al., randomized patients to either IV casirivimab-imdevimab 8 g or standard of care. It included adolescents 12 to 17 but no data were given regarding the number or outcomes of the adolescents included [2]. Outcomes were all-cause mortality, composite outcome of mechanical ventilation or death, and individual outcomes for mechanical ventilation and death. The outcomes from the Horby study were presented according to serologic status (seronegative, seropositive, and overall). The study of Somersan-Karakaya et al. randomized patients to either IV casirivimab-imdevimab (2.4 g or 8 g) or placebo [7]. Outcomes presented were composite outcome for mechanical ventilation or mortality and adverse events.

Horby et al. showed that for seronegative patients, there was decreased risk for mechanical ventilation or death when given 2.4 g casirivimab-imdevimab (RR 0.53, 95% CI 0.35-0.80) [7]. Regardless of serologic status, the intervention was equivalent to placebo for the composite outcome of mechanical ventilation or death for 8 g casirivimab-imdevimab (pooled RR 0.96, 95% CI 0.89-1.03 I²=0) [2,7]. The overall certainty of evidence was very low due to serious risk of bias, serious indirectness, and serious imprecision. It must be noted that the study was funded by the manufacturing company. No other studies done by independent researchers has been published. The GRADE evidence profile is in Appendix 5.

Safety

There was significantly lower risk of adverse events (RR 0.82, 95% CI 0.68-0.99) and serious adverse events (RR 0.77, 95% CI 0.63-0.94) in hospitalized patients given casirivimab-imdevimab CoV 2.4 g compared to placebo. Serious adverse events are defined as adverse events that cause life threatening events or death, required hospitalization or prolonged existing hospitalization. As to the casirivimab-imdevimab CoV 8 g compared to control, there was no significant difference in adverse events (RR

0.92, 95% CI 0.78-1.12) and serious adverse events (RR 0.86, 95% CI 0.71-1.04) in hospitalized patients. Nonserious adverse events were not specified. Serious adverse events included allergy, seizure, oxygen desaturation, and transient loss of consciousness. Some patients had hypotension (4% in casirivimab plus imdevimab compared to 2% in standard of care) and thrombotic events (2% in casirivimab plus imdevimab compared to 1% in standard of care).[2,7]

Non-hospitalized asymptomatic COVID-19 patients

The study by O'Brien et al., which was a preprint, involved early asymptomatic COVID-19 patients aged 12 years and above, who were diagnosed using RT-PCR [5]. Patients were given either casirivimab-imdevimab 1.2 g subcutaneously or placebo. Outcomes were proportion of patients that developed COVID-19 symptoms, duration of symptoms, at least one COVID-19-related hospitalization or ER visit, and adverse events. The results were inconclusive for the outcomes of duration of symptoms (mean difference -5.5 days, 95% CI -13.75 to 2.75) and occurrence of at least 1 COVID-19-related hospitalization or ER visit (RR 0.08, 95% CI 0-1.4). There was decreased risk of adverse events (RR 0.7, 95% CI 0.53-0.92), while for serious adverse events the results were inconclusive RR 0.11, 95% CI 0.01-2.06). Nonserious adverse events were not specified. There were no serious adverse events experienced by the casirivimab-imdevimab group. The overall certainty of evidence was low due to serious indirectness and imprecision. This study was funded by the manufacturing company. The GRADE evidence profile is in Appendix 5.

Non-hospitalized COVID-19 patients (regardless if asymptomatic or symptomatic)

Two studies by Weinreich et al. involved adult outpatient COVID-19 patients [8,9]. The Phase 1-2 results of the trial were available as a preprint [8]. The Phase 3 results of the trial have been published [9]. In the Phase 1-2, patients were given intravenous casirivimab-imdevimab (2.4 g or 8 g) or placebo. In the Phase 3 trial, patients were given intravenous casirivimab-imdevimab (1.2 g, 2.4 g, or 8 g) or placebo. Patients in the phase 3 trial had at least 1 risk factor for severe COVID-19 infection (see Appendix 3). Outcomes were COVID-19 related hospitalization or all cause mortality, time to symptom resolution, proportion of patients with hospitalization, need for mechanical ventilation or ICU admission, and adverse events.

There was significantly decreased risk of COVID-related hospitalization, ER visit or all-cause mortality in patients given 1.2 g casirivimab-imdevimab compared to control (RR 0.27, 95% CI 0.13-0.56). There was inconclusive evidence for the outcome of need for mechanical ventilation (RR 0.51, 95% CI 0.05-5.59) and ICU admission (RR 0.44, 95% CI 0.11-1.68).[9]

There was significantly decreased risk of COVID-related hospitalization, ER visit or all-cause mortality in patients given 2.4 g casirivimab-imdevimab (pooled RR 0.36, 95% CI 0.24-0.54, $I^2=0$), as well as ICU admission (RR 0.33, 95% CI 0.13-0.83). There was inconclusive evidence for the outcome of need for mechanical ventilation (RR 0.16, 95% CI 0.02-1.37).[8,9]

There was decreased risk of COVID-related hospitalization, ER visit or all-cause mortality in patients given 8 g casirivimab-imdevimab (pooled RR 0.37, 95% CI 0.21-0.62, $I^2=0$). There was no specific data for the outcomes of need for mechanical ventilation and ICU admission for the 8 g dose. [8,9]

The overall certainty of evidence was low due to serious indirectness and imprecision. The two studies were funded by the manufacturing company. The GRADE evidence profile is in Appendix 5.

Safety

There was decreased risk of serious adverse events in the casirivimab-imdevimab group, regardless of the dose (RR 0.27; 95% CI 0.14-0.54) [6]. The pooled RR for casirivimab-imdevimab 2.4 g and 8 g were 0.35 (95% CI 0.23-0.54 $I^2=15$) and 0.41 (95% CI 0.25-0.67 $I^2=0$), respectively [6,8]. Most common adverse events were infusion-related reactions or complications of COVID-19. There were two treatment-emergent adverse events leading to death: one presenting with dyspnea and the other presenting with hypoxia.[8,9]

Bamlanivimab plus etesevimab

The studies of Dougan et al. and Gottlieb et al. compared the efficacy of IV bamlanivimab 2.8 g plus etesevimab 2.8 g compared to placebo on non-hospitalized COVID-19 patients [1,10]. The study by Dougan et al. involved patients aged 12 years and above with risk factor for severe COVID-19, but no results specific for adolescents were provided [1]. The outcomes were COVID-19 related hospitalization or all-cause mortality, time to resolution of symptoms, and adverse events. The study by Gottlieb et al. only involved adult patients with mild to moderate COVID-19 infection [10]. Outcomes were change in viral load, time to recovery, COVID-19 related hospitalization or all-cause mortality, and adverse events.

There was a decreased risk of COVID-19 related hospitalization and deaths (pooled RR 0.28, 95% CI 0.15-0.53 $I^2=0$). There was no significant difference in adverse events (pooled RR 0.87, 95% CI 0.49-1.57 $I^2=75$) and serious adverse events (RR 1.4, 95% CI 0.49-4.01 $I^2=0$) between placebo and treatment. Most common adverse events included nausea, rash/pruritus, and dizziness. The serious adverse events in the Dougan et al. study were not specified. The serious adverse event in the Gottlieb et al. study was a urinary tract infection which was considered unrelated to study drug by the investigators. The overall certainty of evidence was low due to serious indirectness and imprecision. Both studies were funded by the manufacturing company. The GRADE evidence profile is in Appendix 5. [1,10]

Sotrovimab

In the studies of Gupta et al. and Self et al., adult COVID-19 patients were given either IV sotrovimab 500 mg or control [3,4]. The study of Gupta et al. involved non-hospitalized patients with mild to moderate COVID-19 infection but with risk factors [3]. Risk factors included were age ≥ 55 years old, diabetes, obesity, chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, and moderate to severe asthma. The control was standard of care. The outcomes were hospitalization or all-cause mortality, adverse events, requirement for supplemental oxygen, mechanical ventilation or ICU admission. The study by Self et al. involved hospitalized patients [4]. The control

was placebo. The outcomes were time to clinical recovery, all-cause mortality, and composite safety outcome of death, serious adverse events, organ failure, and serious coinfection.

Hospitalized COVID-19 patients

For hospitalized patients, there was inconclusive evidence for the outcomes of need for mechanical ventilation (RR 0.65, 95% CI 0.11-3.86) and all-cause mortality (RR 1.05, 95% CI 0.51-2.18). The intervention was equivalent to placebo for the outcome of need for supplemental oxygen (RR 0.9, 95% CI 0.71-1.15). There was no significant difference between sotrovimab and placebo in the outcomes of composite safety outcome (RR 0.88, 95% CI 0.64-1.2) and incidence of infusion reactions (RR 1.26, 95% CI 0.65-2.45). One patient had anaphylaxis. The overall certainty of evidence was low due to serious indirectness and imprecision. The GRADE evidence profile is in Appendix 5. [4]

Non-hospitalized COVID-19 patients

For non-hospitalized patients, sotrovimab significantly decreased the risk for hospitalization (RR 0.14, 95% CI 0.04-0.48) and need for supplemental oxygen (RR 0.11, 95% CI 0.02-0.45). There was inconclusive evidence for the outcomes of need for mechanical ventilation (RR 0.2, 95% CI 0.01-4.16), ICU admission (RR 0.09, 95% CI 0.01-1.64), and all-cause mortality (RR 0.33, 95% CI 0.01-8.18). There was no significant difference in adverse events (RR 0.87, 95% CI 0.66-1.16). Most common adverse event that occurred was diarrhea. One patient had infusion-related reaction (dyspnea). There was decreased risk of serious adverse events (RR 0.27, 95% CI 0.12-0.63). Serious adverse events were hospitalization for COVID-19-related causes. The overall certainty of evidence was low due to serious indirectness and imprecision. This study was funded by the manufacturing company. The GRADE evidence profile is in Appendix 5. [3]

Amubarvimab plus romlusevimab

In one study, adult COVID-19 patients were given either IV combination of amubarvimab 1 g plus romlusevimab 1 g or placebo. The study involved hospitalized patients. The outcomes were time to clinical recovery, all-cause mortality, and composite safety outcome of death, serious adverse events, organ failure, and serious coinfection. The intervention was equivalent to placebo for the outcome of need for supplemental oxygen (RR 0.9, 95% CI 0.7-1.15). There was inconclusive evidence for the outcomes of need for mechanical ventilation (RR 1.35, 95% CI 0.31 to 5.94) and all-cause mortality (RR 1.17, 95% CI 0.57-2.38). There was no significant difference between treatment and placebo for the composite safety outcome (RR 1.03, 95% CI 0.76-1.39) and incidence of infusion reactions (RR 1.66, 95% CI 0.88-3.12). One patient had anaphylaxis. The overall certainty of evidence was low due to serious indirectness and imprecision. The GRADE evidence profile is in Appendix 5. [4]

Regdanvimab

The study by Eom et al., which was a preprint, involved IV regdanvimab. It enrolled adult patients with mild to moderate COVID-19 infection [11]. Patients were given either 40 mg/kg or 80 mg/kg IV regdanvimab or placebo. We analyzed 40 mg/kg regdanvimab versus placebo, basing from the evidence summary in the Philippine adult living COVID-

19 clinical practice guidelines [6]. Outcomes were proportion of patients with clinical recovery at days 7, 14, and 28, requirement for hospitalization, oxygen therapy, mechanical ventilation, ICU admission, rescue therapy (use of other anti-SARS-CoV-2 therapy indicating worsening of symptoms), and all-cause mortality.

The results were inconclusive for the outcomes of hospitalization (RR 0.45; 95% CI 0.14-1.42), need for supplemental oxygen (RR 0.45; 95% CI 0.14-1.42), requirement for rescue therapy (RR 0.48; 95% CI 0.2-1.12), and total adverse events (RR 0.91; 95% CI 0.65-1.29). None of the patients required mechanical ventilation or ICU admission. There was no mortality as well. The most common adverse event was hypertriglyceridemia. One patient had infusion-related reaction, which was fever and dyspnea. The overall certainty of evidence was low due to serious indirectness and imprecision. This study was funded by the manufacturing company. The GRADE evidence profile is in Appendix 5. [11]

There are seven ongoing randomized controlled trials involving children. We plan to include results of these randomized controlled trials once available.

Enrollment of participants in the studies included in this review were done from second half of 2020 until May 2021 [1-5,7-11]. With the emergence of new SARS-CoV-2 variants of concern, the newer variants may be resistant against the currently available anti-SARS-CoV-2 monoclonal antibodies. In November 2021, a new variant of concern, the Omicron variant, was first detected and in January 2022, it has become the dominant variant in the Philippines [12, 13]. In vitro studies showed resistance of the Omicron variant to casirivimab plus imdevimab and bamlanivimab plus etesevimab [14, 15]. Since all studies included in this review were done prior to the detection of the Omicron variant, the results of the studies may not be applicable in the current times.

Other Considerations (Evidence to Decision)

The essential elements of the evidence-to-decision framework are presented in Appendix 7.

Recommendations from Other Groups

Table 2. Summary of Recommendations from Other Groups

Group	Recommendation
Philippine Adult Living COVID-19 CPG Jan. 10, 2022 [6]	<p>For Adults:</p> <p>Bamlanivimab and etesevimab combination was suggested for treatment for mild to moderate, non-hospitalized COVID-19 patients with at least 1 risk factor* for progression to severe disease. (<i>Low quality of evidence; Weak recommendation</i>)</p> <p><i>*Risk factors for severe COVID-19: age ≥65 years, body-mass index ≥35 kg/m², 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.</i></p>

	<p>Casirivimab plus imdevimab was suggested as treatment for symptomatic, non-hospitalized patients with at least 1 risk factor* for severe COVID-19. (Moderate certainty of evidence; Weak recommendation)</p> <p><i>*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.</i></p> <p>Subcutaneous use of casirivimab + imdevimab was suggested as day 4 post-exposure prophylaxis for COVID-19 <u>close contacts*</u>, ages 12 years and above weighing at least 40 kilograms, who are <u>at risk for severe disease or hospitalization**</u>. (Moderate certainty of evidence; weak recommendation)</p> <p><i>**This includes the following people: elderly; BMI >25; those with chronic diseases such as hypertension, diabetes, and chronic kidney disease; those who are not expected to mount an adequate immune response to the vaccine due to immunosuppressive therapy or those in an immunocompromised state.</i></p>
WHO Dec. 7, 2021 [16]	No specific recommendations for children and adolescents
American Academy of Pediatrics Feb. 13, 2022 [17]	<p>Use of SARS-CoV-2 mAb for all indications remains investigational in children and adolescents.</p> <p>An individual risk/benefit assessment should be performed when considering mAb for a child/adolescent who is at high risk for COVID-19.</p> <p>Sotrovimab and tixagevimab copackaged with cilgavimab (Evusheld) are the only mAb anticipated to have retained neutralizing activity against the SARS-CoV-2 Omicron variant.</p> <p>Only high-risk children ≥ 12 yo and ≥ 40 kg would be eligible to receive sotrovimab or tixagevimab and cilgavimab (Evusheld) if they meet the following criteria:</p> <p style="padding-left: 40px;">A. Sotrovimab for COVID-19 treatment:</p> <p style="padding-left: 80px;">Non-hospitalized patient ≥ 12 yo and ≥ 40 kg, and Mild to moderate COVID-19, and Within 10 days of symptom onset, and High risk for progressing to severe COVID-19 and/or hospitalization</p>

	(2) Tixagevimab and cilgavimab (Evusheld) for COVID-19 preexposure prophylaxis: ≥12 years of age and ≥40 kg, and No SARS-CoV-2 infection or exposure, and Moderate or severe immunocompromised or vaccination is contraindicated
US NIH Jan 19, 2022 [18]	<p>For children:</p> <p>There is insufficient evidence for the Panel to recommend either for or against the use of anti-SARS-CoV-2 monoclonal antibody products for children with COVID-19 who are not hospitalized but who have risk factors for severe disease.</p> <p>For adults:</p> <p>The Panel recommends against the use of bamlanivimab plus etesevimab and casirivimab plus imdevimab for high risk, non-hospitalized patients with mild to moderate COVID-19 due to reduced activity against Omicron variant.</p> <p>The Panel recommends using sotrovimab to treat non-hospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression.</p> <p>The Panel recommends using tixagevimab plus cilgavimab as pre-exposure prophylaxis for adults and adolescents (aged ≥12 years and weighing ≥40 kg) for: (1) moderately to severely immunocompromised and; (2) not able to be fully vaccinated due to a history of severe reactions to a COVID-19 vaccine or any of its components.</p>
Australian National COVID-19 Clinical Evidence Taskforce Dec 22, 2021 [19]	<p>Recommendations are not based on evidence but on consensus</p> <p>Consensus recommendations:</p> <p>Consider using, in exceptional circumstances, casirivimab plus imdevimab within 7 days of symptom onset in <i>children and adolescents aged 12 years and over and weighing at least 40 kg with mild COVID-19</i> who are at high risk of deterioration.</p> <p>Consider using, in exceptional circumstances, casirivimab plus imdevimab in <i>seronegative children and adolescents aged 12 years and over and weighing at least 40 kg with moderate to critical COVID-19</i> who are at high risk of disease progression.</p>
Philippine Adult Living COVID-19 CPG Jan. 10, 2022 [6]	<p>For Adults:</p> <p>Bamlanivimab and etesevimab combination was suggested for treatment for mild to moderate, non-hospitalized COVID-19 patients with at least 1 risk factor*</p>

	<p>for progression to severe disease. (<i>Low quality of evidence; Weak recommendation</i>)</p> <p><i>*Risk factors for severe COVID-19: age ≥65 years, body-mass index ≥35 kg/m², 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.</i></p> <p>Casirivimab plus imdevimab was suggested as treatment for symptomatic, non-hospitalized patients with at least 1 risk factor* for severe COVID-19. (<i>Moderate certainty of evidence; Weak recommendation</i>)</p> <p><i>*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.</i></p> <p>Subcutaneous use of casirivimab + imdevimab was suggested as day 4 post-exposure prophylaxis for COVID-19 <u>close contacts</u>*, ages 12 years and above weighing at least 40 kilograms, who are <u>at risk for severe disease or hospitalization</u>**. (<i>Moderate certainty of evidence; weak recommendation</i>)</p> <p><i>**This includes the following people: elderly; BMI >25; those with chronic diseases such as hypertension, diabetes, and chronic kidney disease; those who are not expected to mount an adequate immune response to the vaccine due to immunosuppressive therapy or those in an immunocompromised state.</i></p>
WHO Dec. 7, 2021 [16]	No specific recommendations for children and adolescents
American Academy of Pediatrics Feb. 13, 2022 [17]	<p>Use of SARS-CoV-2 mAb for all indications remains investigational in children and adolescents.</p> <p>An individual risk/benefit assessment should be performed when considering mAb for a child/adolescent who is at high risk for COVID-19.</p> <p>Sotrovimab and tixagevimab copackaged with cilgavimab (Evusheld) are the only mAb anticipated to have retained neutralizing activity against the SARS-CoV-2 Omicron variant.</p> <p>Only high-risk children ≥12 yo and ≥40 kg would be eligible to receive sotrovimab or tixagevimab and cilgavimab (Evusheld) if they meet the following criteria:</p>

	<p>30. Sotrovimab for COVID-19 treatment:</p> <p>Non-hospitalized patient ≥ 12 yo and ≥ 40 kg, and Mild to moderate COVID-19, and Within 10 days of symptom onset, and High risk for progressing to severe COVID-19 and/or hospitalization</p> <p>(2) Tixagevimab and cilgavimab (Evusheld) for COVID-19 preexposure prophylaxis: ≥ 12 years of age and ≥ 40 kg, and No SARS-CoV-2 infection or exposure, and Moderate or severe immunocompromised or vaccination is contraindicated</p>
US NIH Jan 19, 2022 [18]	<p>For children:</p> <p>There is insufficient evidence for the Panel to recommend either for or against the use of anti-SARS-CoV-2 monoclonal antibody products for children with COVID-19 who are not hospitalized but who have risk factors for severe disease.</p> <p>For adults:</p> <p>The Panel recommends against the use of bamlanivimab plus etesevimab and casirivimab plus imdevimab for high risk, non-hospitalized patients with mild to moderate COVID-19 due to reduced activity against Omicron variant.</p> <p>The Panel recommends using sotrovimab to treat non-hospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression.</p> <p>The Panel recommends using tixagevimab plus cilgavimab as pre-exposure prophylaxis for adults and adolescents (aged ≥ 12 years and weighing ≥ 40 kg) for: (1) moderately to severely immunocompromised and; (2) not able to be fully vaccinated due to a history of severe reactions to a COVID-19 vaccine or any of its components.</p>
Australian National COVID-19 Clinical Evidence Taskforce Dec 22, 2021 [19]	<p>Recommendations are not based on evidence but on consensus</p> <p>Consensus recommendations:</p> <p>Consider using, in exceptional circumstances, casirivimab plus imdevimab within 7 days of symptom onset in <i>children and adolescents aged 12 years and over and weighing at least 40 kg with mild COVID-19 who are at high risk of deterioration</i>.</p>

	Consider using, in exceptional circumstances, casirivimab plus imdevimab in seronegative children and adolescents aged 12 years and over and weighing at least 40 kg with moderate to critical COVID-19 who are at high risk of disease progression.
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Research Gaps

There are limited trials studying the efficacy of monoclonal antibodies for treatment of children with COVID-19. Studies that have been published were mostly composed of adult patients. Some studies that included adolescents in their population did not publish the outcomes specific for the adolescents. There are seven (7) ongoing trials studying monoclonal antibodies as treatment specifically for children with COVID-19 (Appendix 6).

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Evidence Summary Appendices

Appendix 1. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	((("Child"[Mesh] OR "Child, Preschool"[Mesh] OR "Adolescent"[Mesh] OR "Infant"[Mesh]) OR (children[tiab]) OR (adolescent[tiab])) AND ((COVID-19"[Mesh] OR (COVID-19[tiab]) OR (coronavirus[tiab]) OR (SARS-CoV-2[tiab]))) AND ((Antibodies, Monoclonal"[Mesh]) OR (bamlanivimab[tiab]) OR (etesevimab[tiab]) OR (casirivimab[tiab]) OR (imdevimab[tiab]) OR (sotrovimab[tiab])))	Jan. 9, 2022	112	3
CENTRAL	Mesh of COVID-19 AND monoclonal antibody AND child	Jan. 9, 2022	3	1
COVID-NMA Initiative	Treatment name: monoclonal antibodies	Jan. 9, 2022	58	6
Google Scholar	Monoclonal antibody AND COVID-19 AND children AND randomized controlled trial	Jan. 9, 2022	895	0
Epistemonikos	(title:(covid-19) OR abstract:(covid-19)) AND (title:(children) OR abstract:(children)) AND (title:(monoclonal antibody) OR abstract:(monoclonal antibody))	Jan. 9, 2022	9	0
<hr/>				
ClinicalTrials.gov	condition:covid-19 age:children intervention:monoclonal antibody	Jan. 9, 2022	17	8
Chinese Clinical Trial Registry	Monoclonal antibody	Jan. 9, 2022	0	0
WHO trials ITCRP	Monoclonal antibody AND COVID-19 Search filter: clinical trials in children	Jan. 9, 2022	2	1
<hr/>				
Chinaxiv.org	Monoclonal antibody AND COVID-19 AND children	Jan. 9, 2022	0	0
Medrxiv.org	Children AND COVID-19 AND “monoclonal antibody”	Jan. 9, 2022	357	1
Medrxiv.org	Casirivimab AND children AND COVID-19	Jan. 9, 2022	25	0
Medrxiv.org	Bamlanivimab AND children AND COVID-19	Jan. 9, 2022	30	0
Medrxiv.org	Sotrovimab AND children AND COVID-19	Jan. 9, 2022	8	0
Biorxiv.org	Monoclonal antibody AND COVID-19 AND children	Jan. 9, 2022	0	0

Appendix 2. Characteristics of Included Studies

Casirivimab plus imdevimab (REGEN-CoV)

Author	Study design	Population and Duration of Follow-up	Intervention	Control	Outcomes
Horby et al. Preprint	RCT Open-label, platform design	Age: 12 years and above Confirmed COVID- 19 patients admitted to the hospitals N=11,464 Follow up: 28 days	Casirivimab plus imdevimab 8000mg cocktail IV	Standard of care	PRIMARY: All-cause mortality SECONDARY: Discharge alive from hospital, use of invasive ventilation among patients, serious adverse events
O'Brien et al. Preprint	RCT	Age: 12 years and above Asymptomatic individuals with known exposure to COVID-19, tested positive for COVID- 19 at baseline N = 314 Follow up: 28 days efficacy assessment, 7 month follow up	Casirivimab plus imdevimab 1200mg cocktail SC	Placebo	PRIMARY: Development of COVID-19 symptoms SECONDARY: Duration of COVID-19 symptoms, number of weeks of high viral load, safety
Somersan-Karakaya et al. Preprint	RCT	Age: 18 years and above Hospitalized COVID-19 patients with little to no oxygen support N = 1336 Follow up: 169 days	Casirivimab plus imdevimab 2400mg cocktail IV Casirivimab plus imdevimab 8000mg cocktail IV	Placebo	PRIMARY: Time-weighted average (TWA) daily change from baseline viral load until day 7, progression of disease (need for invasive mechanical ventilation or death) SECONDARY: All-cause mortality, discharge from/readmission to hospital, safety
Weinreich et al. Published	RCT	Age: 18 years and above Ambulatory confirmed COVID-19 patients with ≥ 1 risk factor for severe COVID-19 Risk factors: >50 yo, obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic meta-bolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and an immunocompromised condition (immunosuppression or receipt of immunosuppressants) N = 4,057 Follow up: 29 days	Casirivimab plus imdevimab 1200mg cocktail IV Casirivimab plus imdevimab 2400mg cocktail IV Casirivimab plus imdevimab 8000mg cocktail IV	Placebo	PRIMARY: COVID-19 related hospitalization or all-cause death SECONDARY: Time to symptom resolution, adverse events

Weinreich et al. Preprint	RCT	Age: 18 years and above Non-hospitalized COVID-19 patients N= 799 Follow up: 29 days	Casirivimab plus imdevimab 2400mg cocktail IV Casirivimab plus imdevimab 8000mg cocktail IV	Placebo	PRIMARY: TWA change in viral load from baseline through day 7 SECONDARY: At least 1 COVID-19- related medically- attended visit (MAV), safety
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Bamlanivimab plus etesevimab

Author	Study design	Population	Intervention	Control	Outcomes
Gottlieb et al.	RCT	Age: 18 years and above Non-hospitalized confirmed COVID-19 patients with mild to moderate symptoms N=268 Follow up: 29 days	Bamlanivimab 2800 mg + Etesevimab 2800 mg IV	Placebo	PRIMARY: Change in SARS- CoV-2 log viral load at day 11 SECONDARY: Time to viral clearance, time to clinical recovery, COVID-19 related hospitalization or all- cause death, adverse events
Dougan et al.	RCT	Age: 12 years and above Ambulatory confirmed COVID-19 patients with ≥ 1 risk factor for severe COVID-19 Risk factors: BMI \geq 85th percentile for age and sex, according to CDC growth charts; sickle cell disease; congenital or acquired heart disease; neurodevelopmental disorders such as cerebral palsy; dependence on a medical-related mechanical device or procedure such as tracheostomy, gastrostomy, or positive-pressure ventilation (not related to Covid-19); asthma, a reactive airway, or another chronic respiratory disease; type 1 or type 2 diabetes mellitus; and an immunocompromised condition or receipt of an immunosuppressive treatment N=1035 Follow up: 29 days	Bamlanivimab 2800 mg + Etesevimab 2800 mg IV	Placebo	PRIMARY: COVID-19 related hospitalization or all-cause death SECONDARY: Time to sustained patient-reported resolution of symptoms, reduction in viral load, time to viral clearance, adverse events

Sotrovimab and Ambuarvimab plus romlusevimab

Author	Study design	Population	Intervention	Control	Outcomes
Gupta et al.	RCT	<p>Age: 18 years and above Mild to moderate High risk, non-hospitalized COVID-19 patients</p> <p>Risk factors: Older age (≥ 55 years), diabetes, obesity, CKD, CHF, COPD, moderate to severe asthma</p> <p>N=583</p> <p>Follow up: 168 days</p>	IV Sotrovimab 500 mg	Placebo	<p>Primary: Hospitalization or All cause mortality through day 29</p> <p>Secondary: Emergency department visit, requirement for supplemental oxygen</p> <p>Safety: Adverse events</p> <p>FF up 72 days</p>
Self et al.	RCT	<p>Adults (≥ 18 yo) hospitalized COVID-19 patients</p> <p>N=546</p> <p>Follow up: 90 days</p>	<p>IV single dose Sotrovimab 500 mg</p> <p>Amubarvimab (BRII-196) 1000mg plus Rомнusevimab (BRII-198) 1000mg</p>	Placebo	<p>Primary: Time to clinical recovery</p> <p>Secondary: all cause mortality, time to discharge</p> <p>Safety: composite of death, serious adverse events, organ failure, serious coinfection</p>

Regdanvimab

Author	Study design	Population	Intervention	Control	Outcomes
Eom et al. 2021 Preprint	RCT	<p>Age ≥ 18 years, with COVID-19 infection mild to moderate infection</p> <p>N=307</p> <p>Follow up: 180 days</p>	Regdanvimab at 2 doses (40 mg/kg and 80 mg/kg) as IV infusion, single dose	Matching placebo	<p>Time to conversion to negative RT PCR; Time to clinical recovery ; Proportion of patients with clinical recovery; Proportion of patients requiring hospitalization, oxygen therapy, mechanical ventilation, ICU admission, or rescue therapy; All cause mortality; Proportion of patients with conversion to negative RT PCR</p>

Appendix 3. Detailed Study Appraisal

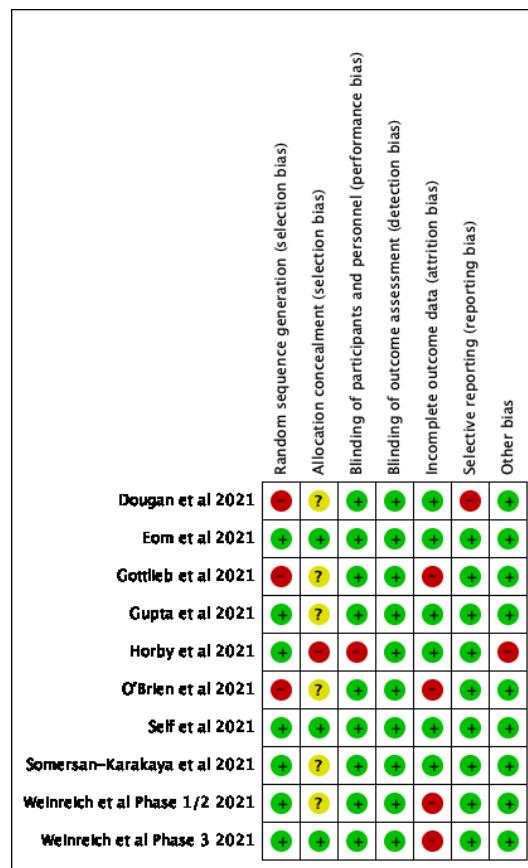


Fig. 1. Risk of bias summary table

Dougan et al. 2021

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. Adolescents were included in patients but the outcomes were not reported specifically for adolescents.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	It was not indicated.
3. Were baseline characteristics similar at the start of the trial?	No. There were more patients with <96% O2 saturation in the placebo group (90/516 or 20.6%) than treatment group (106/514 or 17.4%).
2. Were patients blinded to treatment assignment?	Yes
3. Were caregivers blinded to treatment assignment?	No
4. Were outcome assessors blinded to treatment assignment?	Yes
5. Were all patients analyzed in the groups to which they were originally randomized?	Yes
6. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

Eom et al. 2021

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. The patient population was only composed of adults.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	Yes
3. Were baseline characteristics similar at the start of the trial?	Yes
7. Were patients blinded to treatment assignment?	Yes
8. Were caregivers blinded to treatment assignment?	Yes
9. Were outcome assessors blinded to treatment assignment?	Yes
10. Were all patients analyzed in the groups to which they were originally randomized?	Yes
11. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

Gottlieb et al. 2021

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. The patient population was only composed of adults.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	No. It was not mentioned.
3. Were baseline characteristics similar at the start of the trial?	No. Patients ≥ 65 years old were greater in placebo (23/156 or 14.7%) than in treatment (13/112 or 11.6%). Patients with BMI ≥ 30 but <40 were greater in placebo (63/152 or 41.4%) than in treatment (33/109 or 30.3%). Patients with risk factors for severe COVID-19 were greater in placebo (105/156 or 67.3%) than in treatment (67/112 or 59.8%)
12. Were patients blinded to treatment assignment?	Yes
13. Were caregivers blinded to treatment assignment?	No
14. Were outcome assessors blinded to treatment assignment?	Yes
15. Were all patients analyzed in the groups to which they were originally randomized?	No
16. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

Gupta et al. 2021

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. The patient population was only composed of adults.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	No. It was not mentioned.
3. Were baseline characteristics similar at the start of the trial?	Yes
17. Were patients blinded to treatment assignment?	Yes
18. Were caregivers blinded to treatment assignment?	No
19. Were outcome assessors blinded to treatment assignment?	Yes

20. Were all patients analyzed in the groups to which they were originally randomized?	Yes
21. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

Horby et al. 2021

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. Adolescents were included in patients but the outcomes were not reported specifically for adolescents.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	No. This trial was open-label.
3. Were baseline characteristics similar at the start of the trial?	Yes
22. Were patients blinded to treatment assignment?	No. This is an open-label, platform trial with factorial design. Interactions between treatment can make it difficult to identify if outcome is due to the casirivimab plus imdevimab or due to other treatments the patients received.
23. Were caregivers blinded to treatment assignment?	No
24. Were outcome assessors blinded to treatment assignment?	Yes
25. Were all patients analyzed in the groups to which they were originally randomized?	Yes
26. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

O'Brien et al. 2021

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. Adolescents were included in patients but the outcomes were not reported specifically for adolescents.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	No. It was not mentioned.
3. Were baseline characteristics similar at the start of the trial?	No. There were more patients \geq 65 years of age (13/106 or 12.5% vs 8/101 or 8%), with diabetes (11/106 or 10.6% vs 5/101 or 5%), and with chronic lung disease (10/106 or 9.6% vs 1/101 or 1%) in the placebo group than in the casirivimab plus imdevimab group.
27. Were patients blinded to treatment assignment?	Yes
28. Were caregivers blinded to treatment assignment?	No
29. Were outcome assessors blinded to treatment assignment?	Yes
30. Were all patients analyzed in the groups to which they were originally randomized?	No
31. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

Self et al. 2021

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. The patient population was only composed of adults.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	Yes

3. Were baseline characteristics similar at the start of the trial?	Yes
32. Were patients blinded to treatment assignment?	Yes
33. Were caregivers blinded to treatment assignment?	No
34. Were outcome assessors blinded to treatment assignment?	Yes
35. Were all patients analyzed in the groups to which they were originally randomized?	Yes
36. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

Somersan-Karakaya et al. 2021

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. The patient population was only composed of adults.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	No. It was not mentioned.
3. Were baseline characteristics similar at the start of the trial?	Yes
37. Were patients blinded to treatment assignment?	Yes
38. Were caregivers blinded to treatment assignment?	No
39. Were outcome assessors blinded to treatment assignment?	Yes
40. Were all patients analyzed in the groups to which they were originally randomized?	Yes
41. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

Weinreich et al. 2021 (Phase 1/2)

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. The patient population was only composed of adults.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	No. It was not mentioned.
3. Were baseline characteristics similar at the start of the trial?	Yes
42. Were patients blinded to treatment assignment?	Yes
43. Were caregivers blinded to treatment assignment?	No
44. Were outcome assessors blinded to treatment assignment?	Yes
45. Were all patients analyzed in the groups to which they were originally randomized?	No
46. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

Weinreich et al. 2021 (Phase 3)

Appraising Directness	
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	No. The patient population was only composed of adults.
Appraising Validity	
1. Were patients randomly assigned to treatment groups?	Yes
2. Was allocation concealed?	Yes
3. Were baseline characteristics similar at the start of the trial?	Yes
47. Were patients blinded to treatment assignment?	Yes
48. Were caregivers blinded to treatment assignment?	No
49. Were outcome assessors blinded to treatment assignment?	Yes
50. Were all patients analyzed in the groups to which they were originally randomized?	No
51. Was follow-up rate adequate?	Yes
Appraising Results	
1. How large was the effect of treatment?	See GRADE Evidence Profile
2. How precise was the estimate of the treatment effect?	

Appendix 4A. GRADE Evidence Profile: Casirivimab-imdevimab (hospitalized)

Author(s): Furqaan I. Lim, MD

Question: Should intravenous casirivimab plus imdevimab (REGEN-CoV) compared to standard of care be used as treatment for COVID-19 in hospitalized children?

Setting:

Bibliography:

Horby PW & Landray MJ. Casirivimab and imdevimab in patients admitted to hospital with COVID- 19 (RECOVERY): a randomized, controlled, open-label, platform trial. 2021. Preprint. 10.1101/2021.6.15.21258542.

Somersan-Karakaya S, Mylonakis E, Menon VP, Wells JC, Ali S, Sivapalasingam S, et al. REGEN- COV for Treatment of Hospitalized Patients with Covid-19. 2021. Preprint. 10.1101/2021.11.05.21265656.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Casirivimab-imdevimab	standard of care	Relative (95% CI)	Absolute (95% CI)		
mechanical ventilation or mortality 2.4g (seronegative patients only)												
1	randomised trials	not serious	not serious	serious ^a	not serious	none	32/406 (7.9%)	58/393 (14.8%)	RR 0.53 (0.35 to 0.80)	69 fewer per 1,000 (from 96 fewer to 30 fewer)		CRITICAL
adverse events 2.4g												
1	randomised trials	not serious	not serious	serious ^a	not serious	none	149/672 (22.2%)	180/667 (27.0%)	RR 0.82 (0.68 to 0.99)	49 fewer per 1,000 (from 86 fewer to 3 fewer)		IMPORTANT
serious adverse events 2.4g												
1	randomised trials	not serious	not serious	serious ^a	not serious	none	135/672 (20.1%)	174/667 (26.1%)	RR 0.77 (0.63 to 0.94)	60 fewer per 1,000 (from 97 fewer to 16 fewer)		CRITICAL
mechanical ventilation or mortality 8g (regardless of serologic status)												
2	randomised trials	serious ^b	not serious	serious ^c	serious ^d	none	1139/4954 (23.0%)	1209/5035 (24.0%)	RR 0.96 (0.89 to 1.03)	10 fewer per 1,000 (from 26 fewer to 7 more)		CRITICAL
adverse events 8g												
1	randomised trials	not serious	not serious	serious ^a	serious ^d	none	168/668 (25.1%)	180/667 (27.0%)	RR 0.93 (0.78 to 1.12)	19 fewer per 1,000 (from 59 fewer to 32 more)		IMPORTANT

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Casirivimab-imdevimab	standard of care	Relative (95% CI)	Absolute (95% CI)		
serious adverse events 8g												
1	randomised trials	not serious	not serious	serious ^a	serious ^d	none	150/668 (22.5%)	174/667 (26.1%)	RR 0.86 (0.71 to 1.04)	37 fewer per 1,000 (from 76 fewer to 10 more)		CRITICAL

CI: confidence interval; RR: risk ratio

Explanations

- a. Population studied were adults only
- b. One study had a factorial design.
- c. Population studied were adults and adolescents
- d. The results include the line of null effect

Appendix 4B. GRADE Evidence Profile: Casirivimab-imdevimab (asymptomatic)

Author(s): Furqaan I. Lim, MD

Question: Should subcutaneous casirivimab plus imdevimab (REGEN-CoV) compared to placebo be used as treatment for COVID-19 in non-hospitalized asymptomatic children?

Setting:

Bibliography:

O'Brien MP, Forleo-Neto E, Sarkar N, Isa F, Hou P, et al. Subcutaneous REGEN-COV Antibody Combination in Early Asymptomatic SARS-CoV-2 Infection: A Randomized Controlled Trial. 2021. Preprint. 10.1101/2021.06.14.21258569.

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Casirivimab-imdevimab	placebo	Relative (95% CI)	Absolute (95% CI)		
duration of symptoms												
1	randomised trials	not serious	not serious	serious ^b	serious ^c	none	100	104	-	MD 5.5 lower (13.75 lower to 2.75 higher)		IMPORTANT
at least 1 COVID-related hospitalization or ER visit 1.2g												
1	randomised trials	not serious	not serious	serious ^a	serious ^c	none	0/100 (0.0%)	6/104 (5.8%)	RR 0.08 (0.00 to 1.40)	53 fewer per 1,000 (from - to 23 more)		IMPORTANT
adverse events 1.2g												
1	randomised trials	not serious	not serious	serious ^b	not serious	none	52/155 (33.5%)	75/156 (48.1%)	RR 0.70 (0.53 to 0.92)	144 fewer per 1,000 (from 226 fewer to 38 fewer)		IMPORTANT
serious adverse event 1.2g												
1	randomised trials	not serious	not serious	serious ^a	serious ^c	none	0/155 (0.0%)	4/156 (2.6%)	RR 0.11 (0.01 to 2.06)	23 fewer per 1,000 (from 25 fewer to 27 more)		CRITICAL

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

a. The population studied were adults only

b. The population studied were adults and adolescents

c. There is a wide confidence interval

Appendix 4C. GRADE Evidence Profile: Casirivimab-imdevimab (non-hospitalized)

Author(s): Furqaan I. Lim, MD

Question: Should intravenous casirivimab plus imdevimab (REGEN-CoV) compared to placebo be used as treatment for COVID-19 in non-hospitalized children?

Setting:

Bibliography:

Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19. N Engl J Med [Internet]. 2021 Sep 29 [cited 2021 Oct 10]; Available from <https://doi.org/10.1056/NEJMoa2108163>

Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV Antibody Cocktail in Outpatients with Covid-19. 2021. Preprint. 10.1101/2021.06.09.21257915.

Nº of studies	Study design	Certainty assessment					Casirivimab-imdevimab	placebo	Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			Relative (95% CI)	Absolute (95% CI)		
COVID-related hospitalization, ER visit or all cause mortality (1.2 g)												
1	randomised trials	not serious	not serious	serious ^a	not serious	none	9/736 (1.2%)	34/748 (4.5%)	RR 0.27 (0.13 to 0.56)	33 fewer per 1,000 (from 40 fewer to 20 fewer)		CRITICAL
COVID-related hospitalization, ER visit or all cause mortality (2.4 g)												
2	randomised trials	not serious	not serious	serious ^a	not serious	none	32/1570 (2.0%)	88/1572 (5.6%)	RR 0.36 (0.24 to 0.54)	36 fewer per 1,000 (from 43 fewer to 26 fewer)		CRITICAL
COVID-related hospitalization, ER visit or all cause mortality (8 g)												
2	randomised trials	not serious	not serious	serious ^a	not serious	none	18/844 (2.1%)	48/824 (5.8%)	RR 0.37 (0.21 to 0.62)	37 fewer per 1,000 (from 46 fewer to 22 fewer)		CRITICAL
mechanical ventilation (1.2g)												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	1/736 (0.1%)	2/748 (0.3%)	RR 0.51 (0.05 to 5.59)	1 fewer per 1,000 (from 3 fewer to 12 more)		CRITICAL
mechanical ventilation (2.4g)												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	1/1355 (0.1%)	6/1341 (0.4%)	RR 0.16 (0.02 to 1.37)	4 fewer per 1,000 (from 4 fewer to 2 more)		CRITICAL
ICU admission (1.2g)												

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Casirivimab-imdevimab	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	3/736 (0.4%)	7/748 (0.9%)	RR 0.44 (0.11 to 1.68)	5 fewer per 1,000 (from 8 fewer to 6 more)	 Low	CRITICAL

ICU admission (2.4g)

1	randomised trials	not serious	not serious	serious ^a	not serious	none	6/1355 (0.4%)	18/1341 (1.3%)	RR 0.33 (0.13 to 0.83)	9 fewer per 1,000 (from 12 fewer to 2 fewer)	 Moderate	CRITICAL
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serious adverse events (1.2g)

1	randomised trials	not serious	not serious	serious ^c	serious ^b	none	9/827 (1.1%)	74/1843 (4.0%)	RR 0.27 (0.14 to 0.54)	29 fewer per 1,000 (from 35 fewer to 18 fewer)	 Low	CRITICAL
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serious adverse event (2.4g)

2	randomised trials	not serious	not serious	serious ^a	not serious	none	28/2107 (1.3%)	80/2105 (3.8%)	RR 0.35 (0.23 to 0.54)	25 fewer per 1,000 (from 29 fewer to 17 fewer)	 Moderate	CRITICAL
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serious adverse event (8g)

2	randomised trials	not serious	not serious	serious ^a	not serious	none	19/1272 (1.5%)	80/2105 (3.8%)	RR 0.41 (0.25 to 0.67)	22 fewer per 1,000 (from 29 fewer to 13 fewer)	 Moderate	CRITICAL
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CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

- a. The population studied were adults only
- b. The results include the line of null effect and has a wide confidence interval
- c. The population studied were adults and adolescents

Appendix 4D. GRADE Evidence Profile: Bamlanivimab-etesevimab

Author(s): Furqaan I. Lim, MD

Question: Should Bamlanivimab plus etesevimab compared to placebo be used as treatment for COVID-19 in children?

Setting:

Bibliography:

Dougan M, Nirula, Azizad M et al. Bamlanivimab plus Etesevimab in Mild or Moderate COVID-19. *N Engl J Med.* 2021. [Internet]. Available from: doi:10.1056/NEJMoa2102685.

Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: A randomized clinical trial. *JAMA – J Am Med Assoc.* [Internet]. 2021;325(7):632-644. Available from: doi:10.1001/jama.2021.0202.

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bamlanivimab plus etesevimab	placebo	Relative (95% CI)	Absolute (95% CI)		
Covid-19 related hospitalization and deaths												
2	230andomized trials	not serious	not serious	serious ^a	not serious	none	12/630 (1.9%)	45/673 (6.7%)	RR 0.28 (0.15 to 0.53)	48 fewer per 1,000 (from 57 fewer to 31 fewer)	⊕⊕⊕○ Moderate	CRITICAL
Adverse events												
2	230andomized trials	not serious	not serious	serious ^a	serious ^b	none	88/630 (14.0%)	102/673 (15.2%)	RR 0.87 (0.49 to 1.57)	20 fewer per 1,000 (from 77 fewer to 86 more)	⊕⊕○○ Low	IMPORTANT
Serious adverse events												
2	230andomized trials	not serious	not serious	serious ^a	serious ^b	none	8/630 (1.3%)	6/673 (0.9%)	RR 1.40 (0.49 to 4.01)	4 more per 1,000 (from 5 fewer to 27 more)	⊕⊕○○ Low	CRITICAL

CI: confidence interval; RR: risk ratio

Explanations

a. 1 study included adolescents but only composed 1.1% of participants. The other study only involved adults.

b. The results include the line of null effect and has wide confidence interval

Appendix 4E. GRADE Evidence Profile: Sotrovimab (hospitalized)

Author(s): Furqaan I. Lim, MD

Question: Should sotrovimab compared to placebo be used as treatment of COVID-19 in hospitalized children?

Setting:

Bibliography:

Self, WH, Sandkovsky U, Reilly CS, et al. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and AMUBARVIMAB plus ROMLUSEVIMAB, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. Lancet Infect Dis. 23 Dec 2021. Available from: [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(21\)00751-9/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00751-9/fulltext)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	sotrovimab	placebo	Relative (95% CI)	Absolute (95% CI)		

o2 requirement

1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	73/182 (40.1%)	79/178 (44.4%)	RR 0.90 (0.71 to 1.15)	44 fewer per 1,000 (from 129 fewer to 67 more)	⊕⊕○○ Low	IMPORTANT
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mechanical ventilation

1	randomised trials	not serious	not serious	serious ^a	serious ^c	none	2/182 (1.1%)	3/178 (1.7%)	RR 0.65 (0.11 to 3.86)	6 fewer per 1,000 (from 15 fewer to 48 more)	⊕⊕○○ Low	CRITICAL
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mortality

1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	14/182 (7.7%)	13/178 (7.3%)	RR 1.05 (0.51 to 2.18)	4 more per 1,000 (from 36 fewer to 86 more)	⊕⊕○○ Low	CRITICAL
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composite safety outcome

1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	51/182 (28.0%)	57/178 (32.0%)	RR 0.88 (0.64 to 1.20)	38 fewer per 1,000 (from 115 fewer to 64 more)	⊕⊕○○ Low	CRITICAL
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infusion reaction

1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	18/182 (9.9%)	14/178 (7.9%)	RR 1.26 (0.65 to 2.45)	20 more per 1,000 (from 28 fewer to 114 more)	⊕⊕○○ Low	CRITICAL
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CI: confidence interval; RR: risk ratio

Explanations

a. Population studied were adults

b. There is serious imprecision because the results include the line of null effect

c. There is serious imprecision because the results include the line of null effect and has wide confidence interval

Appendix 4F. GRADE Evidence Profile: Sotrovimab (non-hospitalized)

Author(s): Furqaan I. Lim, MD

Question: Should sotrovimab compared to placebo be used as treatment for COVID-19 in nonhospitalized children?

Setting:

Bibliography:

Gupta, A, Gozales-Rojas Y, Juarez E, et al. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. N Engl J Med. 27 Oct 2021. Available from: <https://www.nejm.org/doi/full/10.1056/NEJMoa2107934>

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	sotrovimab	placebo	Relative (95% CI)	Absolute (95% CI)		
hospitalization												
1	randomised trials	not serious	not serious	serious ^a	not serious	none	3/291 (1.0%)	21/292 (7.2%)	RR 0.14 (0.04 to 0.48)	62 fewer per 1,000 (from 69 fewer to 37 fewer)	 Moderate	CRITICAL
all cause mortality												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	0/291 (0.0%)	1/292 (0.3%)	RR 0.33 (0.01 to 8.18)	2 fewer per 1,000 (from 3 fewer to 25 more)	 Low	CRITICAL
o2 requirement												
1	randomised trials	not serious	not serious	serious ^a	not serious	none	2/291 (0.7%)	19/292 (6.5%)	RR 0.11 (0.02 to 0.45)	58 fewer per 1,000 (from 64 fewer to 36 fewer)	 Moderate	IMPORTANT
mechanical ventilation												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	0/291 (0.0%)	2/292 (0.7%)	RR 0.20 (0.01 to 4.16)	5 fewer per 1,000 (from 7 fewer to 22 more)	 Low	CRITICAL
ICU admission												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	0/291 (0.0%)	5/292 (1.7%)	RR 0.09 (0.01 to 1.64)	16 fewer per 1,000 (from 17 fewer to 11 more)	 Low	CRITICAL
adverse event												

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	sotrovimab	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	73/430 (17.0%)	85/438 (19.4%)	RR 0.87 (0.66 to 1.16)	25 fewer per 1,000 (from 66 fewer to 31 more)	 Low	IMPORTANT
serious adverse event												
1	randomised trials	not serious	not serious	serious ^a	not serious	none	7/430 (1.6%)	26/438 (5.9%)	RR 0.27 (0.12 to 0.63)	43 fewer per 1,000 (from 52 fewer to 22 fewer)	 Moderate	CRITICAL

CI: confidence interval; RR: risk ratio

Explanations

a. Population studied were adults.

b. The outcome has imprecision because the results include the line of null effect and has a wide confidence interval.

Appendix 4G. GRADE Evidence Profile: Amubarvimab-romlusevimab

Author(s): Furqaan I. Lim, MD

Question: Should amubarvimab plus romlusevimab compared to placebo be used as treatment for covid-19 in hospitalized children?

Setting:

Bibliography:

Self, WH, Sandkovsky U, Reilly CS, et al. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. Lancet Infect Dis. 23 Dec 2021. Available from: [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(21\)00751-9/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00751-9/fulltext)

Certainty assessment							№ of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amubarvimab - romlusevimab	Placebo	Relative (95% CI)	Absolute (95% CI)		
o2 requirement												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	70/176 (39.8%)	79/178 (44.4%)	RR 0.90 (0.70 to 1.15)	44 fewer per 1,000 (from 133 fewer to 67 more)	⊕⊕○○ Low	IMPORTANT
mechanical ventilation												
1	randomised trials	not serious	not serious	serious ^a	serious ^c	none	4/176 (2.3%)	3/178 (1.7%)	RR 1.35 (0.31 to 5.94)	6 more per 1,000 (from 12 fewer to 83 more)	⊕⊕○○ Low	CRITICAL
mortality												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	15/176 (8.5%)	13/178 (7.3%)	RR 1.17 (0.57 to 2.38)	12 more per 1,000 (from 31 fewer to 101 more)	⊕⊕○○ Low	CRITICAL
composite safety outcomes												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	58/176 (33.0%)	57/178 (32.0%)	RR 1.03 (0.76 to 1.39)	10 more per 1,000 (from 77 fewer to 125 more)	⊕⊕○○ Low	CRITICAL
infusion reaction												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	23/176 (13.1%)	14/178 (7.9%)	RR 1.66 (0.88 to 3.12)	52 more per 1,000 (from 9 fewer to 167 more)	⊕⊕○○ Low	CRITICAL

CI: confidence interval; RR: risk ratio

Explanations

a. Population studied were adults

b. There is imprecision because results include the line of null effect

c. There is imprecision because results include the line of null effect and have wide confidence interval.

Appendix 4H. GRADE Evidence Profile: Regdanvimab

Author(s): Furqaan I. Lim, MD

Question: Should regdanvimab compared to placebo be used as treatment for COVID-19 in children?

Setting:

Bibliography:

Eom, JS, Ison M, Streinu-Cercel A, et al. Efficacy and safety of CT-P59 plus standard of care: a phase 2/3 randomized, double-blind, placebocontrolled trial in outpatients with mild-to-moderate SARS-CoV-2 infection. 15 March 2021. Preprint. Available from <https://www.researchsquare.com/article/rs-296518/v1>

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	regdanvimab	placebo	Relative (95% CI)	Absolute (95% CI)		
hospitalization												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	4/101 (4.0%)	9/103 (8.7%)	RR 0.45 (0.14 to 1.42)	48 fewer per 1,000 (from 75 fewer to 37 more)	 Low	IMPORTANT
supplemental oxygen												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	4/101 (4.0%)	9/103 (8.7%)	RR 0.45 (0.14 to 1.42)	48 fewer per 1,000 (from 75 fewer to 37 more)	 Low	CRITICAL
need for rescue therapy												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	7/101 (6.9%)	15/103 (14.6%)	RR 0.48 (0.20 to 1.12)	76 fewer per 1,000 (from 117 fewer to 17 more)	 Low	CRITICAL
total adverse events												
1	randomised trials	not serious	not serious	serious ^a	serious ^b	none	58/215 (27.0%)	34/110 (30.9%)	RR 0.87 (0.61 to 1.25)	40 fewer per 1,000 (from 121 fewer to 77 more)	 Low	IMPORTANT

CI: confidence interval; RR: risk ratio

Explanations

a. Population studied were adults only.

b. The results include the line of null effect and has wide confidence interval

Appendix 5. Forest Plots

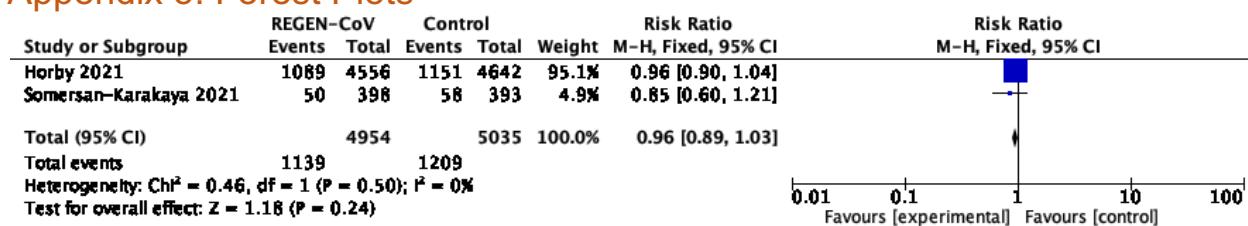


Figure 1. Mechanical ventilation or mortality (Casirivimab-imdevimab 8g), hospitalized patients

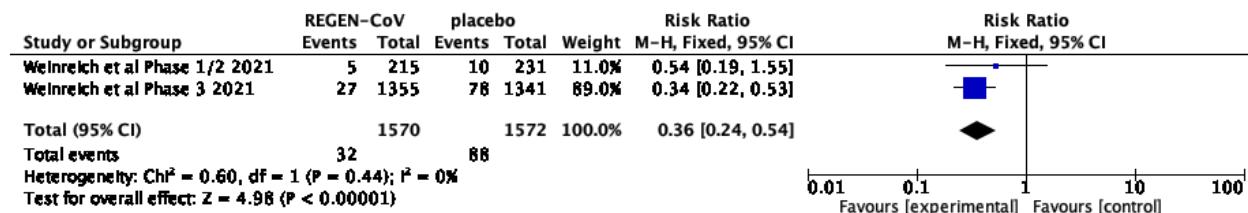


Figure 2. COVID-related hospitalization, ER visit or all-cause mortality (Casirivimab-imdevimab 2.4 g), non-hospitalized patients

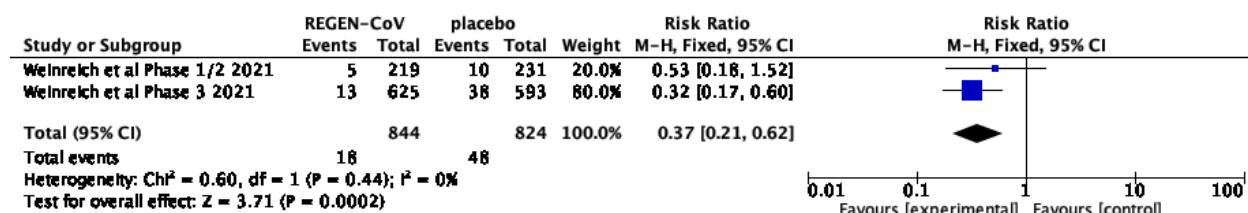


Figure 3. COVID-related hospitalization, ER visit or all-cause mortality (Casirivimab-imdevimab 8 g), non-hospitalized patients

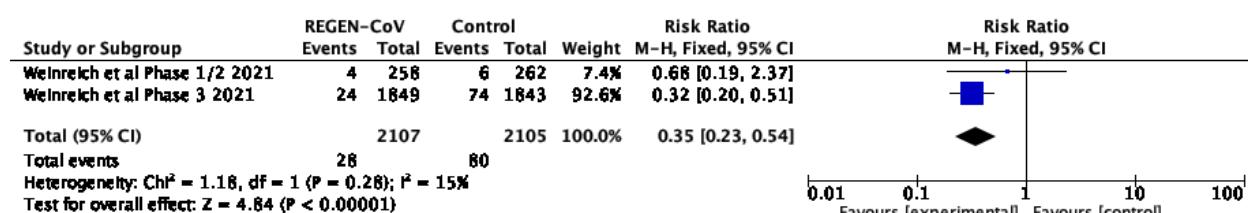


Figure 4. Serious adverse event (Casirivimab-imdevimab 2.4g), non-hospitalized patients

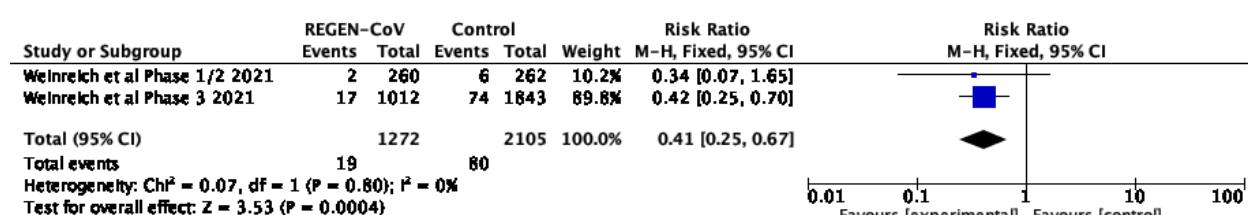


Figure 5. Serious adverse event (Casirivimab-imdevimab 8g), non-hospitalized patients

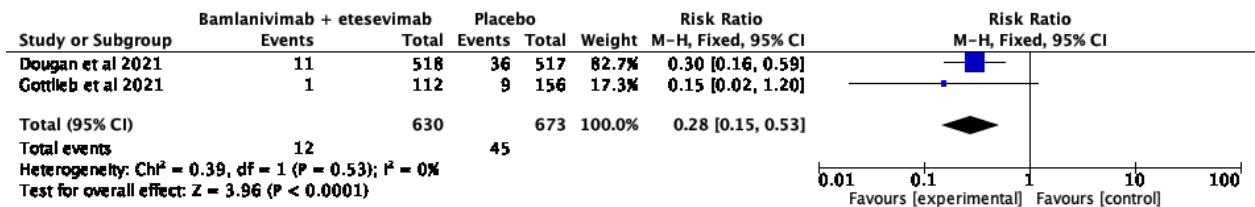


Figure 6. COVID-19 related hospitalization or death (Bamlanivimab-etesevimab)

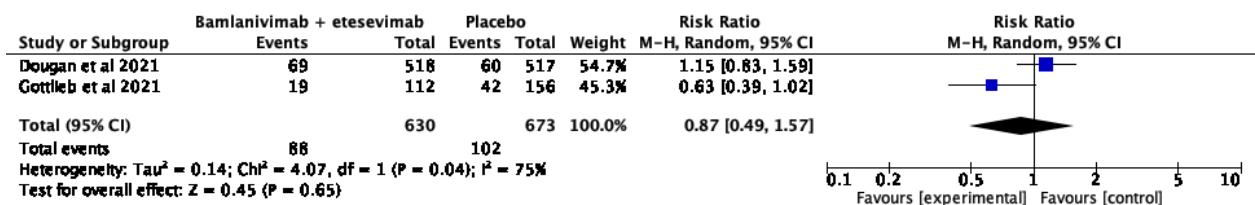


Figure 7. Adverse events (Bamlanivimab-etesevimab)

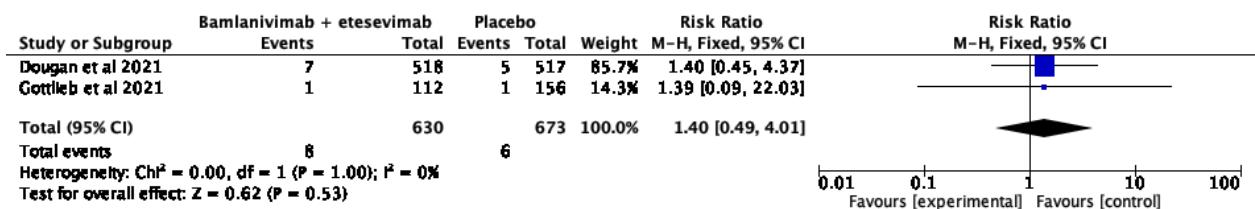


Figure 8. Serious adverse events (Bamlanivimab-etesevimab)

Appendix 6. Characteristics of Ongoing Studies

Study ID and Title	Population	Intervention	Outcomes	Expected Completion Date
NCT05092581 A Phase 1b, Open-Label, Single Dose Study Assessing the Pharmacokinetics, Safety, Tolerability, and Efficacy of Intravenous Anti-Spike(s) SARS-CoV-2 Monoclonal Antibodies (Casirivimab+Imdevimab) for the Treatment of Pediatric Patients Hospitalized Due to COVID-19	Children ≤17 years Hospitalized COVID-19 patients	Casirivimab plus Imdevimab Control: not mentioned	Concentrations of casirivimab+imdevimab in serum over time Adverse events	June 2023
NCT04992273 A Phase 2A, Open-Label Study Assessing Pharmacokinetics, Safety, Tolerability, and Immunogenicity of Single-Dose Subcutaneous Anti- Spike(s) SARS-CoV-2 Monoclonal Antibodies (Casirivimab and Imdevimab) in High-Risk Pediatric Subjects Under 12 Years of Age	Children ≤12 years Hospitalized COVID-19 patients	Casirivimab plus Imdevimab Control: not mentioned	Concentrations of casirivimab+imdevimab in serum over time Adverse events Immunogenicity	Nov 2022
NCT04840459 Use of Monoclonal Antibodies (Bamlanivimab and Casirivimab + Imdevimab) for the Treatment of Mild to Moderate COVID-19 in Non-Hospitalized Setting	Age 12 years and older COVID-19 patients at high risk for progression to severe COVID-19	Bamlanivimab Casirivimab plus Etesevimab Control: not mentioned	Progression to severe COVID-19 and/or hospitalization Rate of Recovery	Jan 31, 2022
NCT04425629 A Master Protocol Assessing the Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Patients With COVID-19	All ages including children COVID-19 patients	Casirivimab plus Imdevimab Control: not mentioned	Adverse events Change in viral load Hospitalization or death Concentration over time COVID-19 related medically-attended visit O2 requirement ICU admission Mechanical ventilation	May 2022
NCT05074433 A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies as Pre-Exposure Prophylaxis to Prevent COVID-19 in Immunocompromised Participants	Age: 12 years and older Immunocompromised seronegative patients	Casirivimab plus Imdevimab Control: Placebo	Incidence of symptomatic COVID-19 infection Adverse events	June 2023
NCT04790786 The UPMC Optimizing Treatment and Impact of	Age: 12 years and older	Bamlanivimab Bamlanivimab plus Etesevimab	Proportion of alive and non-hospitalized patients	Dec 2022

Monoclonal antibodyS Through Evaluation for COVID-19 Trial	COVID-19 patients	Casirivimab plus Imdevimab Sotrovimab Control: not mentioned	Mortality Viral loads Antibody titers Immunogenicity	
NCT04913675 A Phase 3 Randomized, Multi-center, Open Label Study to Assess the Efficacy, Safety, and Tolerability of Monoclonal Antibody VIR-7831 (Sotrovimab) Given Intramuscularly Versus Intravenously for the Treatment of Mild-Moderate Coronavirus Disease 2019 (COVID-19) in High-risk Non-hospitalized Patients	Age: 12 years and older COVID-19 patients with high risk of progression to severe COVID-19	Sotrovimab Control: not mentioned	Progression of COVID-19 Adverse events Change in viral load Serum concentrations	Aug 2022

Appendix 7. Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 9)

FACTORS		JUDGEMENT (N = 9)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS	
Problem	No	Yes (9)		Varies		Uncertain			
Benefits	Large (3)	Moderate (6)	Small	Trivial	Varies	Uncertain		<ul style="list-style-type: none"> IV casirivimab plus imdevimab: decreased risk for MV/death in hospitalized, decreased risk of COVID-19 related hospitalization/death in non-hospitalized Bamlanivimab plus etesevimab: decreased risk of hospitalization/death Sotrovimab: decreased risk of hospitalization and oxygen requirement 	
Harm	Large	Moderate (2)	Small (7)	Trivial	Varies	Uncertain		<ul style="list-style-type: none"> No significant difference between interventions and control 	
Certainty of evidence	High	Moderate		Low (2)		Very low (7)			
Balance of effects	Favors drug (4)	Probably favors drug (5)	Does not favor drug or no drug	Probably favors no drug	Favors no drug	Varies	Uncertain		
Values	Important uncertainty or variability	Possibly important uncertainty or variability (5)		Probably no important uncertainty or variability (4)		No important uncertainty or variability			
Resources required	Uncertain	Varies	Large costs (9)	Moderate costs	Negligible costs or savings	Moderate savings	Large savings	<ul style="list-style-type: none"> Casirivimab plus imdevimab: Php 25,551.00 Bamlanivimab plus etesevimab: \$2,100.00 (Php 107,704.00) Sotrovimab: \$2,100.00 (Php 107,04.00) Amubarvimap plus romlusevimab: no info Regdanvimab: Php 25,000.00 	
Certainty of evidence of resources required	No included studies (4)		Very low (1)	Low	Moderate (3)	High (1)		<ul style="list-style-type: none"> Only casirivimab plus imdevimab approved by Phil FDA Other prices from international data 	
Cost-effectiveness	No included studies (8)	Varies	Favors the comparison	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention (1)	Favors the intervention		
Equity	Uncertain (6)	Varies (1)	Reduced (1)	Probably reduced (1)	Probably no impact	Probably increased	Increased		
Acceptability	Uncertain (5)	Varies (2)	No	Probably no	Probably yes (2)	Yes			
Feasibility	Uncertain (4)	Varies (1)	No	Probably no (1)	Probably yes (3)	Yes		<ul style="list-style-type: none"> Only casirivimab plus imdevimab with EUA in Philippines for mild to moderate cases aged 12 years and older with risk of progression to severe COVID but not yet oxygen requiring 	

C.Prophylactic Interventions of COVID-19 in Children

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.

Evidence Summary

Key Findings

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.

Introduction

Vitamin D is a fat-soluble vitamin essential in calcium and phosphorus homeostasis and in the maintenance of bone, skin, and tooth enamel. Receptors for vitamin D are nearly universally expressed in human cells, including in cells of the immune system, and it can exhibit anti-inflammatory effects by modulating macrophage maturation, preventing excessive expression of antiviral cytokines, downregulating inflammatory T_H1 and T_H17 responses, and promoting regulatory T cell (T_{reg}) differentiation [1].

There are several studies that attempted to establish the link between respiratory illness and vitamin D deficiency. We identified two systematic reviews, done in the pre-pandemic period, that evaluated the efficacy of vitamin D supplementation as primary prevention of any respiratory tract infection in children, but these yielded inconsistent results. A meta-analysis of six studies in children showed inconclusive results for incidence of RTI with vitamin D supplementation (Intervention group: N=3,400; control group: N=3,443, RR 0.88, 95% CI 0.66–1.11, I²= 80.4%, p=.000) [2]. However, evidence from another meta-analysis showed significant benefit of supplementation in trials where vitamin D was given to participants aged one year to less than 16 years old (IG=5994, CG=5877, OR 0.71, 95% CI 0.57-0.90, I² 46%, P=0.027) [3].

In relation to COVID-19, vitamin D deficiency is postulated to contribute to increased risk of COVID-19 infection and severity. A previously published meta-analysis of 23 studies in adults found a significant correlation between low serum vitamin D levels and COVID-19 infection (OR 3.3, 95% CI 2.5-4.3) as well as low serum vitamin D and severe COVID-19 (OR 5.1, 95% CI 2.6-10.3) [4]. Another meta-analysis of 13 studies in adults reported significantly higher levels of vitamin D in healthy patients compared to COVID-19 patients (MD = 3.93; 95% CI 2.84–5.02) [5]. A study involving hospitalized very elderly patients reported that bolus vitamin D supplementation was associated with decreased risk of severe COVID-19 and mortality [6]. Similar findings have also been reported in a meta-analysis of eight studies done in pediatric patients, showing significant correlation between vitamin D deficiency and severe COVID-19 (OR 5.5, 95% CI 1.560-19.515) [7]. These reports make vitamin D a supplement of interest for clinicians to prescribe in both prevention and treatment of COVID-19. This review seeks to determine the efficacy and safety of vitamin D as an adjunct for the prevention and treatment of COVID-19 in pediatric patients.

Review Methods

A database search of MEDLINE, the Cochrane COVID-19 Study Register, LitCOVID, the CADTH COVID-19 Evidence Portal, and the World Health Organization (WHO) COVID-19 database was done with a combination of free-text and MeSH terms including “COVID-19” and “vitamin D” was done to search for clinical practice guidelines (CPGs), randomized controlled trials (RCTs), cohort studies, case series, systematic reviews, and meta-analyses that report the effect of vitamin D compared to placebo or standard of care as prevention of COVID-19 in at-risk patients and as adjunct treatment in the management of COVID-19 patients. Preprints were obtained by searching the WHO COVID-19 database, which includes studies found in medRxiv. An additional search was done for CPGs using the CPG Infobase. Ongoing clinical trials were searched through the Cochrane COVID-19 Study Register and the WHO COVID-19 database, which includes trials from ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. The final search date was on January 12, 2022. Studies meeting the criteria described in Table 1 were included in the review.

Table 1. PICO criteria for vitamin D and COVID-19.

Population	Healthy children 18 years old and below without COVID-19
Intervention/Exposure	Vitamin D
Comparison	No vitamin D
Outcomes	Incidence of COVID, forward transmission, viral load, adverse events

No restrictions on patient COVID-19 severity status, treatment outcome, or country were applied. Studies that were not original research, studies not in English, in-vitro studies, studies combining vitamin D with another drug, and those that compare vitamin D to treatments that are not placebo or standard of care were excluded.

The risk of bias of included studies was assessed using guide questions derived from Painless Evidence-Based Medicine [8] for RCTs. Certainty of evidence was assessed using the GRADE evidence profile [9]. Review Manager 5.4.1 was used for meta-analysis.

Results

At this time, there is no direct evidence that answers our research question. A recently published observational study was done in the Catalonia region in Spain among individuals ≥ 18 years old, [10] which determined whether cholecalciferol or calcifediol supplementation achieving 25OHD levels ≥ 30 ng/ml offered protection against COVID-19. However, the overall certainty of evidence for this study was rated very low due to the observational study design and indirectness. (Appendix 4A).

Subgroup analyses of the cholecalciferol-supplemented and calcifediol-supplemented cohorts showed mixed results as follows: cholecalciferol was found to offer slight protection from SARS-CoV2 infection ($n= 4352$ [4.0%] vs $9142/216,686$ [4.2%] in controls; HR 0.95, CI 95% 0.91–0.98, $p=0.004$); however, calcifediol did not confer protection ($n = 5,662$ [4.2%] vs $11,401$ [4.2%] in controls; HR 0.99, CI 95% 0.96–1.03, $p=0.646$) (Appendix 3A). But overall effect, based on combined analysis of the two formulations, showed that vitamin D and control were equivalent for the outcome of SARS-CoV2 infection (RR 0.97, CI 95% 0.95–1.00) (Appendix 4A).

Other Considerations (Evidence to Decision)

Table 2. Evidence to Decision Considerations

Cost	<p>No evidence was found on the cost-effectivity of Vitamin D supplementation for COVID-19 in children.</p> <p>The approximate prices of vitamin D oral drops, syrup and capsule from local pharmacies are as follows:</p> <p><i>Vitamin D3 100 IU/mL oral drops = Php 200.00 per 30 mL bottle</i> <i>Vitamin D3 200 IU/5 mL oral syrup = Php 250.00 per 250 ml bottle</i> <i>Vitamin D3 800 IU/capsule = Php 6.75 per capsule</i></p> <p>As per the Interim Guidelines on COVID-19 from the Pediatric Infectious Disease Society of the Philippines (31 Aug 2020) [20], the recommended dose for vitamin D is as follows, to be given for 5 days:</p> <p><2 years: 1,000 IU/day >2 years: 2,000 IU/day</p>
Availability	Available as an over-the-counter medication in most local pharmacies.

Factors to Impact Acceptability or Compliance	The rationale of vitamin D supplementation in SARS-CoV-2 infection in children is based on the reduction of influenza A incidence with vitamin D supplementation [21].
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Recommendations from Other Groups

The recommendations of other groups on the use of vitamin D for the prevention or treatment of COVID-19 are summarized in the table below.

Table 3. Summary of recommendations from other groups.

Group	Recommendation
US NIH (April 2021) [23]	There is insufficient evidence to recommend either for or against the use of vitamin D for the treatment of COVID-19.
Australian COVID-19 Living CPG (December 2021) [24]	Do not use vitamin D analogues for the treatment of COVID-19 outside of 244 Philippine trials with appropriate ethical approval.
NICE COVID-19 rapid guideline: Vitamin D (December 2021) [25]	Do not offer a vitamin D supplement to people solely to prevent or to treat COVID-19, except as part of a clinical trial.
Cochrane: Vitamin D supplementation for the treatment of COVID-19: a living systematic review (March 2021) [26]	<p>There is insufficient evidence to determine the benefits and harms of vitamin D supplementation as a treatment of COVID-19.</p> <p>Moreover, we found only limited safety information, and were concerned about consistency in measurement and recording of these outcomes.</p>
Alberta Scientific Advisory Group: Vitamin D in the Treatment and Prevention of COVID-19 (7 Jan 2021) [27]	There is no high-quality evidence that suggests taking vitamin D supplements is specifically effective in the prevention or treatment of COVID-19.
Ontario COVID-19 Science Advisory Table (18 October 2021) [28]	Vitamin D is currently not recommended for the treatment of COVID-19.
Philippine COVID-19 Living CPG (18 March 2021) [11]	<p>We recommend against the use of Vitamin D supplementation to prevent COVID-19 Infection.</p> <p>There is insufficient evidence to recommend the use of Vitamin D supplementation as an adjunct treatment for patients with COVID-19 infection.</p>

Philippine Pediatric Society. A Parent's Guide on Covid-19 Infection in Children (December 2021) [29]	Supplementation of nutrients such as vitamin C, vitamin D, folate and omega fatty acids may be beneficial to overall health but are not completely validated as preventive or therapeutic medications.
Pediatric Infectious Disease Society of the Philippines. Interim Guidelines on Covid-19. (08 January 2022) [30]	There is no evidence for or against multivitamins and minerals as prevention or treatment of COVID-19 in children. Nutritional support may be given upon the attending physician's discretion with doses not exceeding the Recommended Dietary Allowance.

Research Gaps

There is a need for randomized controlled trials of vitamin D supplementation as a preventive and treatment measure against COVID-19 in children. These studies should aim to determine the optimal vitamin D doses to achieve benefit while balancing safety. As of January 2022, there is one ongoing pediatric clinical trial on vitamin D as adjunctive treatment of COVID-19 and one trial on vitamin D as COVID-19 prevention (Appendix 6).

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Evidence Summary Appendices

Appendix 1. Search Yield and Results

1. For Prevention

Database	#	Keywords/MeSH	Yield
MEDLINE (Pubmed)	1	((("COVID-19" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [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 epidemic 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])) AND (((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])) OR (((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])) AND (pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens)((("COVID-19" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [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 epidemic 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])) AND (((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])) OR (((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])) AND (pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens)	6,164
	2	"vitamin D" OR ergocalciferol OR cholecalciferol OR "vitamin D2" OR "vitamin D3" OR calcifediol OR calcidiol OR 25-hydroxycholecalciferol OR "25-hydroxyvitamin D ₃ " OR calcitriol OR "1,25-dihydroxycholecalciferol" or "1,25-hydroxyvitamin D ₃ "	97,329
	3	((("Incidence of COVID" OR "attack rate" OR "incidence rate" OR "incidence proportion") OR ("covid prevention" OR "forward transmission")) OR ("viral load" OR "virus titer" OR "viral burden))) OR ("adverse event" OR "adverse events")	112,758

	4	#1 #2 #3 (all studies)	23
	5	#1 #2 #3 (Meta-analysis, RCTs, Systematic reviews)	6
Cochrane Library	1	(pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens)	302,323
	2	"vitamin d" or ergocalciferol or cholecalciferol or "vitamin d2 or "vitamin d3 or calcifediol or calcidiol or calcitriol	15,755
	3	"Incidence of COVID" OR "attack rate" OR "incidence rate" OR "incidence proportion" OR "prevention" OR "forward transmission" OR "viral load" OR "virus titer" OR "viral burden" OR "adverse event"	234,422
	4	#1 #2 #3	6
	5	#1 #2 #3 (Interventional study)	5
	6	#1 #2 #3 (Rapid review)	1
LitCOVID	1	(pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens) AND ("vitamin D" or ergocalciferol or cholecalciferol or "vitamin D2" or "vitamin D3" or calcifediol or calcidiol or 25-hydroxycholecalciferol or "25-hydroxyvitamin D ₃ " or calcitriol or "1,25-dihydroxycholecalciferol" or "1,25-hydroxyvitamin D ₃ ") AND "Incidence of COVID" OR "attack rate" OR "incidence rate" OR "incidence proportion" OR "prevention" OR "forward transmission" OR "viral load" OR "virus titer" OR "viral burden" OR "adverse event"	13
	2	#1 AND <i>Chemicals: Vitamin D OR Cholecalciferol</i>	2
WHO COVID Database	1	(tw:((pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens) AND ("vitamin D" or ergocalciferol or cholecalciferol or "vitamin D2" or "vitamin D3" or calcifediol or calcidiol or 25-hydroxycholecalciferol or "25-hydroxyvitamin D ₃ " or calcitriol or "1,25-dihydroxycholecalciferol" or "1,25-hydroxyvitamin D ₃ ") AND (hospitalization OR hospitalized OR admission) or (mortality OR death) or (recovery OR remission OR improvement) or ("mechanical ventilation" OR MV OR intubation) or ("length of stay" OR "hospital stay" OR "length of admission" OR "time admitted" OR "time hospitalized") or ("intensive care unit" OR ICU OR "ICU admission" OR "intensive care unit admission" OR "ICU stay") or ("adverse event" OR "adverse events" OR complication OR complications) or ("viral conversion" OR "negative viral conversion")))	123
	2	#1 AND controlled clinical trial OR Systematic review OR Clinical Practice Guide OR Evidence synthesis	18

2. As Adjunct Treatment

Database	#	Keywords	Yield
MEDLINE (Pubmed)	1	((("COVID-19" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [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	214,506

	"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 epidemic 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]))	
2	"vitamin D" OR ergocalciferol OR cholecalciferol OR "vitamin D2" OR "vitamin D3" OR calcifediol OR calcidiol OR 25-hydroxycholecalciferol OR "25-hydroxyvitamin D ₃ " OR calcitriol OR "1,25-dihydroxycholecalciferol" or "1,25-hydroxyvitamin D ₃ "	97,423
3	(hospitalization OR hospitalized OR admission) OR (mortality OR death) OR (recovery OR remission OR improvement) OR ("mechanical ventilation" OR MV OR intubation) OR ("length of stay" OR "hospital stay" OR "length of admission" OR "time admitted" OR "time hospitalized") OR ("intensive care unit" OR ICU OR "ICU admission" OR "intensive care unit admission" OR "ICU stay") OR ("adverse event" OR "adverse events" OR complication OR complications) OR ("viral conversion" OR "negative viral conversion")	11,629,542
4	(pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens)	4,835,990
5	#1 AND #2 AND #3	763
6	#1 AND #2 AND #3 AND Filters: Randomized Clinical Trial, Systematic Review, Meta-analysis	58
7	#1 AND #2 AND #3 AND #4	103
Cochrane COVID-19 Study Register	1 ("vitamin D" or ergocalciferol or cholecalciferol or "vitamin D2" or "vitamin D3" or calcifediol or calcidiol or 25-hydroxycholecalciferol or "25-hydroxyvitamin D ₃ " or calcitriol or "1,25-dihydroxycholecalciferol" or "1,25-hydroxyvitamin D ₃ ") AND (hospitalization OR hospitalized OR admission) or (mortality OR death) or (recovery OR remission OR improvement) or ("mechanical ventilation" OR MV OR intubation) or ("length of stay" OR "hospital stay" OR "length of admission" OR "time admitted" OR "time hospitalized") or ("intensive care unit" OR ICU OR "ICU admission" OR "intensive care unit admission" OR "ICU stay") or ("adverse event" OR "adverse events" OR complication OR complications) or ("viral conversion" OR "negative viral conversion")	2,600
	2 #1 AND <i>Interventional</i> study type	289
	3 #1 AND (pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens	1,057
WHO COVID Database	1 ("vitamin D" or ergocalciferol or cholecalciferol or "vitamin D2" or "vitamin D3" or calcifediol or calcidiol or 25-hydroxycholecalciferol or "25-hydroxyvitamin D ₃ " or calcitriol or "1,25-dihydroxycholecalciferol" or "1,25-hydroxyvitamin D ₃ ") AND (hospitalization OR hospitalized OR admission) or (mortality OR death) or (recovery OR remission OR improvement) or ("mechanical ventilation" OR MV OR intubation) or ("length of stay" OR "hospital stay" OR "length of admission" OR "time admitted" OR "time hospitalized") or ("intensive care unit" OR ICU OR "ICU admission" OR "intensive care unit admission" OR "ICU stay") or ("adverse event" OR "adverse events" OR complication OR complications) or ("viral conversion" OR "negative viral conversion")	781
CPG Infobase	1 (("vitamin d") AND treatment AND la:en	1
	2 (("vitamin d") AND pedia OR children AND la:en	0

3. CADTH COVID-19 Evidence Portal

	Keywords	Yield
1	(("vitamin d") OR ergocalciferol (D2) OR cholecalciferol (D3) OR Calcifediol OR 25-hydroxyvitamin D3 OR oral 25OHD OR Cholecalciferol OR vitamin D3 OR Ergocalciferol OR vitamin D2	0

4. COVID-Evidence medRxiv

	Keywords	Yield
1	"COVID 19" AND "Vitamin D"	15
2	"COVID 19" AND "Vitamin D" AND (Pedia OR Children)	0

Appendix 2. Characteristics of Included Studies

Table 2A. Characteristics of studies on Vitamin D as preventive measure for COVID-19 in adults.

	Author, Year, Title, Setting	Study Design	Population	Sample Size	Intervention	Comparator	Outcomes
1	Oristrell 2022 Vitamin D supplementation and COVID-19 risk: a population-based, cohort study Spain	Retrospective Cohort	≥ 18 years old supplemented with cholecalciferol or calcifediol	N=711,138	N=243,046 Cholecalciferol n = 108,343 Calcifediol use n = 134,703	N=468,092 Unsupplemented patients n=216,686 (Cholecalciferol group) n=269,406 (Calcifediol group)	- SARS-COV2 Infection - COVID-19 Mortality - Severe COVID

Table 2B. Characteristics of randomized controlled trials on vitamin D as adjunct COVID-19 treatment in adults (from Joson, Tolosa, and Infantado 2021)

	Clinical Trial ID/Title	Population	Sample Size	Intervention	Comparator	Outcomes
1	Murai 2020 Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19 Brazil	Hospitalized patients with mild to severe COVID-19 Adults aged 18>yrs Positive for SARS-CoV-2 PCR or positive CT scan findings compatible with COVID-19	N=240	200,000 IU of vitamin D3 per orem given on day of admission (N=120)	Placebo (N=120)	Length of Hospital stay Mortality ICU admission Need for mechanical ventilator Duration of mechanical ventilator Serum vitamin D levels
2	Entrenas Castillo 2020 Effect of Calcifediol Treatment and best Available Therapy versus best Available Therapy on Intensive Care Unit Admission and Mortality Among Patients Hospitalized for COVID-19: A Pilot Randomized Clinical study Spain	Hospitalized patients with moderate to severe COVID-19 infection clinical picture of acute respiratory infection confirmed by a radiographic pattern of viral pneumonia positive SARS-CoV-2 PCR with CURB65 severity scale (recommending hospital admission in case of total score > 1).	N=76	Day of admission: 2 capsules of calcifediol (0.266 mg/cap). 1 capsule on days 3, 7, 14, 21, 28 until discharge or ICU admission. Plus standard of care (N=50)	Standard of care (N=26) defined as: 1) Hydroxychloroquine 400mg every 12 hours on first day and 200 mg every 12 hours for the following 5 days 2) Azithromycin 500 mg orally for 5 days, 3) For patients with pneumonia and NEWS score >5,	ICU admission Mortality

					Ceftriaxone 2 g intravenously every 24 hours was given for 5 days.	
3	Rastogi 2020 Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomized, placebo-controlled, study (SHADE study) India	Hospitalized patients with asymptomatic to mild COVID-19 with or without co-morbidities (hypertension, diabetes mellitus, chronic obstructive airway disease, chronic liver disease, chronic kidney disease) with vitamin D deficiency defined as levels below 20 ng/ml	N=40	Daily 60,000 IU of cholecalciferol (5 ml oral solution in nano droplet form) for 7 days with the aim to achieve 25(OH)D level > 50 ng/ml (N=16) Subsequently, 25(OH)D levels were assessed at day 7 and a weekly supplementation of 60,000IU provided to those with 25(OH)D > 50 ng/ml or else continued daily vitamin D 60,000 IU supplementation for another 7 days up until day-14 in participants with 25(OH)D < 50 ng/ml Plus standard of care	Placebo (5 ml distilled water) (N=24) Plus standard of care	Proportion of participants who turn SARS-CoV-2 RNA negative at days 5, 7, 10, 14, 18 and 21 (real-time PCR, CFX-96 IVD, Bio-Rad)
4	Lakkireddy 2021 Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease India	Hospitalized patients with mild to moderate COVID-19 with vitamin D defined as levels below 30 ng/mL	N=130	60,000 IU of cholecalciferol (aqueous nano solution/Deksel) per orem daily for 8 days if with body mass index (BMI) between 18-25 and for 10 days if with BMI more than 25 (N=65) Plus standard of care	Standard of care (N=65)	Inflammatory markers and vitamin D levels before and after intervention (vitamin D levels, CRP, LDH, IL6, Ferritin, N/L ratio) Mortality ICU admission Mean hospital stay Adverse events
5	Elamir 2021 A randomized pilot study using calcitriol in hospitalized COVID-19 patients USA	Hospitalized patients with COVID-19 with moderate to severe COVID-19	N=50	Calcitriol 0.5 ug daily for 14 days or discharge whichever came first. Plus standard of care: remdesivir (200 mg for one day followed by 100 mg for 4 days), dexamethasone (6 mg daily for 10 days), or convalescent plasma	Standard of care Standard of care: remdesivir (200 mg for one day followed by 100 mg for 4 days), dexamethasone (6 mg daily for 10 days), or convalescent plasma	Oxygen requirements Length of hospital stay Need for ICU admission Mortality Readmission.

				days), or convalescent plasma		
6	Maghbooli 2021 Treatment With 25-Hydroxyvitamin D3 (Calcifediol) Is Associated With a Reduction in the Blood Neutrophil-to-Lymphocyte Ratio Marker of Disease Severity in Hospitalized Patients With COVID-19: A Pilot Multicenter, Randomized, Placebo-Controlled, Double-Blinded Clinical Trial Iran	Hospitalized patients with moderate to severe COVID-19	N=106	Calcifediol 25 mcg per orem once daily for 30 days Plus standard of care: a combination of hydroxychloroquine, azithromycin, and ceftriaxone for patients with pneumonia	Placebo Plus standard of care: a combination of hydroxychloroquine, azithromycin, and ceftriaxone for patients with pneumonia	Length of Stay Need for Mechanical Ventilation Mortality ADE Admission to ICU
7	Soliman 2021 Impact of Vitamin D Therapy on the Progress COVID-19: Six Weeks Follow-Up Study of Vitamin D Deficient Elderly Diabetes Patients Egypt	Hospitalized elderly diabetes patients with SARS-CoV-2 with vitamin D deficiency.	N=56	200,000 units of high dose cholecalciferol single dose IM	Placebo	Mortality Need for Mechanical Ventilation
8	Sánchez-Zuno 2021 Vitamin D Levels in COVID-19 Outpatients from Western Mexico: Clinical Correlation and Effect of Its Supplementation Mexico	Outpatient adults with mild COVID-19	N=42	10,000 IU daily of vitamin D3 in soft capsule form for 14 days	Standard of care	Clinical Improvement (D7) Virologic Clearance (D14)

Appendix 3: Grade Evidence Profile

3A. Grade Evidence Profile: Vitamin D for Prevention of COVID-19 in Children

Author(s): Buban, Racoma, Tolosa, and Perez

Question: Should vitamin D be used as a preventive measure for COVID-19 in children?

Bibliography: Oristrell 2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	no Vitamin D	Relative (95% CI)	Absolute (95% CI)		
SARS-CoV2 Infection												
1	observational studies	serious ^a	not serious	serious ^b	not serious	none	10014/243046 (4.1%)	20543/468092 (4.4%)	RR 0.97 (0.95 to 1.00)	1 fewer per 1,000 (from 2 fewer to 0 fewer)	 Very low	CRITICAL

CI: confidence interval; RR: risk ratio

Explanations

a. Retrospective review of records and absence of blinding

b. Population studied included adults ≥ 18 years old with different vitamin D dose recommendations from children

3B. Grade Evidence Profile For Treatment (updated for pediatric patients; from Joson, Tolosa, and Infantado 2021)

Question: Should Vitamin D supplements compared to placebo be used as adjunct treatment for COVID-19?

Bibliography: Murai, Entrenas-Castillo, Rastogi, Lakkireddy, Elamir, Maghbooli, and Soliman

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D supplements	Placebo/Standard of Care	Relative (95% CI)	Absolute (95% CI)		

Mortality (ITT) (follow-up: range 30 days to 60 days)

6 ^a	randomised trials	serious ^b	serious ^c	serious ^d	serious ^e	none	21/353 (5.9%)	24/305 (7.9%)	RR 0.73 (0.38 to 1.40)	21 fewer per 1,000 (from 49 fewer to 31 more)	 Very low	CRITICAL
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ICU admission (ITT) (follow-up: range 30 days to 60 days)

5	randomised trials	serious ^e	serious ^{c,f}	serious ⁱ	serious ^j	none	35/313 (11.2%)	61/289 (21.1%)	RR 0.54 (0.28 to 1.05)	97 fewer per 1,000 (from 152 fewer to 11 more)	 Very low	CRITICAL
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Need for Mechanical Ventilation (ITT) (follow-up: range 30 days to 60 days)

4	randomised trials	not serious	serious ^{a,c}	serious ⁱ	serious ^j	none	25/238 (10.5%)	31/214 (14.5%)	RR 0.61 (0.38 to 1.00)	56 fewer per 1,000 (from 90 fewer to 0 fewer)	 Very low	CRITICAL
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Hospital length of stay

3	randomised trials	not serious	serious ^c	serious ⁱ	serious ^d	none	210	210	-	MD 0.48 days lower (1.91 lower to 0.94 higher)	 Very low	CRITICAL
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Clinical Improvement (follow-up: mean 7 days)

1	randomised trials	very serious ^b	not serious	serious ⁱ	serious ^d	none	7/21 (33.3%)	11/19 (57.9%)	RR 0.58 (0.28 to 1.18)	243 fewer per 1,000 (from 417 fewer to 104 more)	 Very low	CRITICAL
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Virologic Clearance (follow-up: range 14 days to 21 days)

2	randomised trials	serious ⁱ	not serious	serious ⁱ	serious ^d	none	7/38 (18.4%)	19/44 (43.2%)	RR 0.58 (0.19 to 1.79)	181 fewer per 1,000 (from 350 fewer to 341 more)	 Very low	IMPORTANT
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CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

- a. Serious inconsistency due to different direction of effect by one study Murai which contributed to 32.7% of the over all effect and with risk of bias rated as not serious.
- b. serious risk of bias due to high drop out rate in the study of Murai, Lakkireddy and Maghbooli which contributed to 66.8% of the overall treatment effect
- c. Serious inconsistency due to differences in dosage and formulation of vitamin D.
- d. serious imprecision due to wide confidence interval
- e. serious risk of bias due to high drop out rate in the study of Murai, Lakkireddy and Maghbooli which contributed to 69.7% of the overall treatment effect
- f. serious risk for inconsistency; high heterogeneity I²=55%
- g. Imprecision downgraded by 1 level: due to low number of event rate and wide confidence interval.
- h. serious risk of bias due to unblinded patients and outcome assessors which may have affected how symptoms were reported
- i. Risk of bias downgraded by 1 level: some concerns due to unclear randomization and allocation concealment, and lack of blinding in participants and personnel.
- j. Serious indirectness as studies recruited adults exclusively.

Appendix 4A: Forest Plots from Included Studies (Prevention, January 27, 2022)



Figure 1.1. Prevention

Appendix 4B: Forest Plots from Included Studies (from Joson, Tolosa, and Infantado 2021)

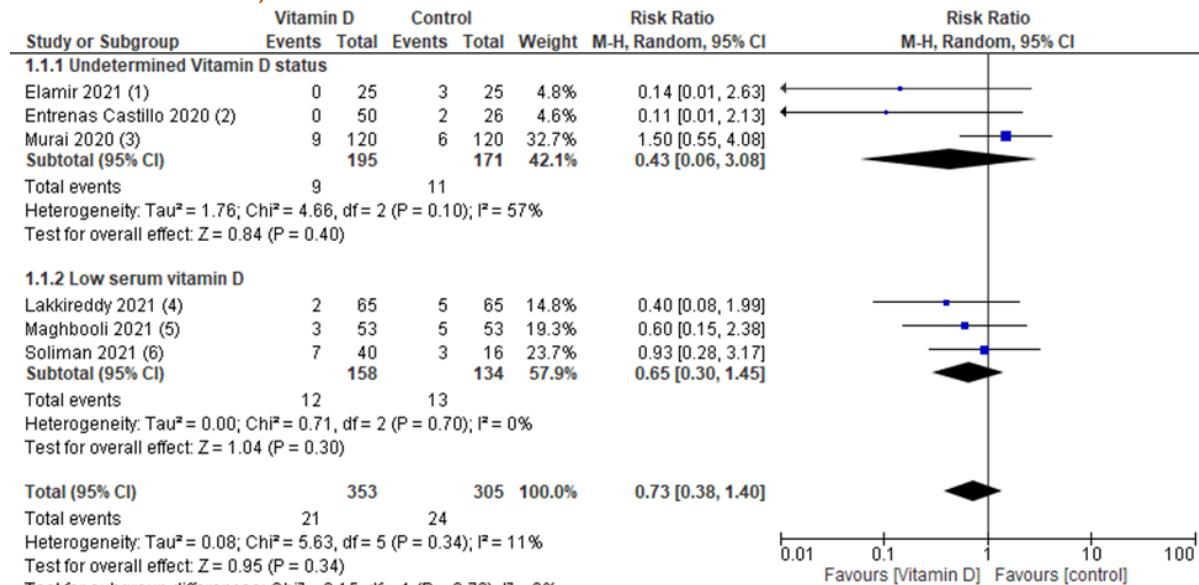


Figure 1.2. Mortality, overall (ITT).

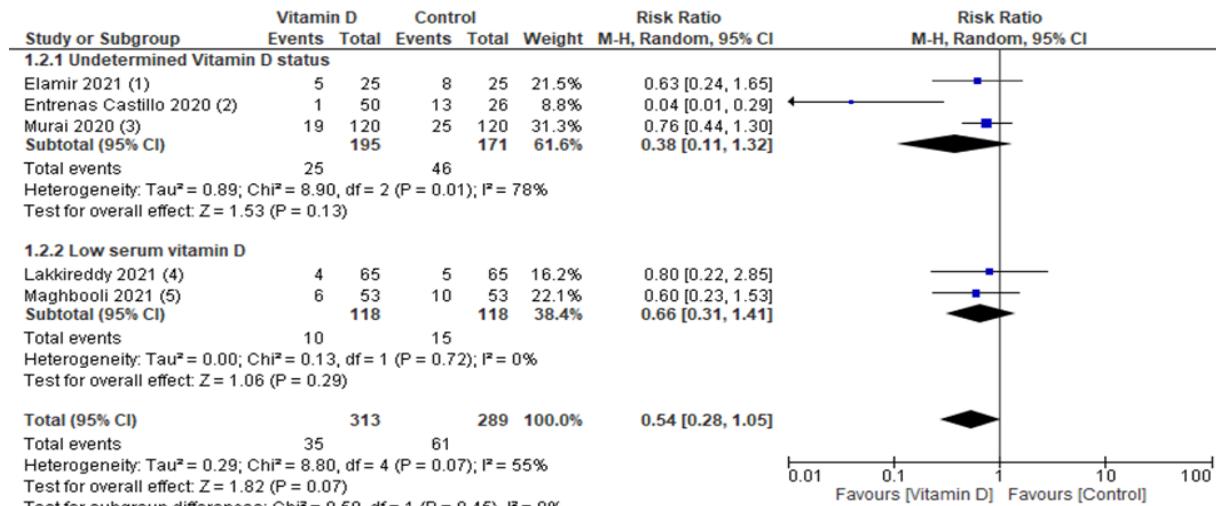


Figure 1.3. ICU admission (ITT).

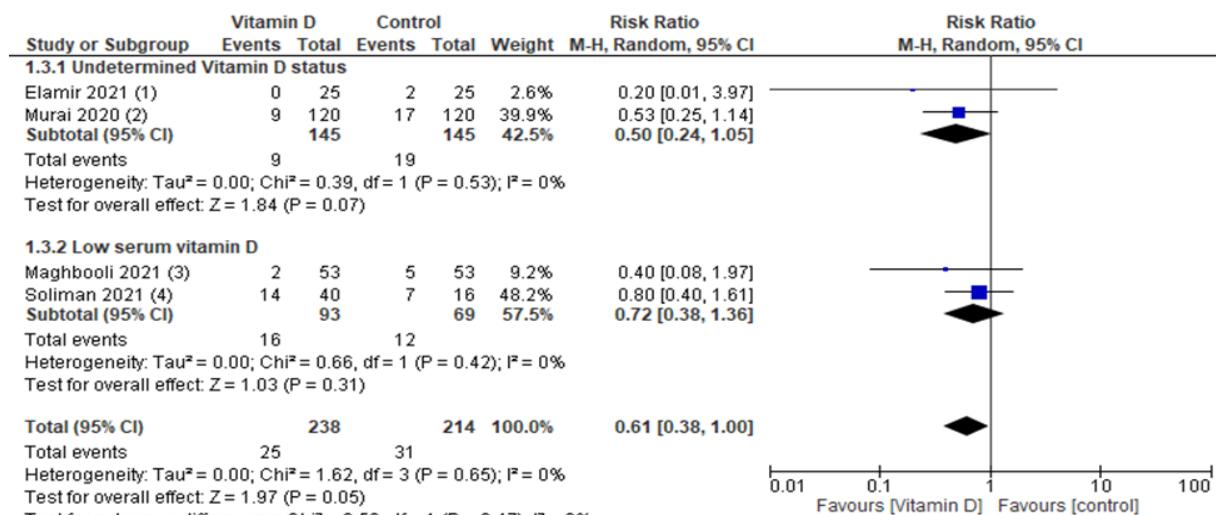


Figure 1.4. Need for Mechanical Ventilation (ITT).

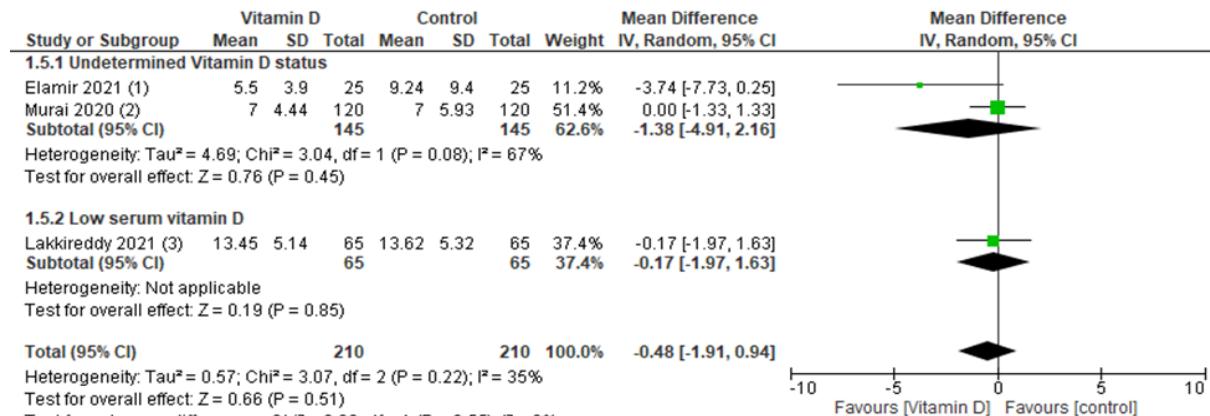


Figure 1.5. Length of Hospital Stay (ITT).

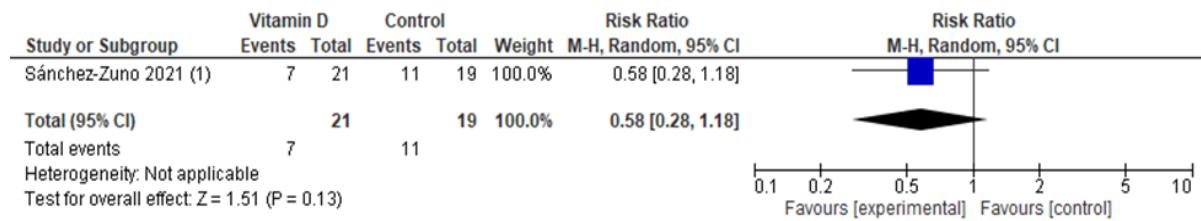


Figure 1.6. Clinical Improvement (ITT).

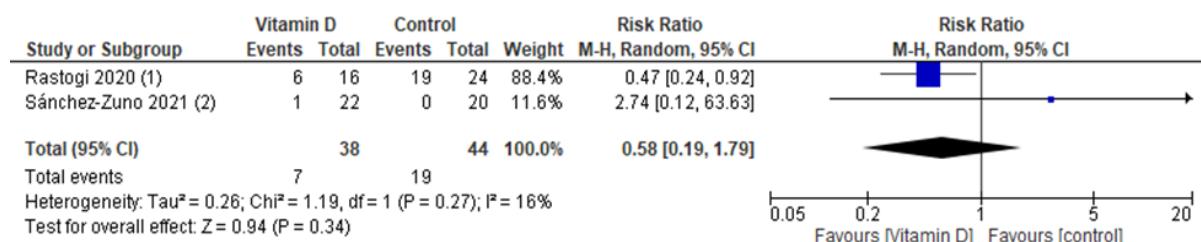


Figure 1.7. Virologic Clearance (ITT).

Appendix 5: Table of Ongoing Studies

Clinical Trial Identifier (Location)	Official Title	Methodology	Outcome Measures	Population	Estimated Date of Completion
NCT04502667 Mexico	Efficacy of Vitamin D Treatment in Pediatric Patients Hospitalized by COVID-19: Open Controlled Clinical Trial	Randomized open controlled trial	<p>Primary outcomes: Serum interleukins, ferritin, D-dimer levels at 7 days post-admission</p> <p>Secondary outcome: Serum vitamin D level at study completion (average of 21 days)</p>	40 children hospitalized with COVID-19	April 2022
NCT05043116 Denmark	High-dose Vitamin D Supplement for the Prevention of Acute Asthma-like Symptoms in Preschool Children - a Double-blind, Randomized, Controlled Trial	Double-blind randomized controlled trial	<p>Primary outcome: Number of acute asthma exacerbations within 1 year</p> <p>Secondary outcome: Time to first asthma exacerbation, duration of symptoms, need for medical treatment Blood/urine calcium levels Adverse events COVID-19 infection risk, symptom burden, infection length</p>	320 preschool children	October 2031

Appendix 6. Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 9)

FACTORS		JUDGEMENT (N = 9)					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS		
Problem	No (1)	Yes (6)		Varies (1)		Uncertain (1)			
Benefits	Large	Moderate	Small (1)	Trivial (1)	Varies	Uncertain (7)	<ul style="list-style-type: none"> Inconclusive results for prevention and treatment 		
Harm	Large	Moderate	Small (2)	Trivial (1)	Varies	Uncertain (6)			
Certainty of evidence	High	Moderate		Low (1)		Very low (8)	<ul style="list-style-type: none"> Rated very low due to indirectness, imprecision and serious risks of bias 		
Balance of effects	Favors drug	Probably favors drug (2)	Does not favor drug or no drug	Probably favors no drug	Favors no drug	Varies	Uncertain (7)		
Values	Important uncertainty or variability	Possibly important uncertainty or variability (1)		Probably no important uncertainty or variability (5)		No important uncertainty or variability (3)			
Resources required	Uncertain (1)	Varies	Large costs (1)	Moderate costs (5)	Negligible costs or savings (2)	Moderate savings	Large savings	<ul style="list-style-type: none"> Vitamin D3 100 IU/mL oral drops: Php 200.00/30mL bottle Vitamin D3 200 IU/5mL oral syrup: Php 250.00/250mL bottle Vitamin D3 800 IU/capsule: Php 6.75/cap 	
Certainty of evidence of resources required	No included studies (9)		Very low	Low	Moderate	High			
Cost-effectiveness	No included studies (9)	Varies	Favors the comparison	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention	Favors the intervention		
Equity	Uncertain (8)	Varies	Reduced	Probably reduced (1)	Probably no impact	Probably increased	Increased		
Acceptability	Uncertain (6)	Varies	No	Probably no	Probably yes (3)	Yes			
Feasibility	Uncertain (3)	Varies	No (1)	Probably no	Probably yes (4)	Yes (1)			

Additional Comments

- Vitamin D may be too expensive for the mid- to low-income families.
- Supplementation may be beneficial for the Filipino children with already low vitamin D levels.

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.

Evidence Summary

Key Findings

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.

Introduction

Vitamin C or ascorbic acid is a water-soluble vitamin, which works as a co-factor for various enzymes processes [1]. It scavenges free radicals and reactive oxygen species which are products of physiological cell metabolism or associated with inflammatory diseases, and oxidative damage. It also decreases release of pro-inflammatory cytokines, supports phagocytosis and chemotaxis of leukocytes, enhances neutrophil clearance by macrophages, and promotes development and maturation of T-lymphocytes [2-8]. Various animal models have exhibited its immunomodulatory effects [9-10].

A Cochrane systematic review concluded that 1 to 2 g vitamin C per day is safe, inexpensive, and has a consistent effect on decreasing the duration and severity of the common cold [11]. This review, however, has not shown that regular intake of vitamin C decreases incidence of common colds among the general population [11], even at higher doses of $\geq 1\text{g/day}$ [12].

A study done among Filipino children showed that mean intake of vitamin C was above adequate intake levels among 6-11.9 month-old infants, but inadequate in 35% of toddlers aged 24-35.9 months and in 60% of children aged 36-59.9 months old [13]. A more recent study done by Angeles-Agdeppa et al. in 2019 among Filipino school children and adolescents in the low socioeconomic status found that 68-96% of the study population had inadequate vitamin C intake [14]. These children may benefit from additional supplementation. This review seeks to determine the efficacy and safety of vitamin C supplementation as prophylaxis for COVID-19 in the pediatric population.

Review Methods

We performed a comprehensive systematic search of related literature from MEDLINE via PubMed, Cochrane Library, ClinicalTrials.gov, MedRxIV.com, WHO COVID database, and HERDIN Plus. Freehand search using Google was also done. There was no limit in terms of date, language, and country of publication. The search was conducted using the following terms: COVID-19, SARS-CoV-2, nCOV-19, vitamin C, ascorbic acid and sodium ascorbate. Methodologies included randomized controlled trials, observational studies, case reports and case series, systematic reviews and meta-analyses. Our PICO for this review was as follows:

Table 1. PICO criteria for vitamin C and COVID-19.

Population	Children without COVID-19
Intervention/Exposure	Vitamin C or Sodium Ascorbate or Ascorbic Acid as prophylaxis or preventive treatment
Comparison	Usual care, standard of care, placebo, any active control
Outcomes	Incidence of COVID-19, forward transmission, viral load, adverse events

Results

We found no published articles that directly matched our criteria. We found two studies in adults, included in this review as indirect evidence.

Two observational studies evaluated use of vitamin C as prophylaxis among adult outpatients. Behera et al. did a case-control study among 372 health care workers who were matched for profession, gender, age and date of diagnosis [15]. A total of 186 cases and 186 controls were asked if they took ivermectin, hydrochloroquine or vitamin C prior to testing. The study showed inconclusive results of vitamin C for the prevention of SARS CoV2 infection ($OR = 0.72$; $95\%CI = 0.42, 1.27$).

Louca et al. did an observational cross-sectional survey including 372,720 UK participants 16 to 90 years old who answered a self-reported questionnaire on COVID-19-related information through an app [16]. Exposure was self-reported, regular and constant dietary supplement usage in the previous 3 months during the first waves of the pandemic up to 31 July 2020, while outcome was incidence of SARS-CoV-2 infection before 31 July 2020. This study reported no significant association of vitamin C and COVID-19 infection for all participants ($OR=1.02$, $95\%CI = 0.99$ to 1.06 $p=0.197$). Meanwhile, a positive association was found in men aged >60 years taking vitamin C supplements ($OR=1.22$, $95\%CI = 1.05$ to 1.41 , $p=0.008$) for testing positive for SARS-CoV-2.

Overall certainty of evidence was very low due to risk of bias, indirectness, and imprecision. Both studies enrolled adult populations primarily, and although Louca et al. also included adolescents aged 16-18 years old [16], the report did not quantify how many participants were in this adolescent age group. In addition, the study did not completely provide the raw numbers needed to compute the vitamin C supplementation of persons who tested positive and negative for SARS CoV2 across the UK, US and Sweden

(reporting only the Odds Ratios for the UK component). Both studies included intake of multiple prophylactic agents, thus the effect of vitamin C alone cannot be isolated from the results.

Other Considerations (Evidence to Decision)

Vitamin C is widely available in all pharmacies and drugstores nationwide. According to the 2021 Philippine Drug Price Reference Index (DPRI), the mean prices for oral vitamin C syrup (100mg/5ml preparation) ranges from Php 17.50 for a 15ml bottle to Php 28.00 for a 120ml bottle. Meanwhile, ascorbic acid 500mg tablets costs Php 0.80 [17].

Recommendations from Other Groups

The PPS parent guide [18] and PIDSP interim guidelines [19] have stated that nutritional support may be given at the attending physician's discretion as long as it does not exceed the recommended dietary allowance [20]. The latest Pediatric Infectious Diseases Society of the Philippines (PIDSP) COVID-19 recommendations on multivitamins and minerals stated no evidence for or against its use in the treatment of COVID-19 in children. Nutritional support may be given upon the discretion of the attending physician with doses not exceeding the Recommended Dietary Allowance [19].

The Philippine Pediatric Society Parent's Guide on COVID-19 Infection in Children states that supplementation of nutrients (including vitamin C) may be beneficial to overall health but are not completely validated as preventive or therapeutic medications [18].

Research Gaps

There are no ongoing clinical trials on use of vitamin C as prophylaxis against COVID-19 in children. Further research is needed to evaluate its efficacy and safety in preventing COVID-19 infection among children.

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Evidence Summary Appendices

Appendix 1. Search Yield and Results

Database	#	Keywords	Yield
MEDLINE (Pubmed)	1	((("pediatric COVID-19" [Supplementary Concept] OR "COVID-19" [Supplementary Concept] "COVID-19 diagnostic testing" [Supplementary Concept] OR "COVID-19 drug treatment" [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 "coronavirus 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 "coronavirus" [MeSH Terms] OR coronavirus*[all] OR corona-virus*[all] OR cov[tiab]) AND (((((((Vitamin C [tiab]) OR (sodium ascorbate [tiab])) OR (ascorbic acid [tiab])) OR (ascorbic [tiab])) OR (antioxidant [tiab])) OR (supplement [tiab])) OR (vitamin c* [tiab])) OR (vitamin C[MeSH Terms])) OR (ascorbic acid [MeSH Terms])) OR (sodium ascorbate [MeSH Terms])) OR (ascorbic [MeSH Terms])) OR (antioxidant[MeSH Terms])) OR (supplement[MeSH Terms] AND (pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens)	1,112
	2	"vitamin C" OR "ascorbic acid" OR "sodium ascorbate" OR "ascorbic" OR "ascorbate"	1,166
	3	(incidence of COVID-19) OR (forward transmission) OR (prevalence of COVID-19) OR ("viral conversion") OR (hospitalization OR hospitalized OR admission) or (mortality OR death) or (recovery OR remission OR improvement) or ("mechanical ventilation" OR MV OR intubation) or ("length of stay" OR "hospital stay" OR "length of admission" OR "time admitted" OR "time hospitalized") or ("intensive care unit" OR ICU OR "ICU admission" OR "intensive care unit admission" OR "ICU stay") or ("adverse event" OR "adverse events" OR complication OR complications)	5,437
	4	#1 AND #2 AND #3	97
	5	#1 AND #2 AND #3 AND Filters: Randomized Clinical Trial, Systematic Review, Meta-analysis	9
Cochrane COVID-19 Study Register	1	("vitamin C" or "sodium ascorbate" or "ascorbic acid" or "ascorbate" or "ascorbic") AND (incidence of COVID-19) OR (forward transmission) OR (prevalence of COVID-19) OR ("viral conversion") OR (hospitalization OR hospitalized OR admission) or (mortality OR death) or (recovery OR remission OR improvement) or ("mechanical ventilation" OR MV OR intubation) or ("length of stay" OR "hospital stay" OR "length of admission" OR "time admitted" OR "time hospitalized") or ("intensive care unit" OR ICU OR "ICU admission" OR "intensive care unit admission" OR "ICU stay") or ("adverse event" OR "adverse events" OR complication OR complications)	2,041
	2	#1 AND (pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens)	200
WHO COVID Database	1	("vitamin C" or "sodium ascorbate" or "ascorbic acid" or "ascorbate" or "ascorbic") AND (incidence of COVID-19) OR (forward transmission) OR (prevalence of COVID-19) OR ("viral conversion") OR (hospitalization OR hospitalized OR admission) or (mortality OR death) or (recovery OR remission OR improvement) or ("mechanical ventilation" OR MV OR intubation) or ("length of stay" OR "hospital stay" OR "length of admission" OR "time admitted" OR "time hospitalized") or ("intensive care unit" OR ICU OR "ICU admission" OR "intensive care unit admission" OR "ICU stay") or ("adverse event" OR "adverse events" OR complication OR complications) AND (pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens)	40
clinicalTrial .gov		"vitamin c" OR "sodium ascorbate" OR "ascorbic acid" AND "pediatric covid"	15
MedRxiv		title "vitamin c" (match all words) and abstract or title "vitamin c" (match all words) and full text or abstract or title "vitamin c" (match whole all)	49
HERDIN		Vitamin c AND Pediatric COVID-19	0
Google Scholar		Vitamin c AND Pediatric COVID-19	8,740

Appendix 2. Characteristics of Included Studies

Author/ Year/ Study Design	Population	Intervention	Comparator	Outcome
Louca et al., 2021 Observational cross sectional survey	App users of self-reported Sarscov2 related information from UK (N=372,720), USA (N= 45, 757), and Sweden (N= 27, 373) aged 16 to 90 years old	Self-reported regular dietary supplement usage (constant use during previous 3 months) in the first waves of the pandemic up to 31 July 2020 among app users who had COVID-19 infection	No self-reported regular usage of dietary supplements in the first waves of the pandemic up to 31 July 2020 among app users who had COVID-19 infection	Outcome measure: SARS-CoV-2 infection before 31 July 2020. No significant association of vitamin C and covid-19 infection for all participants (OR=1, p=1) Positive association in men aged >60 years taking vitamin C supplements (1.22, 95%CI 1.05 to 1.41, p=0.008) for testing positive for SARS-CoV-2.
Behera et al., 2021 Observational case control study	Healthcare workers matched for profession, gender, age and date of diagnosis (Case=covid positive, control=covid negative) (N=372)	Intake of ivermectin and/or hydroxychloroquine and/or vitamin-C and/or other prophylaxis for COVID-19 among HCW who tested positive for COVID-19 (case)	Intake of ivermectin and/or hydroxychloroquine and/or vitamin-C and/or other prophylaxis for COVID-19 among HCW who tested negative for COVID-19 (control)	Outcome measure: COVID-19 infection Vitamin-C prophylaxis not associated with +/- SARS-CoV-2 infection (OR 0.72, 95%CI 0.42 to 1.27, p=0.23)

Appendix 3. GRADE Evidence Profile

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin C intake	No Vitamin C intake	Relative (95% CI)	Absolute (95% CI)		
COVID-19 Infection												
1	case control	serious ^a	not serious	serious ^b	serious ^c	none	29/67 (43.3%)	157/305 (51.5%)	OR 0.72 (0.42 to 1.23)	82 fewer per 1,000 (from 207 fewer to 51 more)	 Very Low	CRITICAL
1	cross sectional	very serious ^{a,d}	not serious	serious ^b	serious ^c	none	-	-	OR 1.02 (0.99 to 1.06)	Not estimatable	 Very low	CRITICAL

CI: confidence interval; OR: odds ratio

Explanations

- a. Included intake of multiple prophylactic agents; effect of Vitamin C alone cannot be isolated from results
- b. Adult patients enrolled
- c. Confidence interval crosses the null value
- d. Reported findings from UK data only (did not include findings from USA, Sweden)

Appendix 4. Forest Plots

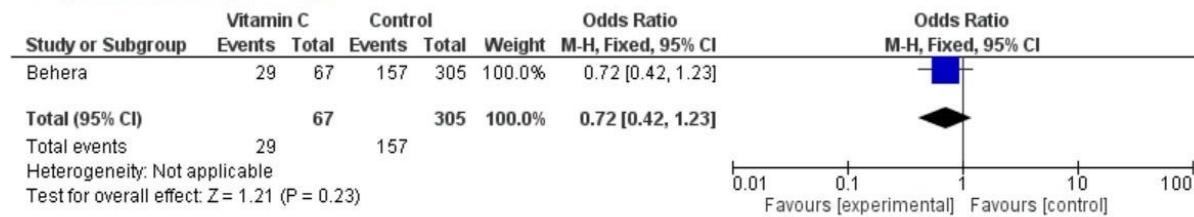


Figure 1. Intake of vitamin C and COVID-19 infection

Appendix 5. Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 11)

FACTORS		JUDGEMENT (N = 11)					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS	
Problem	No (2)	Yes (6)		Varies (2)		Uncertain (1)		
Benefits	Large	Moderate (1)	Small	Trivial (3)	Varies	Uncertain (7)		<ul style="list-style-type: none"> Indirect evidence from observational studies done among adults showed no significant benefit with vitamin C use in preventing COVID-19 infection.
Harm	Large	Moderate	Small	Trivial (4)	Varies	Uncertain (7)		
Certainty of evidence	High	Moderate		Low (1)		Very low (10)		<ul style="list-style-type: none"> Rated very low due to risk of bias, indirectness and imprecision
Balance of effects	Favors drug	Probably favors drug (2)	Does not favor drug or no drug (3)	Probably favors no drug	Favors no drug	Varies	Uncertain (6)	
Values	Important uncertainty or variability	Possibly important uncertainty or variability (4)		Probably no important uncertainty or variability (4)		No important uncertainty or variability (3)		<ul style="list-style-type: none"> Vitamin C is relatively inexpensive and low risk for toxicity
Resources required	Uncertain (1)	Varies	Large costs	Moderate costs (5)	Negligible costs or savings (4)	Moderate savings	Large savings (1)	<ul style="list-style-type: none"> 100mg/5mL preparation: Php 17.50/15mL bottle to Php 28.00/120mL bottle Ascorbic acid 500mg tablets: Php 0.80/tab
Certainty of evidence of resources required	No included studies (10)		Very low (1)	Low	Moderate	High		
Cost-effectiveness	No included studies (11)	Varies	Favors the comparison	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention	Favors the intervention	
Equity	Uncertain (7)	Varies (2)	Reduced	Probably reduced	Probably no impact (2)	Probably increased	Increased	
Acceptability	Uncertain (5)	Varies	No	Probably no	Probably yes (5)	Yes (1)		
Feasibility	Uncertain (4)	Varies (1)	No	Probably no	Probably yes (5)	Yes (1)		

Additional Comments

- It may be cost-beneficial to those with low vitamin C intake.

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.

Evidence Summary

Key Findings

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.

Introduction

Zinc has potent immunoregulatory and antiviral properties. It is postulated that Zinc may work for the treatment of SARS-CoV-2 because of its ability to modulate the viral entry, fusion, replication, viral protein translation and virus budding of respiratory viruses [1,2]. Zn²⁺ cations especially in combination with Zinc ionophore pyritohione were shown to inhibit SARS-coronavirus RNA polymerase (RNA dependent RNA polymerase, RdRp) activity by suppressing its replication [3].

Zinc deficiency is often linked to impaired functions of all immune cells and is related to susceptibility by at least 16% to various respiratory infection worldwide, implying a crucial link between zinc deficiency and the risk of infections and progression of the severity of COVID-19 hence suggesting the benefits of zinc supplementation [4].

Among children, the use of 10mg elemental zinc for </=11 months and 20mg elemental zinc for >11months for longer than 3 months has been shown effective for preventing pneumonia. A meta-analysis done in the pre-COVID time, among children ages two months and five years of age in resource-limited countries, showed that zinc significantly reduced the incidence of clinically confirmed pneumonia by approximately 20% (RR 0.79, 95% CI 0.71-0.88) [5,6]. The included studies were performed in Bangladesh, India, Peru,

and South Africa. One study found a shorter course of pneumonia in children under five years of age in Mexico [7].

This review aims to determine the efficacy and safety of zinc in the prevention of COVID-19 among pediatric patients.

Review Methods

We performed a comprehensive systematic search of related literature from MEDLINE, MedRxiv.org, WHO Clinical Trials Registry, WHO Therapeutics and COVID 19 Living Guidance, WHO Institutional Repository for Information Sharing, HERDIN Plus, and clinicaltrials.gov. Freehand search using Google was also done. There was no limit as to date, language, and country of publication. Search was conducted using the following terms: Zinc, Zinc Deficiency, pediatric-COVID-19, Severe Acute Respiratory Syndrome Coronavirus 2, 2019-nCoV, viral illness, cough and diarrhea. The table below summarizes our inclusion criteria:

Table 1. Inclusion criteria for zinc for the prevention of COVID-19 among children

Population	Children without COVID-19
Intervention/Exposure	Zinc, zinc sulfate, zinc gluconate
Comparison	No zinc, placebo
Outcomes	Incidence of COVID, forward transmission, viral load, adverse events

We searched for randomized controlled trials, observational studies, systematic reviews and meta-analyses. The risk of bias of included studies was assessed using guide questions derived from Painless Evidence-Based Medicine for RCTs. Certainty of evidence was assessed using the GRADE evidence profile. Review Manager 5.4.1 was used for meta-analysis.

Results

There was no direct evidence on the use of Zinc to prevent COVID-19 among pediatric patients. Only indirect evidence was available, wherein Zinc was used among adults for the prevention of COVID-19 infection.

One RCT was included in this review. The study of Seet et al. used four different arms to prevent COVID-19 among participants living in a dormitory: Zinc (40 mg) + vitamin C (250 mg) twice daily (total, zinc 80 mg and vitamin C 500 mg day), vitamin C (500 mg) once daily, hydroxychloroquine 400 mg (four tablets) once, followed by 200 mg (two tablets) daily, and ivermectin 12 mg/tab (1 tablet) daily given for 6 weeks [8]. For the analysis of this review, we compared the first two arms.

The overall certainty was low. Downgrading was done due risk of bias (due to lack of blinding and allocation concealment) and indirectness.

Seet et al. reported that there was a significantly lower proportion of persons who tested positive for SARS-CoV 2 on RT PCR within six weeks among those given zinc + vitamin

C (50/634) than those given vitamin C alone (85/619) (RR 0.57; 95% CI 0.41; 0.80). Seropositivity to SARS-CoV 2 was also significantly lower among those given zinc + vitamin C (250/634) than those given with vitamin C alone (348/619) (RR 0.7; 95% CI 0.62; 0.79).

The study also reported that among those given zinc + vitamin C versus vitamin C alone, there was a significantly lower proportion of 1) persons who experienced acute respiratory symptoms (34/634 vs. 69/619) (RR 0.57; 95% CI 0.32; 0.71) and 2) persons who developed symptomatic COVID- 19 (33/634 vs. 64/619) (RR 0.50; 95% CI 0.34, 0.75).

This study reported no hospitalization or death due to COVID-19 within the six-week period, in any of the groups. [8]

Other Considerations (Evidence to Decision)

Zinc Sulfate is available in drugstores and health outlets, as well as online shopping sites, which show one price at P101 for a 27.5mg/mL (10mg elemental zinc) per 15mL bottle and P107.5 per 60mL bottle [9,10]. The 2021 Philippine Drug Price Reference Index (DPRI) shows the mean price of P 34.75 for a 27.5mg/mL (10mg elemental zinc) 15ml oral drops and P 38.00 for a 55mg/5mL (20mg elemental zinc) 60mL syrup [11].

Zinc gluconate is also available in the market as a 70mg/tab chewable tablet P10.34 each containing 10mg of elemental Zinc per tablet [12]. No available data on the 2021 Philippine Drug Price Reference Index (DPRI).

Recommendations from Other Groups

Currently, there are no recommendations from NIH [13], CDC [14], WHO [15], and the American Pediatric Academy [16] on the use of zinc specifically in children, to prevent pediatric-COVID-19.

Research Gaps

As of January 2022, there are no ongoing trials investigating the effectiveness of zinc as adjunctive treatment for pediatric COVID-19.

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Evidence Summary Appendices

Appendix 1. Search Yields and Results

Database	Search terms	Yield	Hits
PubMed	((((Zinc) OR (Zinc Sulfate) OR (Zinc Gluconate) OR (integrative medicine[MeSH Terms])) OR (complementary medicine[MeSH Terms])) AND ("pediatric COVID-19" [Supplementary Concept] OR "COVID-19 prevention" [Supplementary Concept] OR "COVID-19 serotherapy" [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 epidemic 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 (((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])	3	0
PubMed	((((Zinc) OR (Zinc Sulfate) OR (Zinc Gluconate) OR (integrative medicine[MeSH Terms])) OR (complementary medicine[MeSH Terms])) AND ("COVID-19" [Supplementary Concept] OR "COVID-19 prevention" [Supplementary Concept] OR "COVID-19 serotherapy" [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 epidemic 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 (((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])	75	1
Medrxiv	Zinc AND Prevention AND Pediatric COVID-19	52	0
Medrxiv	Zinc AND Prevention AND COVID-19	52	5
HERDIN	Zinc AND Prevention AND Pediatric COVID-19	0	0
Google Scholar	Zinc AND Prevention AND Pediatric COVID-19	16,600	1
Clinical Trial Registry	Zinc AND Prevention AND COVID-19	2	2

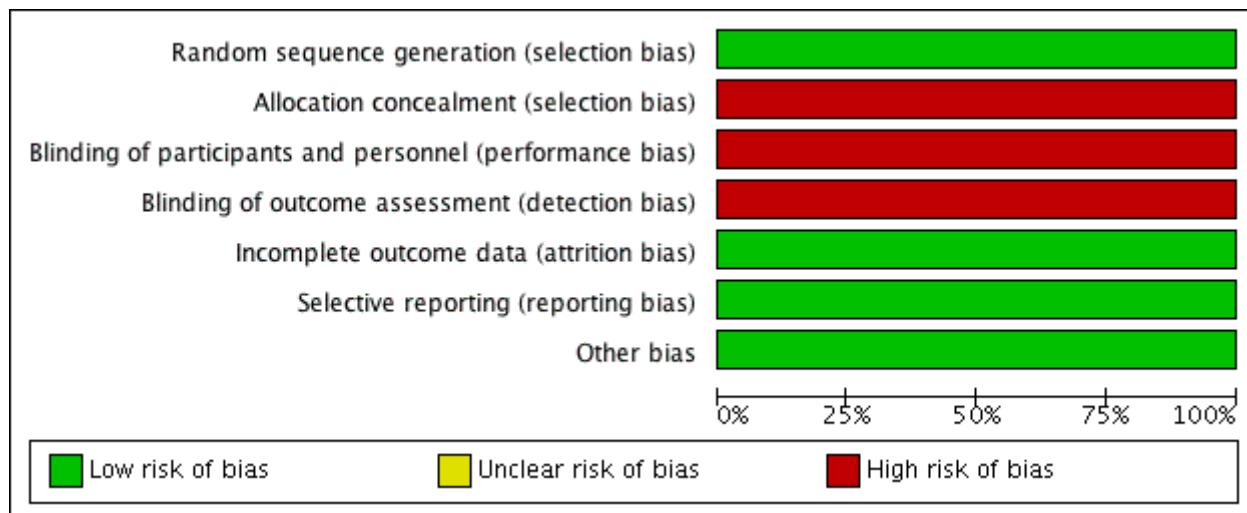
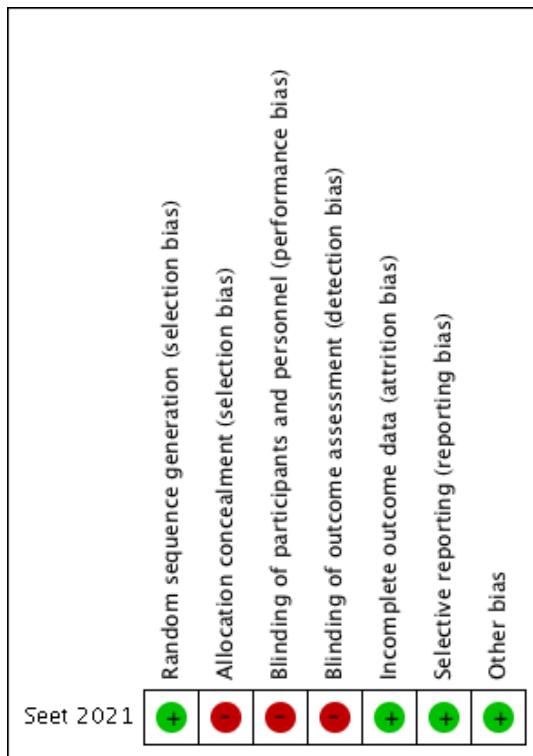
Appendix 2. Characteristics of Included Studies

Study author	Population	Intervention	Control	Outcome
Seet Open Label RCT Men Dormitory in Singapore 2021 Singapore	N=3037 Men mean age 33 Vitamin C + Zinc: 634 Vitamin C: 619 HCQ: 432 Ivermectin: 617 Povidone Throat Spray: 735	Zinc (40 mg) + Vitamin C (250 mg) twice daily (total, zinc 80 mg) for 6 weeks.	Vitamin C (500 mg day) administered once daily for 6 weeks	Positive serologic test within 6 weeks Positive RT PCR test within 6 weeks Acute respiratory symptoms Symptomatic COVID Incidence of hospitalization and death

Appendix 3. Detailed Study Appraisal

Directness	Seet The population is Adult with COVID 19 instead of Pediatric, Intervention used was Vitamin C with Zinc instead of Zinc Alone. Outcome were the same.
Validity	
Randomly assigned to treatment groups	Yes
Allocation Concealment	No
Similar Baseline characteristic	Yes
Patient blinding and participants	This is an Open label, no blinding
Outcome assessor blinding	No blinding
Analyzed to group originally randomized	Yes
Adequate follow up	Yes
RESULTS	
Treatment Effect	3037 adult with mean age of 33years, VitC+Zn n 634 vs Vit C n 619 - Seropositivity: 250 vs 342 RR 0.7 (0.62,0.79) - RT pcr positivity: 50 vs 85 RR 0.57 (0.41, 0.8) - Acute Respiratory Syndrome: 34 vs 69 RR 0.48 (0.32, 0.71) - Symptomatic COVID 19: 33 vs 64 RR 0.5 (0.34, 0.75) - Hospitalization and Mortality: 0 vs 0
APPLICABILITY	
Biologic Issues	None
Socioeconomic Issues	None

Appendix 4. Risk of Bias



Appendix 5. GRADE Evidence Profile

Author(s): Joanna Marie Tan, MD DPPS, Maria Teresa Tolosa, MD D Clin Epi, FPDS , Ma. Lucila Perez MD MSc FPPS

Question: Should Zinc be used as a preventive measure for COVID-19 in children?

Setting: General pediatric population

Bibliography: Seet, et al. 2021

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zinc	Standard of care	Relative (95% CI)	Absolute (95% CI)		
Serologic Positivity												
1	randomised trials	serious ^a	not serious	serious ^b	not serious	none	250/634 (39.4%)	348/619 (56.2%)	RR 0.70 (0.62 to 0.79)	169 fewer per 1,000 (from 214 fewer to 118 fewer)		CRITICAL
RT PCR Positivity												
1	randomised trials	serious ^a	not serious	serious ^b	not serious	none	50/634 (7.9%)	85/619 (13.7%)	RR 0.57 (0.41 to 0.80)	59 fewer per 1,000 (from 81 fewer to 27 fewer)		CRITICAL
Acute Respiratory Syndrome												
1	randomised trials	serious ^a	not serious	serious ^b	not serious	none	34/634 (5.4%)	69/619 (11.1%)	RR 0.48 (0.32 to 0.71)	58 fewer per 1,000 (from 76 fewer to 32 fewer)		CRITICAL
Symptomatic COVID 19												
1	randomised trials	serious ^a	not serious	serious ^b	not serious	none	33/634 (5.2%)	64/619 (10.3%)	RR 0.50 (0.34 to 0.75)	52 fewer per 1,000 (from 68 fewer to 26 fewer)		CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. the study of Seet is not blinded and had no allocation concealment

b. the study of Seet used Adult COVID 19 patients and used Vitamin C with Zinc vs Vitamin C

Appendix 6. Forest Plots

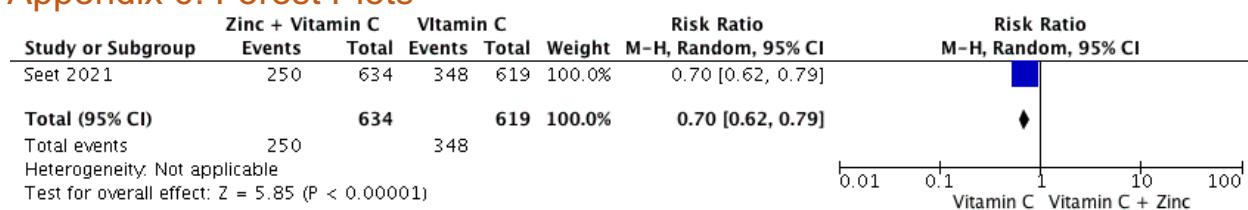


Figure 1. Positivity of serology

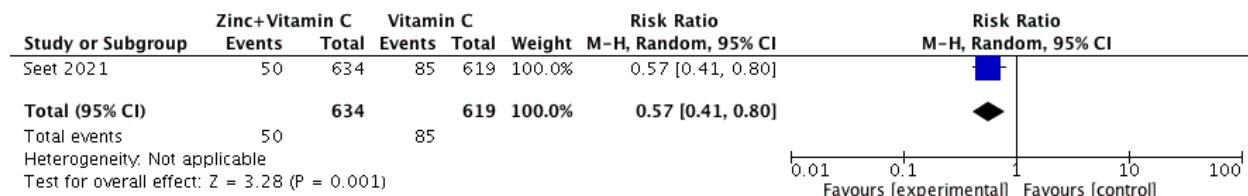


Figure 2. Positivity of RT-PCR

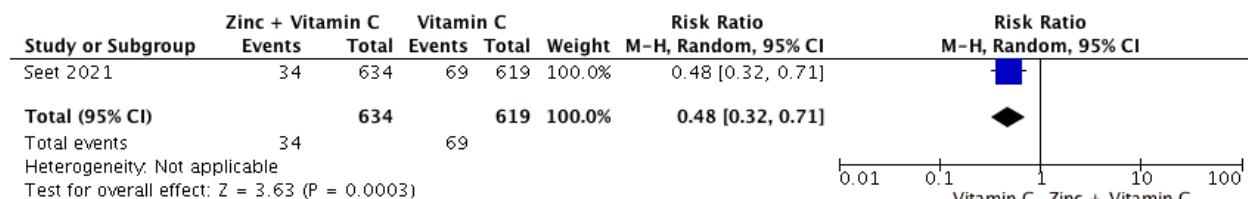


Figure 3. Acute respiratory syndrome

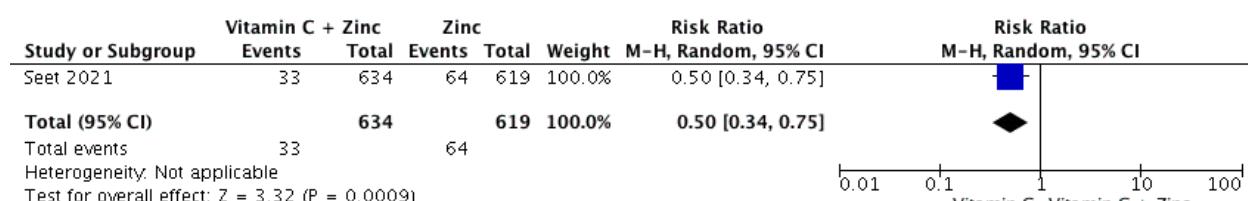


Figure 4. Symptomatic COVID-19

Appendix 7. Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 11)

FACTORS		JUDGEMENT (N = 11)				RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS		
Problem	No	Yes (10)	Varies		Uncertain (1)			
Benefits	Large	Moderate (8)	Small	Trivial (1)	Varies	Uncertain (2)	<ul style="list-style-type: none"> Indirect evidence showed significant benefit of zinc + vit C for lab-confirmed COVID, acute respiratory symptoms and symptoms of COVID-19 	
Harm	Large	Moderate (1)	Small (2)	Trivial (4)	Varies	Uncertain (4)	<ul style="list-style-type: none"> No significant adverse events 	
Certainty of evidence	High	Moderate		Low (11)		Very low		<ul style="list-style-type: none"> Rated low due to indirectness, risk of bias
Balance of effects	Favors drug (6)	Probably favors drug (4)	Does not favor drug or no drug	Probably favors no drug	Favors no drug	Varies	Uncertain (1)	
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (1)		Probably no important uncertainty or variability (7)		No important uncertainty or variability (1)		
Resources required	Uncertain (1)	Varies	Large costs	Moderate costs (5)	Negligible costs or savings (3)	Moderate savings (2)	Large savings	<ul style="list-style-type: none"> Zinc sulfate 27.5mg/mL: Php 101.00/15mL bottle Zinc sulfate 27.5mg/mL: Php 107.50/60mL bottle Zinc gluconate 70mg/tab: Php 10.34/tab
Certainty of evidence of resources required	No included studies (4)		Very low	Low (1)	Moderate (6)	High		
Cost-effectiveness	No included studies (9)	Varies	Favors the comparison	Probably favors the comparison (1)	Does not favor the comparison or the intervention (1)	Probably favors the intervention (1)	Favors the intervention	
Equity	Uncertain (6)	Varies	Reduced (1)	Probably reduced (1)	Probably no impact (1)	Probably increased (2)	Increased	
Acceptability	Uncertain (4)	Varies	No	Probably no	Probably yes (7)	Yes		
Feasibility	Uncertain (3)	Varies	No (1)	Probably no	Probably yes (6)	Yes (1)		

Additional Comments

- Low levels of zinc in the Filipino children is a factor to consider in preventive care.

D.Adjunct Interventions for COVID-19 in Children

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.

Evidence Summary

Key Findings

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.

Introduction

Vitamin D is a fat-soluble vitamin essential in calcium and phosphorus homeostasis and in the maintenance of bone, skin, and tooth enamel. Receptors for vitamin D are nearly universally expressed in human cells, including in cells of the immune system, and it can exhibit anti-inflammatory effects by modulating macrophage maturation, preventing excessive expression of antiviral cytokines, downregulating inflammatory T_H1 and T_H17 responses, and promoting regulatory T cell (T_{reg}) differentiation [1].

There are several studies that attempted to establish the link between respiratory illness and vitamin D deficiency. We identified two systematic reviews, done in the pre-pandemic period, that evaluated the efficacy of vitamin D supplementation as primary prevention of any respiratory tract infection in children, but these yielded inconsistent results. A meta-analysis of six studies in children showed inconclusive results for incidence of RTI with vitamin D supplementation (Intervention group: N=3,400; control group: N=3,443, RR 0.88, 95% CI 0.66–1.11, I²= 80.4%, p=.000) [2]. However, evidence from another meta-analysis showed significant benefit of supplementation in trials where vitamin D was given to participants aged one year to less than 16 years old (IG=5994, CG=5877, OR 0.71, 95% CI 0.57-0.90, I² 46%, P=0.027) [3].

In relation to COVID-19, vitamin D deficiency is postulated to contribute to increased risk of COVID-19 infection and severity. A previously published meta-analysis of 23 studies in adults found a significant correlation between low serum vitamin D levels and COVID-19 infection (OR 3.3, 95% CI 2.5-4.3) as well as low serum vitamin D and severe COVID-19 (OR 5.1, 95% CI 2.6-10.3) [4]. Another meta-analysis of 13 studies in adults reported significantly higher levels of vitamin D in healthy patients compared to COVID-19 patients (MD = 3.93; 95% CI 2.84–5.02) [5]. A study involving hospitalized very elderly patients reported that bolus vitamin D supplementation was associated with decreased risk of severe COVID-19 and mortality [6]. Similar findings have also been reported in a meta-analysis of eight studies done in pediatric patients, showing significant correlation between vitamin D deficiency and severe COVID-19 (OR 5.5, 95% CI 1.560-19.515) [7]. These reports make vitamin D a supplement of interest for clinicians to prescribe in both prevention and treatment of COVID-19. This review seeks to determine the efficacy and safety of vitamin D as an adjunct for the prevention and treatment of COVID-19 in pediatric patients.

Review Methods

A database search of MEDLINE, the Cochrane COVID-19 Study Register, LitCOVID, the CADTH COVID-19 Evidence Portal, and the World Health Organization (WHO) COVID-19 database was done with a combination of free-text and MeSH terms including “COVID-19” and “vitamin D” was done to search for clinical practice guidelines (CPGs), randomized controlled trials (RCTs), cohort studies, case series, systematic reviews, and meta-analyses that report the effect of vitamin D compared to placebo or standard of care as prevention of COVID-19 in at-risk patients and as adjunct treatment in the management of COVID-19 patients. Preprints were obtained by searching the WHO COVID-19 database, which includes studies found in medRxiv. An additional search was done for CPGs using the CPG Infobase. Ongoing clinical trials were searched through the Cochrane COVID-19 Study Register and the WHO COVID-19 database, which includes trials from ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. The final search date was on January 12, 2022. Studies meeting the criteria described in Table 1 were included in the review.

Table 1. PICO criteria for vitamin D and COVID-19.

Population	Children 18 years old and below with COVID-19
Intervention/Exposure	Vitamin D with standard of care
Comparison	Placebo, standard of care, no vitamin D
Outcomes	Hospitalization, mortality, recovery, clinical improvement, need for mechanical ventilation, duration of hospital stay, duration of ICU stay, adverse events, negative viral conversion

No restrictions on patient COVID-19 severity status, treatment outcome, or country were applied. Studies that were not original research, studies not in English, in-vitro studies, studies combining vitamin D with another drug, and those that compare vitamin D to treatments that are not placebo or standard of care were excluded.

The risk of bias of included studies was assessed using guide questions derived from Painless Evidence-Based Medicine [8] for RCTs. Certainty of evidence was assessed using the GRADE evidence profile [9]. Review Manager 5.4.1 was used for meta-analysis.

Results

We found no RCTs, cohort studies, case series, systematic reviews, or meta-analyses that determined the effectiveness of vitamin D as an adjunct treatment for COVID-19 in pediatric patients, either exclusively or as a subgroup. The most recent CPG found that addressed vitamin D supplementation for COVID-19 treatment was that of the Philippine COVID-19 Living CPG, updated in December 2021 [11]. In this CPG, a systematic search was conducted with a final date of 14 November 2021 and eight RCTs (Appendix 3B) that used vitamin D as adjunct treatment for hospitalized adult patients were included. These studies enrolled a total sample size of 740 adults [12-19]. Subgroup analysis was done based on vitamin D status, with subgroups of four studies with low serum vitamin D and four studies with undetermined vitamin D status [14-15,17-18]. Outcomes considered for this review were: mortality, ICU admission, need for mechanical ventilation, length of hospital stay, clinical improvement, virologic clearance, and adverse effects. Certainty of evidence (Appendix 4B) was judged to be very low because of risk of bias, inconsistency, indirectness and imprecision. Pooled analysis (Appendices 4-5) showed inconclusive results for the outcomes of overall mortality (RR 0.73, 95% CI 0.38-1.40), ICU admission (RR 0.54, 95% CI 0.28-1.05), incidence of mechanical ventilation (RR 0.61, 95% CI 0.38-1.00), length of hospital stay (MD -0.48, 95% CI -1.91-0.94), clinical improvement (RR 0.58, 95% CI 0.28-1.18) and virologic clearance (RR 0.58, 95% CI 0.19-1.79). Subgroup analysis showed that mortality, ICU admission, mechanical ventilation, or hospital length of stay were not significantly affected by vitamin D supplementation for patients with undetermined and low baseline serum vitamin D. No adverse effects directly attributable to vitamin D supplementation were found in any of the RCTs. The CPG concluded that there was insufficient evidence to recommend the use of Vitamin D supplementation as an adjunct treatment for adult or pediatric patients with COVID-19 infection.

Other Considerations (Evidence to Decision)

Table 2. Evidence to Decision Considerations

Cost	No evidence was found on the cost-effectivity of Vitamin D supplementation for COVID-19 in children. The approximate prices of vitamin D oral drops, syrup and capsule from local pharmacies are as follows: <i>Vitamin D3 100 IU/mL oral drops = Php 200.00 per 30 mL bottle</i> <i>Vitamin D3 200 IU/5 mL oral syrup = Php 250.00 per 250 ml bottle</i> <i>Vitamin D3 800 IU/capsule = Php 6.75 per capsule</i>
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	<p>As per the Interim Guidelines on COVID-19 from the Pediatric Infectious Disease Society of the Philippines (31 Aug 2020) [20], the recommended dose for vitamin D is as follows, to be given for 5 days:</p> <p><2 years: 1,000 IU/day >2 years: 2,000 IU/day</p>
Availability	Available as an over-the-counter medication in most local pharmacies.
Factors to Impact Acceptability or Compliance	The rationale of vitamin D supplementation in SARS-CoV-2 infection in children is based on the reduction of influenza A incidence with vitamin D supplementation [21].

Recommendations from Other Groups

The recommendations of other groups on the use of vitamin D for the prevention or treatment of COVID-19 are summarized in the table below.

Table 3. Summary of recommendations from other groups.

Group	Recommendation
US NIH (April 2021) [23]	There is insufficient evidence to recommend either for or against the use of vitamin D for the treatment of COVID-19.
Australian COVID-19 Living CPG (December 2021) [24]	Do not use vitamin D analogues for the treatment of COVID-19 outside of 285 Philippine trials with appropriate ethical approval.
NICE COVID-19 rapid guideline: Vitamin D (December 2021) [25]	Do not offer a vitamin D supplement to people solely to prevent or to treat COVID-19, except as part of a clinical trial.
Cochrane: Vitamin D supplementation for the treatment of COVID-19: a living systematic review (March 2021) [26]	<p>There is insufficient evidence to determine the benefits and harms of vitamin D supplementation as a treatment of COVID-19.</p> <p>Moreover, we found only limited safety information, and were concerned about consistency in measurement and recording of these outcomes.</p>
Alberta Scientific Advisory Group: Vitamin D in the Treatment and Prevention of COVID-19 (7 Jan 2021) [27]	There is no high-quality evidence that suggests taking vitamin D supplements is specifically effective in the prevention or treatment of COVID-19.

Ontario COVID-19 Science Advisory Table (18 October 2021) [28]	Vitamin D is currently not recommended for the treatment of COVID-19.
Philippine COVID-19 Living CPG (18 March 2021) [11]	We recommend against the use of Vitamin D supplementation to prevent COVID-19 Infection. There is insufficient evidence to recommend the use of Vitamin D supplementation as an adjunct treatment for patients with COVID-19 infection.
Philippine Pediatric Society. A Parent's Guide on Covid-19 Infection in Children (December 2021) [29]	Supplementation of nutrients such as vitamin C, vitamin D, folate and omega fatty acids may be beneficial to overall health but are not completely validated as preventive or therapeutic medications.
Pediatric Infectious Disease Society of the Philippines. Interim Guidelines on Covid-19. (08 January 2022) [30]	There is no evidence for or against multivitamins and minerals as prevention or treatment of COVID-19 in children. Nutritional support may be given upon the attending physician's discretion with doses not exceeding the Recommended Dietary Allowance.

Research Gaps

There is a need for randomized controlled trials of vitamin D supplementation as a preventive and treatment measure against COVID-19 in children. These studies should aim to determine the optimal vitamin D doses to achieve benefit while balancing safety. As of January 2022, there is one ongoing pediatric clinical trial on vitamin D as adjunctive treatment of COVID-19 and one trial on vitamin D as COVID-19 prevention (Appendix 6).

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Evidence Summary Appendices

Appendix 1. Search Yield and Results

5. For Prevention

Database	#	Keywords/MeSH	Yield
MEDLINE (Pubmed)	1	((("COVID-19" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [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 epidemic 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])) AND (((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])) OR (((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])) AND (pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens)((("COVID-19" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [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 epidemic 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])) AND (((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])) OR (((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])) AND (pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens)	6,164
	2	"vitamin D" OR ergocalciferol OR cholecalciferol OR "vitamin D2" OR "vitamin D3" OR calcifediol OR calcidiol OR 25-hydroxycholecalciferol OR "25-hydroxyvitamin D ₃ " OR calcitriol OR "1,25-dihydroxycholecalciferol" or "1,25-hydroxyvitamin D ₃ "	97,329
	3	((("Incidence of COVID" OR "attack rate" OR "incidence rate" OR "incidence proportion") OR ("covid prevention" OR "forward transmission")) OR ("viral load" OR "virus titer" OR "viral burden))) OR ("adverse event" OR "adverse events")	112,758

	4	#1 #2 #3 (all studies)	23
	5	#1 #2 #3 (Meta-analysis, RCTs, Systematic reviews)	6
Cochrane Library	1	(pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens)	302,323
	2	"vitamin d" or ergocalciferol or cholecalciferol or "vitamin d2 or "vitamin d3 or calcifediol or calcidiol or calcitriol	15,755
	3	"Incidence of COVID" OR "attack rate" OR "incidence rate" OR "incidence proportion" OR "prevention" OR "forward transmission" OR "viral load" OR "virus titer" OR "viral burden" OR "adverse event"	234,422
	4	#1 #2 #3	6
	5	#1 #2 #3 (Interventional study)	5
	6	#1 #2 #3 (Rapid review)	1
LitCOVID	1	(pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens) AND ("vitamin D" or ergocalciferol or cholecalciferol or "vitamin D2" or "vitamin D3" or calcifediol or calcidiol or 25-hydroxycholecalciferol or "25-hydroxyvitamin D ₃ " or calcitriol or "1,25-dihydroxycholecalciferol" or "1,25-hydroxyvitamin D ₃ ") AND "Incidence of COVID" OR "attack rate" OR "incidence rate" OR "incidence proportion" OR "prevention" OR "forward transmission" OR "viral load" OR "virus titer" OR "viral burden" OR "adverse event"	13
	2	#1 AND <i>Chemicals: Vitamin D OR Cholecalciferol</i>	2
WHO COVID Database	1	(tw:((pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens) AND ("vitamin D" or ergocalciferol or cholecalciferol or "vitamin D2" or "vitamin D3" or calcifediol or calcidiol or 25-hydroxycholecalciferol or "25-hydroxyvitamin D ₃ " or calcitriol or "1,25-dihydroxycholecalciferol" or "1,25-hydroxyvitamin D ₃ ") AND (hospitalization OR hospitalized OR admission) or (mortality OR death) or (recovery OR remission OR improvement) or ("mechanical ventilation" OR MV OR intubation) or ("length of stay" OR "hospital stay" OR "length of admission" OR "time admitted" OR "time hospitalized") or ("intensive care unit" OR ICU OR "ICU admission" OR "intensive care unit admission" OR "ICU stay") or ("adverse event" OR "adverse events" OR complication OR complications) or ("viral conversion" OR "negative viral conversion")))	123
	2	#1 AND controlled clinical trial OR Systematic review OR Clinical Practice Guide OR Evidence synthesis	18

6. As Adjunct Treatment

Database	#	Keywords	Yield
MEDLINE (Pubmed)	1	((("COVID-19" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [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	214,506

	"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 epidemic 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]))	
2	"vitamin D" OR ergocalciferol OR cholecalciferol OR "vitamin D2" OR "vitamin D3" OR calcifediol OR calcidiol OR 25-hydroxycholecalciferol OR "25-hydroxyvitamin D ₃ " OR calcitriol OR "1,25-dihydroxycholecalciferol" or "1,25-hydroxyvitamin D ₃ "	97,423
3	(hospitalization OR hospitalized OR admission) OR (mortality OR death) OR (recovery OR remission OR improvement) OR ("mechanical ventilation" OR MV OR intubation) OR ("length of stay" OR "hospital stay" OR "length of admission" OR "time admitted" OR "time hospitalized") OR ("intensive care unit" OR ICU OR "ICU admission" OR "intensive care unit admission" OR "ICU stay") OR ("adverse event" OR "adverse events" OR complication OR complications) OR ("viral conversion" OR "negative viral conversion")	11,629,542
4	(pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens)	4,835,990
5	#1 AND #2 AND #3	763
6	#1 AND #2 AND #3 AND Filters: Randomized Clinical Trial, Systematic Review, Meta-analysis	58
7	#1 AND #2 AND #3 AND #4	103
Cochrane COVID-19 Study Register	1 ("vitamin D" or ergocalciferol or cholecalciferol or "vitamin D2" or "vitamin D3" or calcifediol or calcidiol or 25-hydroxycholecalciferol or "25-hydroxyvitamin D ₃ " or calcitriol or "1,25-dihydroxycholecalciferol" or "1,25-hydroxyvitamin D ₃ ") AND (hospitalization OR hospitalized OR admission) or (mortality OR death) or (recovery OR remission OR improvement) or ("mechanical ventilation" OR MV OR intubation) or ("length of stay" OR "hospital stay" OR "length of admission" OR "time admitted" OR "time hospitalized") or ("intensive care unit" OR ICU OR "ICU admission" OR "intensive care unit admission" OR "ICU stay") or ("adverse event" OR "adverse events" OR complication OR complications) or ("viral conversion" OR "negative viral conversion")	2,600
	2 #1 AND <i>Interventional</i> study type	289
	3 #1 AND (pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens	1,057
WHO COVID Database	1 ("vitamin D" or ergocalciferol or cholecalciferol or "vitamin D2" or "vitamin D3" or calcifediol or calcidiol or 25-hydroxycholecalciferol or "25-hydroxyvitamin D ₃ " or calcitriol or "1,25-dihydroxycholecalciferol" or "1,25-hydroxyvitamin D ₃ ") AND (hospitalization OR hospitalized OR admission) or (mortality OR death) or (recovery OR remission OR improvement) or ("mechanical ventilation" OR MV OR intubation) or ("length of stay" OR "hospital stay" OR "length of admission" OR "time admitted" OR "time hospitalized") or ("intensive care unit" OR ICU OR "ICU admission" OR "intensive care unit admission" OR "ICU stay") or ("adverse event" OR "adverse events" OR complication OR complications) or ("viral conversion" OR "negative viral conversion")	781
CPG Infobase	1 (("vitamin d") AND treatment AND la:en	1
	2 (("vitamin d") AND pedia OR children AND la:en	0

7. CADTH COVID-19 Evidence Portal

	Keywords	Yield
1	(("vitamin d") OR ergocalciferol (D2) OR cholecalciferol (D3) OR Calcifediol OR 25-hydroxyvitamin D3 OR oral 25OHD OR Cholecalciferol OR vitamin D3 OR Ergocalciferol OR vitamin D2	0

8. COVID-Evidence medRxiv

	Keywords	Yield
1	"COVID 19" AND "Vitamin D"	15
2	"COVID 19" AND "Vitamin D" AND (Pedia OR Children)	0

Appendix 2. Characteristics of Included Studies

Table 2A. Characteristics of studies on Vitamin D as preventive measure for COVID-19 in adults.

	Author, Year, Title, Setting	Study Design	Population	Sample Size	Intervention	Comparator	Outcomes
1	Oristrell 2022 Vitamin D supplementation and COVID-19 risk: a population-based, cohort study Spain	Retrospective Cohort	≥ 18 years old supplemented with cholecalciferol or calcifediol	N=711,138	N=243,046 Cholecalciferol n = 108,343 Calcifediol use n = 134,703	N=468,092 Unsupplemented patients n=216,686 (Cholecalciferol group) n=269,406 (Calcifediol group)	- SARS-CoV2 Infection - COVID-19 Mortality - Severe COVID

Table 2B. Characteristics of randomized controlled trials on vitamin D as adjunct COVID-19 treatment in adults (from Joson, Tolosa, and Infantado 2021)

	Clinical Trial ID/Title	Population	Sample Size	Intervention	Comparator	Outcomes
1	Murai 2020 Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19 Brazil	Hospitalized patients with mild to severe COVID-19 Adults aged 18>yrs Positive for SARS-CoV-2 PCR or positive CT scan findings compatible with COVID-19	N=240	200,000 IU of vitamin D3 per orem given on day of admission (N=120)	Placebo (N=120)	Length of Hospital stay Mortality ICU admission Need for mechanical ventilator Duration of mechanical ventilator Serum vitamin D levels
2	Entrenas Castillo 2020 Effect of Calcifediol Treatment and best Available Therapy versus best Available Therapy on Intensive Care Unit Admission and Mortality Among Patients Hospitalized for COVID-19: A Pilot Randomized Clinical study Spain	Hospitalized patients with moderate to severe COVID-19 infection clinical picture of acute respiratory infection confirmed by a radiographic pattern of viral pneumonia positive SARS-CoV-2 PCR with CURB65 severity scale (recommending hospital admission in case of total score > 1).	N=76	Day of admission: 2 capsules of calcifediol (0.266 mg/cap). 1 capsule on days 3, 7, 14, 21, 28 until discharge or ICU admission. Plus standard of care (N=50)	Standard of care (N=26) defined as: 1) Hydroxychloroquine 400mg every 12 hours on first day and 200 mg every 12 hours for the following 5 days 2) Azithromycin 500 mg orally for 5 days, 3) For patients with pneumonia and NEWS score >5,	ICU admission Mortality

					Ceftriaxone 2 g intravenously every 24 hours was given for 5 days.	
3	Rastogi 2020 Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomized, placebo-controlled, study (SHADE study) India	Hospitalized patients with asymptomatic to mild COVID-19 with or without co-morbidities (hypertension, diabetes mellitus, chronic obstructive airway disease, chronic liver disease, chronic kidney disease) with vitamin D deficiency defined as levels below 20 ng/ml	N=40	Daily 60,000 IU of cholecalciferol (5 ml oral solution in nano droplet form) for 7 days with the aim to achieve 25(OH)D level > 50 ng/ml (N=16) Subsequently, 25(OH)D levels were assessed at day 7 and a weekly supplementation of 60,000IU provided to those with 25(OH)D > 50 ng/ml or else continued daily vitamin D 60,000 IU supplementation for another 7 days up until day-14 in participants with 25(OH)D < 50 ng/ml Plus standard of care	Placebo (5 ml distilled water) (N=24) Plus standard of care	Proportion of participants who turn SARS-CoV-2 RNA negative at days 5, 7, 10, 14, 18 and 21 (real-time PCR, CFX-96 IVD, Bio-Rad)
4	Lakkireddy 2021 Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease India	Hospitalized patients with mild to moderate COVID-19 with vitamin D defined as levels below 30 ng/mL	N=130	60,000 IU of cholecalciferol (aqueous nano solution/Deksel) per orem daily for 8 days if with body mass index (BMI) between 18-25 and for 10 days if with BMI more than 25 (N=65) Plus standard of care	Standard of care (N=65)	Inflammatory markers and vitamin D levels before and after intervention (vitamin D levels, CRP, LDH, IL6, Ferritin, N/L ratio) Mortality ICU admission Mean hospital stay Adverse events
5	Elamir 2021 A randomized pilot study using calcitriol in hospitalized COVID-19 patients USA	Hospitalized patients with COVID-19 with moderate to severe COVID-19	N=50	Calcitriol 0.5 ug daily for 14 days or discharge whichever came first. Plus standard of care: remdesivir (200 mg for one day followed by 100 mg for 4 days), dexamethasone (6 mg daily for 10 days), or convalescent plasma	Standard of care Standard of care: remdesivir (200 mg for one day followed by 100 mg for 4 days), dexamethasone (6 mg daily for 10 days), or convalescent plasma	Oxygen requirements Length of hospital stay Need for ICU admission Mortality Readmission.

				days), or convalescent plasma		
6	Maghbooli 2021 Treatment With 25-Hydroxyvitamin D3 (Calcifediol) Is Associated With a Reduction in the Blood Neutrophil-to-Lymphocyte Ratio Marker of Disease Severity in Hospitalized Patients With COVID-19: A Pilot Multicenter, Randomized, Placebo-Controlled, Double-Blinded Clinical Trial Iran	Hospitalized patients with moderate to severe COVID-19	N=106	Calcifediol 25 mcg per orem once daily for 30 days Plus standard of care: a combination of hydroxychloroquine, azithromycin, and ceftriaxone for patients with pneumonia	Placebo Plus standard of care: a combination of hydroxychloroquine, azithromycin, and ceftriaxone for patients with pneumonia	Length of Stay Need for Mechanical Ventilation Mortality ADE Admission to ICU
7	Soliman 2021 Impact of Vitamin D Therapy on the Progress COVID-19: Six Weeks Follow-Up Study of Vitamin D Deficient Elderly Diabetes Patients Egypt	Hospitalized elderly diabetes patients with SARS-CoV-2 with vitamin D deficiency.	N=56	200,000 units of high dose cholecalciferol single dose IM	Placebo	Mortality Need for Mechanical Ventilation
8	Sánchez-Zuno 2021 Vitamin D Levels in COVID-19 Outpatients from Western Mexico: Clinical Correlation and Effect of Its Supplementation Mexico	Outpatient adults with mild COVID-19	N=42	10,000 IU daily of vitamin D3 in soft capsule form for 14 days	Standard of care	Clinical Improvement (D7) Virologic Clearance (D14)

Appendix 3: Grade Evidence Profile

3A. Grade Evidence Profile: Vitamin D for Prevention of COVID-19 in Children

Author(s): Buban, Racoma, Tolosa, and Perez

Question: Should vitamin D be used as a preventive measure for COVID-19 in children?

Bibliography: Oristrell 2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D	no Vitamin D	Relative (95% CI)	Absolute (95% CI)		
SARS-CoV2 Infection												
1	observational studies	serious ^a	not serious	serious ^b	not serious	none	10014/243046 (4.1%)	20543/468092 (4.4%)	RR 0.97 (0.95 to 1.00)	1 fewer per 1,000 (from 2 fewer to 0 fewer)	 Very low	CRITICAL

CI: confidence interval; RR: risk ratio

Explanations

a. Retrospective review of records and absence of blinding

b. Population studied included adults ≥ 18 years old with different vitamin D dose recommendations from children

3B. Grade Evidence Profile For Treatment (updated for pediatric patients; from Joson, Tolosa, and Infantado 2021)

Question: Should Vitamin D supplements compared to placebo be used as adjunct treatment for COVID-19?

Bibliography: Murai, Entrenas-Castillo, Rastogi, Lakkireddy, Elamir, Maghbooli, and Soliman

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D supplements	Placebo/Standard of Care	Relative (95% CI)	Absolute (95% CI)		

Mortality (ITT) (follow-up: range 30 days to 60 days)

6 ^a	randomised trials	serious ^b	serious ^c	serious ^d	serious ^e	none	21/353 (5.9%)	24/305 (7.9%)	RR 0.73 (0.38 to 1.40)	21 fewer per 1,000 (from 49 fewer to 31 more)	 Very low	CRITICAL
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ICU admission (ITT) (follow-up: range 30 days to 60 days)

5	randomised trials	serious ^e	serious ^{c,f}	serious ⁱ	serious ^j	none	35/313 (11.2%)	61/289 (21.1%)	RR 0.54 (0.28 to 1.05)	97 fewer per 1,000 (from 152 fewer to 11 more)	 Very low	CRITICAL
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Need for Mechanical Ventilation (ITT) (follow-up: range 30 days to 60 days)

4	randomised trials	not serious	serious ^{a,c}	serious ⁱ	serious ^j	none	25/238 (10.5%)	31/214 (14.5%)	RR 0.61 (0.38 to 1.00)	56 fewer per 1,000 (from 90 fewer to 0 fewer)	 Very low	CRITICAL
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Hospital length of stay

3	randomised trials	not serious	serious ^c	serious ⁱ	serious ^d	none	210	210	-	MD 0.48 days lower (1.91 lower to 0.94 higher)	 Very low	CRITICAL
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Clinical Improvement (follow-up: mean 7 days)

1	randomised trials	very serious ^b	not serious	serious ⁱ	serious ^d	none	7/21 (33.3%)	11/19 (57.9%)	RR 0.58 (0.28 to 1.18)	243 fewer per 1,000 (from 417 fewer to 104 more)	 Very low	CRITICAL
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Virologic Clearance (follow-up: range 14 days to 21 days)

2	randomised trials	serious ⁱ	not serious	serious ⁱ	serious ^d	none	7/38 (18.4%)	19/44 (43.2%)	RR 0.58 (0.19 to 1.79)	181 fewer per 1,000 (from 350 fewer to 341 more)	 Very low	IMPORTANT
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CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

- a. Serious inconsistency due to different direction of effect by one study Murai which contributed to 32.7% of the over all effect and with risk of bias rated as not serious.
- b. serious risk of bias due to high drop out rate in the study of Murai, Lakkireddy and Maghbooli which contributed to 66.8% of the overall treatment effect
- c. Serious inconsistency due to differences in dosage and formulation of vitamin D.
- d. serious imprecision due to wide confidence interval
- e. serious risk of bias due to high drop out rate in the study of Murai, Lakkireddy and Maghbooli which contributed to 69.7% of the overall treatment effect
- f. serious risk for inconsistency; high heterogeneity I²=55%
- g. Imprecision downgraded by 1 level: due to low number of event rate and wide confidence interval.
- h. serious risk of bias due to unblinded patients and outcome assessors which may have affected how symptoms were reported
- i. Risk of bias downgraded by 1 level: some concerns due to unclear randomization and allocation concealment, and lack of blinding in participants and personnel.
- j. Serious indirectness as studies recruited adults exclusively.

Appendix 4A: Forest Plots from Included Studies (Prevention, January 27, 2022)



Figure 1.1. Prevention

Appendix 4B: Forest Plots from Included Studies (from Joson, Tolosa, and Infantado 2021)

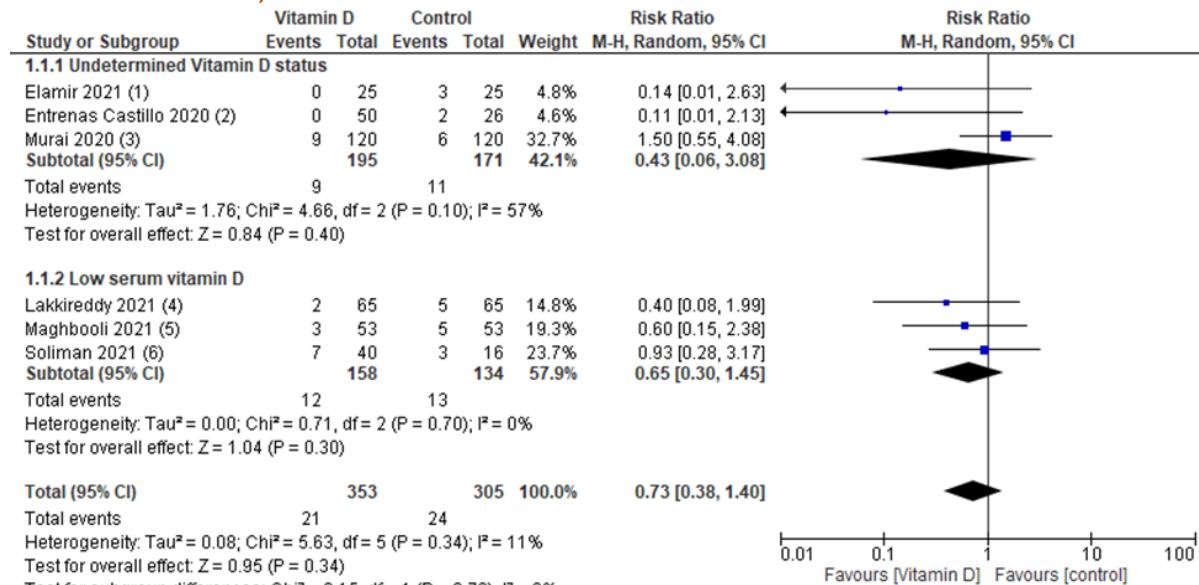


Figure 1.2. Mortality, overall (ITT).

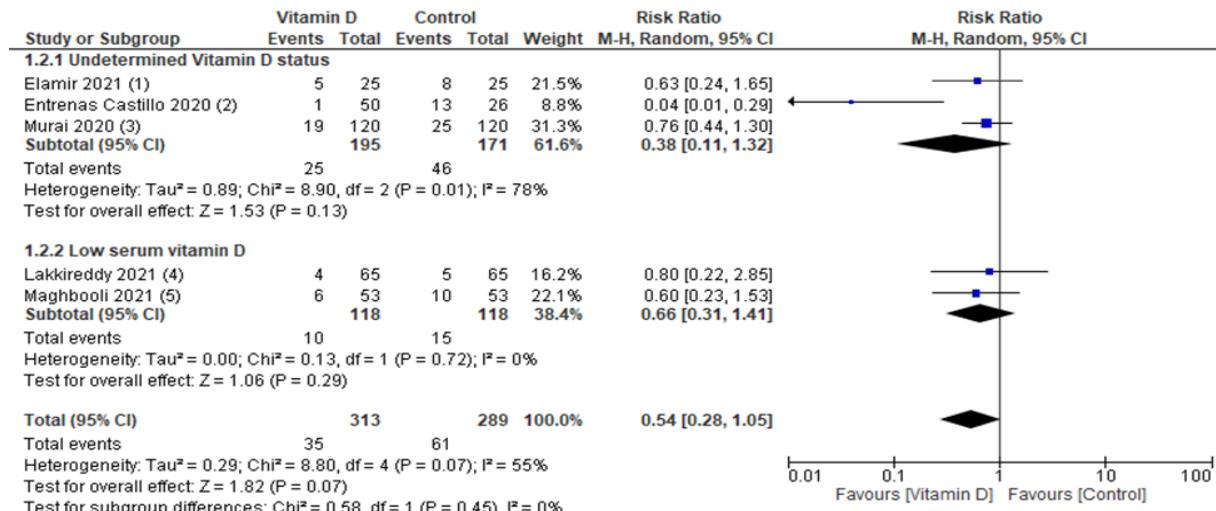


Figure 1.3. ICU admission (ITT).

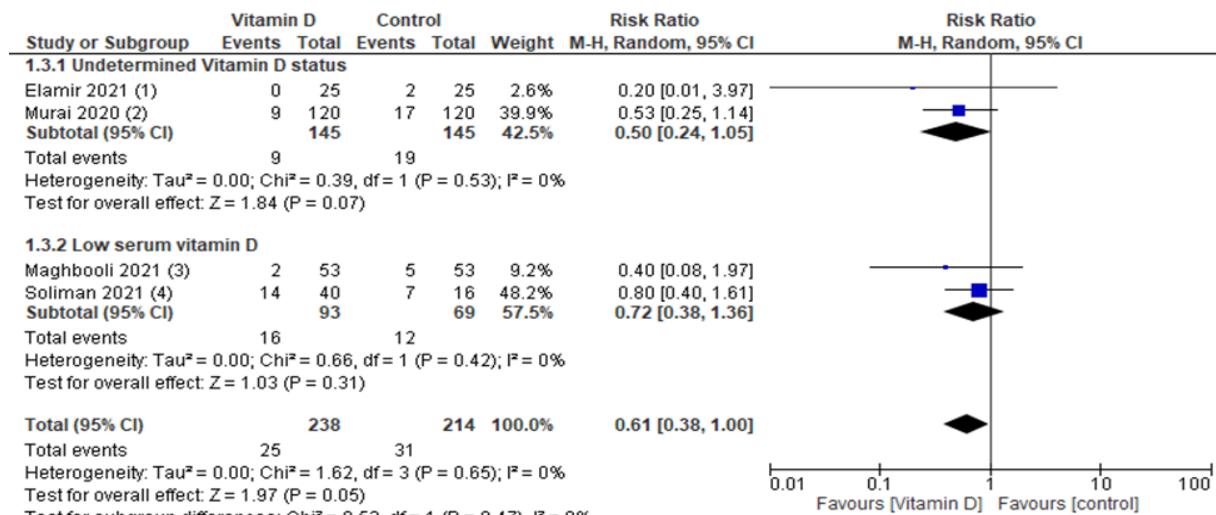


Figure 1.4. Need for Mechanical Ventilation (ITT).

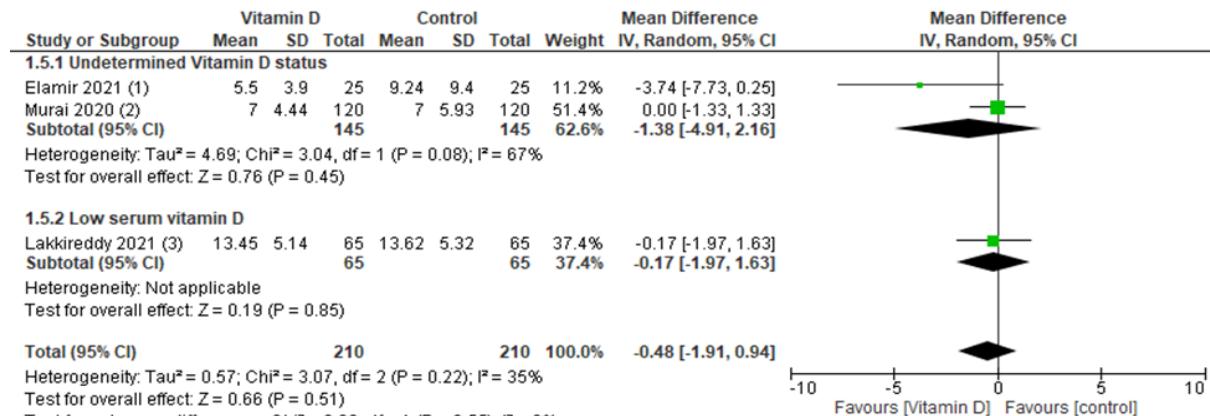


Figure 1.5. Length of Hospital Stay (ITT).

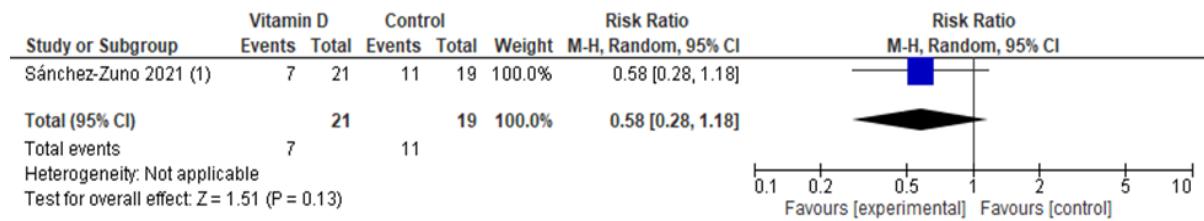


Figure 1.6. Clinical Improvement (ITT).

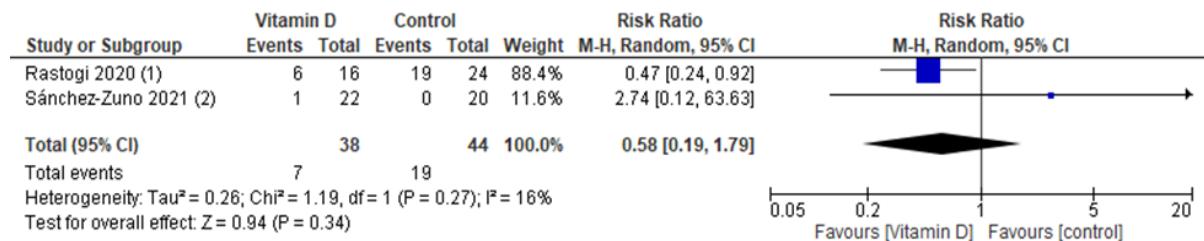


Figure 1.7. Virologic Clearance (ITT).

Appendix 5: Table of Ongoing Studies

Clinical Trial Identifier (Location)	Official Title	Methodology	Outcome Measures	Population	Estimated Date of Completion
NCT04502667 Mexico	Efficacy of Vitamin D Treatment in Pediatric Patients Hospitalized by COVID-19: Open Controlled Clinical Trial	Randomized open controlled trial	<p>Primary outcomes: Serum interleukins, ferritin, D-dimer levels at 7 days post-admission</p> <p>Secondary outcome: Serum vitamin D level at study completion (average of 21 days)</p>	40 children hospitalized with COVID-19	April 2022
NCT05043116 Denmark	High-dose Vitamin D Supplement for the Prevention of Acute Asthma-like Symptoms in Preschool Children - a Double-blind, Randomized, Controlled Trial	Double-blind randomized controlled trial	<p>Primary outcome: Number of acute asthma exacerbations within 1 year</p> <p>Secondary outcome: Time to first asthma exacerbation, duration of symptoms, need for medical treatment Blood/urine calcium levels Adverse events COVID-19 infection risk, symptom burden, infection length</p>	320 preschool children	October 2031

Appendix 6. Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 9)

FACTORS		JUDGEMENT (N = 9)					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No (1)	Yes (6)	Varies (1)	Uncertain (1)			
Benefits	Large	Moderate	Small (1)	Trivial (1)	Varies	Uncertain (7)	<ul style="list-style-type: none"> Inconclusive results for prevention and treatment
Harm	Large	Moderate	Small (2)	Trivial (1)	Varies	Uncertain (6)	
Certainty of evidence	High	Moderate		Low (1)	Very low (8)		<ul style="list-style-type: none"> Rated very low due to indirectness, imprecision and serious risks of bias
Balance of effects	Favors drug	Probably favors drug (2)	Does not favor drug or no drug	Probably favors no drug	Favors no drug	Varies	Uncertain (7)
Values	Important uncertainty or variability	Possibly important uncertainty or variability (1)		Probably no important uncertainty or variability (5)		No important uncertainty or variability (3)	
Resources required	Uncertain (1)	Varies	Large costs (1)	Moderate costs (5)	Negligible costs or savings (2)	Moderate savings	Large savings <ul style="list-style-type: none"> Vitamin D3 100 IU/mL oral drops: Php 200.00/30mL bottle Vitamin D3 200 IU/5mL oral syrup: Php 250.00/250mL bottle Vitamin D3 800 IU/capsule: Php 6.75/cap
Certainty of evidence of resources required	No included studies (9)		Very low	Low	Moderate	High	
Cost-effectiveness	No included studies (9)	Varies	Favors the comparison	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention	Favors the intervention
Equity	Uncertain (8)	Varies	Reduced	Probably reduced (1)	Probably no impact	Probably increased	Increased
Acceptability	Uncertain (6)	Varies	No	Probably no	Probably yes (3)	Yes	
Feasibility	Uncertain (3)	Varies	No (1)	Probably no	Probably yes (4)	Yes (1)	

Additional Comments

- Vitamin D may be too expensive for the mid- to low-income families.
- Supplementation may be beneficial for the Filipino children with already low vitamin D levels.

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.

Evidence Summary

Key Findings

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.

Introduction

Vitamin C or ascorbic acid is an essential water-soluble vitamin that works as a co-factor for enzymes involved in biosynthesis of neurotransmitters, L-carnitine, and collagen among others. [1]. It plays a role in scavenging free oxygen radicals, reducing pro-inflammatory cytokines, promoting phagocytosis and chemotaxis of leukocytes and development and maturation of T-lymphocytes [2-5]. Vitamin C is widely promoted and used to treat respiratory infections. Some evidence supports its use in severe respiratory infections requiring ventilation [6] and in mitigating the duration and severity of common colds [7]. It has also been found to benefit children with viral myocarditis [8]. However, these studies have failed to show clinically significant benefit of vitamin C in children with viral respiratory illness [6,7], and currently is not considered as standard-of-care.

Studies among Filipino children showed inadequate levels of Vitamin C intake in 35% of toddlers aged 24-35.9 months and in 60% of children aged 36-59.9 months old. [9] This finding was more apparent among Filipino school children and adolescents in the low

socioeconomic status, with 68-96% reported to have inadequate vitamin C intake [10]. These children may benefit from adjunctive treatment with Vitamin C during COVID-19 illness. This systematic review seeks to determine the efficacy and safety of Vitamin C as adjunctive treatment in pediatric patients with COVID-19 infection.

Review Methods

We performed a comprehensive systematic search of related literature from MEDLINE via PubMed, Cochrane Library, ClinicalTrials.gov, MedRxIV.com, WHO COVID database, and HERDIN Plus. Freehand search using Google was also done. There was no limit in terms of date, language, and country of publication. The search was conducted using the following terms: COVID-19, SARS-CoV-2, nCOV-19, vitamin C, ascorbic acid and sodium ascorbate. Methodologies included randomized controlled trials, observational studies, case reports and case series, systematic reviews and meta-analyses. Our inclusion criteria for this review were as follows:

Table 1. PICO criteria for vitamin C and COVID-19.

Population	Children with COVID-19
Intervention/Exposure	Vitamin C or Sodium Ascorbate or Ascorbic Acid as adjunctive treatment
Comparison	Usual care, standard of care, placebo, any active control
Outcomes	Hospitalization, mortality, recovery, clinical improvement, need for mechanical ventilation, duration of hospital stay, duration of ICU stay, adverse events, negative viral conversion, adverse effects

Results

We found no published articles that matched our criteria. Results from the Philippine COVID-19 Living Clinical Practice Guidelines for adults were used as indirect evidence [11]. The guideline was appraised using AGREE II tool [Appendix 3].

Eight RCTs on adults were included in the updated guideline last November 2021 [Appendix 3]. Pooled analysis was done for 4 RCTs with hospitalized patients with moderate to severe COVID-19 as their inclusion population [12-15]. Vitamin C doses ranged from 50mg/kg/day to 24g/day and compared against standard of care or study-defined controls. Outcomes included mortality, length of hospital stay, length of ICU stay, need for mechanical ventilation, and adverse events. All four RCTs were used to determine outcomes on mortality rate and length of hospital stay.

Overall estimate on in-hospital mortality rate showed only a trend towards benefit with small negligible harm (RR 0.59; 95%CI 0.34 to 1.03). Overall estimate for length of hospital stay from the four pooled studies showed inconclusive results (MD -0.96, 95%CI -3.84 to 1.92). Two RCTs were pooled to determine outcome for length of ICU stay and showed inconclusive results (MD 1.35, 95%CI -0.12 to 2.83) [12,14]. Three RCTs were included to evaluate outcome of need for mechanical ventilation [12-14] and pooled estimates also showed inconclusive results (RR 0.93; 95% 0.60 to 1.44). Outcomes on adverse events were reported in only two RCTs [10, 14]. No adverse events were

reported with use of intravenous vitamin C [12]. Meanwhile, adverse events such as flushing, headache, nausea and vomiting, stomach pain and diarrhea were reported 21.7% of patients who used high dose oral Vitamin C [16].

Three RCTs studied Vitamin C in conjunction with other adjunct treatments [17-19], while one study included adult COVID-19 patients managed as outpatient [16]. The study by Thomas et al. included adult patients with COVID-19 managed as outpatient [14]. They received either oral vitamin C, oral zinc gluconate, both agents or placebo. The study showed inconclusive results in terms of symptom reduction, hospitalization, mortality and adverse events, and was discontinued due to futility.

The studies of Darban et al. [17], Beigmohammadi et al. [18], and Hakamifard et al. [19] used vitamin C in combination with other adjunctive therapies. The study by Hakamifard et al. showed inconclusive results for the use of vitamins C and E in terms of mortality, length of hospitalization and improvement in clinical response [19]. The study by Darban et al. [17] did not show significant improvement in inflammatory markers and hypoxemia for adults given vitamin C, melatonin and zinc sulfate. Meanwhile, the study by Beigmohammadi et al. [18] showed significantly shorter duration of hospital stay, lower inflammatory markers and SOFA scores for patients given vitamin C in conjunction with vitamins A, B complex, D and E, but effect on mortality reduction was not significant.

The overall certainty of evidence from the studies included in the Philippine LCPG for adults was rated as low due to imprecision and inconsistency. For this review intended for the pediatric population, the overall certainty was further downgraded to very low because of indirectness. Evidence for vitamin C in COVID-19 was only found in adult studies.

Other Considerations (Evidence to Decision)

Intravenous vitamin C administration was the route used by majority of the studies included in this review. According to the search for pricing of available intravenous vitamin C in drugstores in the country, the cost is Php 110.00 for 10 ampules of 500mg/2ml [20], while price ranges from Php 85.00 to 300.00 per 10 ampules from various online sellers. According to the 2021 Philippine Drug Price Reference Index [21], the average cost is Php 28.19 per ampule.

No evidence was found In terms of cost-benefit use, patient's value or preferences and social impact, acceptability or compliance and feasibility in children.

Recommendations from Other Groups

The latest Pediatric Infectious Diseases Society of the Philippines (PIDSP) COVID-19 recommendations on multivitamins and minerals stated no evidence for or against its use in the treatment of COVID-19 in children. Nutritional support may be given upon the discretion of the attending physician with doses not exceeding the Recommended Dietary Allowance [22].

The Philippine Pediatric Society Parent's Guide on COVID-19 Infection in Children states that supplementation of nutrients (including vitamin C) may be beneficial to overall health but are not completely validated as preventive or therapeutic medications [23].

The US-NIH COVID-19 Treatment Guidelines Panel also stated that there is insufficient evidence to recommend for or against the use of vitamin C for the treatment of COVID-19 in both non-critically ill and critically ill patients [24].

The Philippine COVID-19 LCPG (last updated December 2021) stated that there was insufficient evidence to recommend vitamin C as an adjunct treatment for adult patients with COVID-19.

Research Gaps

There are two ongoing studies on the efficacy of vitamin C as adjunctive treatment for COVID-19 that includes children in their population [Appendix 6]. Further research is needed to evaluate efficacy and safety of both oral and intravenous vitamin C in children with COVID-19, with stratification in terms of severity of illness.

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Evidence Summary Appendices

Appendix 1. Search Yield and Results

Database	#	Keywords	Yield
MEDLINE (Pubmed)	1	((("pediatric COVID-19" [Supplementary Concept] OR "COVID-19" [Supplementary Concept] "COVID-19 diagnostic testing" [Supplementary Concept] OR "COVID-19 drug treatment" [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 "coronavirus"[MeSH Terms] OR coronavirus*[all] OR corona-virus*[all] OR cov[tiab]) AND (((((((Vitamin C [tiab]) OR (sodium ascorbate [tiab])) OR (ascorbic acid [tiab])) OR (ascorbic acid [tiab])) OR (antioxidant [tiab])) OR (supplement[tiab])) OR (vitamin c*[tiab])) OR (vitamin C[MeSH Terms])) OR (ascorbic acid [MeSH Terms])) OR (sodium ascorbate [MeSH Terms])) OR (ascorbic [MeSH Terms])) OR (antioxidant[MeSH Terms])) OR (supplement[MeSH Terms]) AND (pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens)	1,112
	2	"vitamin C" OR "ascorbic acid" OR "sodium ascorbate" OR "ascorbic" OR "ascorbate"	1,166
	3	(hospitalization OR hospitalized OR admission) OR (mortality OR death) OR (recovery OR remission OR improvement) OR ("mechanical ventilation" OR MV OR intubation) OR ("length of stay" OR "hospital stay" OR "length of admission" OR "time admitted" OR "time hospitalized") OR ("intensive care unit" OR ICU OR "ICU admission" OR "intensive care unit admission" OR "ICU stay") OR ("adverse event" OR "adverse events" OR complication OR complications) OR ("viral conversion" OR "negative viral conversion")	11,629,542
	4	#1 AND #2 AND #3	482
	5	#1 AND #2 AND #3 AND Filters: Randomized Clinical Trial, Systematic Review, Meta-analysis	31
Cochrane COVID-19 Study Register	1	("vitamin C" or "sodium ascorbate" or "ascorbic acid" or "ascorbate" or "ascorbic") AND (hospitalization OR hospitalized OR admission) or (mortality OR death) or (recovery OR remission OR improvement) or ("mechanical ventilation" OR MV OR intubation) or ("length of stay" OR "hospital stay" OR "length of admission" OR "time admitted" OR "time hospitalized") or ("intensive care unit" OR ICU OR "ICU admission" OR "intensive care unit admission" OR "ICU stay") or ("adverse event" OR "adverse events" OR complication OR complications) or ("viral conversion" OR "negative viral conversion")	5,907
	2	#1 AND (pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens)	543
WHO COVID Database	1	("vitamin C" or "sodium ascorbate" or "ascorbic acid" or "ascorbate" or "ascorbic") AND (hospitalization OR hospitalized OR admission) or (mortality OR death) or (recovery OR remission OR improvement) or ("mechanical ventilation" OR MV OR intubation) or ("length of stay" OR "hospital stay" OR "length of admission" OR "time admitted" OR "time hospitalized") or ("intensive care unit" OR ICU OR "ICU admission" OR "intensive care unit admission" OR "ICU stay") or ("adverse event" OR "adverse events" OR complication OR complications) or ("viral conversion" OR "negative viral conversion") AND (pediatric OR paediatric OR child OR children OR neonates OR infants OR toddlers OR pre-adolescents OR adolescent OR adolescents OR adolescence OR teenager OR teenagers OR teens)	781
clinicalTrials. gov		"vitamin c" OR "sodium ascorbate" OR "ascorbic acid" AND "pediatric covid"	31
MedRxiv		title "vitamin c" (match all words) and abstract or title "vitamin c" (match all words) and full text or abstract or title "vitamin c" (match whole all)	154
HERDIN		Vitamin c AND Pediatric COVID-19	0
Google Scholar		Vitamin c AND Pediatric COVID-19	1,300

Appendix 2. AGREE II Appraisal of the Philippine COVID-19 Living CPG

Domain	Scope and Purpose	Stakeholder Involvement	Rigour of Development	Clarity of Presentation	Applicability	Editorial Independence	Overall quality of guideline
Assessment	89%	83%	88%	98%	85%	100%	83%

Appendix 3. Characteristics of Included Studies (from Tiu, Milan, Tolosa, and Infantado 2021 [9])

Author/Year / Study Design	Population (N)	Intervention	Comparator	Outcomes
Jamalimogha damsiahkali et al., 2021 Open label RCT	COVID-19 confirmed patients by RT-PCR or by clinical symptoms, Chest CT/HRCT, low oxygen saturation N=60	Vitamin C 1.5g Q6 x 5 days (6g/day) with lopinavir/ritonavir and HCQ	Lopinavir/ritonavir and HCQ with no Vitamin C	No significant difference in terms of mortality ($p>0.05$), Patients on vitamin C: -Longer length of hospital stay (median 8.5 vs 6.5 days, $p=0.028$) -Higher SpO ₂ on 3rd day of admission (90.5% vs 88%; $p=0.014$)
Kumari et al. 2020	Severe COVID-19 patients (n=150)	50mg/kg/day intravenous vitamin C with standard Therapy	Standard therapy, no vitamin C	There were no statistically significant differences between the two groups in terms of mortality and need for mechanical ventilation. Patients on HDIVC group had earlier symptom free status (7.1 ± 1.8 vs 9.6 ± 2.1 days, $p<0.001$) and spent fewer days in the hospital (8.1 ± 1.8 vs 10.7 ± 2.2 days, $p<0.0001$) compared to patients without vitamin C
Zhang et al. 2021 Randomized placebo controlled	Severe COVID-19 confirmed patients N=56	Vitamin C 24g/day IV x 7 days (HDIVC)	No vitamin C	No statistically significant difference in terms of invasive mechanical ventilation-free days, 28-day mortality, 28-day mortality for severe (SOFA ≥ 3). Patients on HDIVC had higher P/F ratio, lower SOFA score The delta P/F from day 1 to 7 was (20 ± 96.7 in HDIVC and - 51.9 ± 150.7 in the control group No study related adverse events in the trial.
Tehrani, et al., 2021 Single center clinical trial	Patients diagnosed with COVID-19 with moderate to severe	Vitamin C 2g every 6 hours for 5 days in addition to standard treatment	Standard treatment (Hydroxicholoroquine, Kaletra and Interferon beta-1a)	Oxygen saturation, respiratory rates, serum C-Reactive Protein (CRP) levels, lymphopenia and lung parenchymal involvement on CT, length of hospital stay, mortality Due to the

	symptoms (n=54)			effectiveness of high doses of intravenous vitamin C on reducing lung involvement and improving clinical symptoms, further studies with a larger sample size are recommended to demonstrate the effects of this drug supplement.
Thomas et al, 2021 Open label RCT *study discontinued	COVID-19 confirmed Patients treated as Outpatient N=214	Vitamin C 8,000mg/day Zinc gluconate 50mg; both zinc and vitamin c	Standard of care, no vitamin C	No significant difference among the 4 study groups in terms of days required to reach a 50% reduction in symptoms. No significant difference in any of the secondary outcomes.
Darban, et al, 2021 Randomized single center trial	Patients with severe COVID admitted to the ICU (n=20)	IV Vitamin C (2g q6hr), oral melatonin (6mg q6hr), oral zinc sulfate (220mg containing 50mg elemental zinc q6hr) for 10 days + standard of care	Standard of Care	High-dose vitamin C, melatonin and zinc added to standard of care is not associated with improvement in hypoxemia (PaO2/FiO2 ratio), and inflammatory markers including LDH, ESR, ferritin, CRP
Hakamifard, et al, 2021 RCT	Hospitalized non-severe COVID-19 patients (n=72)	Oral Vitamin C 1g daily and oral vitamin E 400IU daily + standard treatment	Standard treatment	Co-administration of Vitamin C and E did not have a improvement in clinical response of patients at the end of treatment (either cure, improvement, or failure), the duration of hospitalization, and the mortality rate
Beigmohammadi et al, 2021 RCT, single-blinded	ICU-admitted patients with COVID-19 (n=60)	25,000 IU daily of vitamins A, 600,000 IU once during the study of D, 300 IU twice daily of E, 500 mg four	No vitamins (placebo)	Significant changes were detected in serum levels of vitamins (p < 0.001 for all vitamins), ESR (p < 0.001), CRP (p = 0.001), IL6 (p = 0.003), TNF-a (p = 0.001), and SOFA score (p < 0.001) after intervention compared with the control group. The effect of vitamins on

		<p>times daily of C, and one amp daily of B complex for 7 days.</p>	<p>the mortality rate was not statistically significant ($p=0.112$). The prolonged hospitalization rate to more than 7 days was significantly lower in the intervention group than the control group ($p=0.001$). Supplementation with vitamins A, B, C, D, and E could improve the inflammatory response and decrease the severity of disease in ICU-admitted patients with COVID-19.</p>
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Appendix 4. GRADE Evidence Profile

Author(s): Patricia C. Orduña, MD, DPPS, María Teresa S. Tolosa, MD, D Clin Epi, FPDS; Ma. Lucila M. Pérez, MD, MSc, FPPS

Question: Vit C with standard treatment compared to standard treatment alone for adjunctive treatment of COVID-19 in children

Setting: Inpatient

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Mortality												
4	randomised trials	not serious	not serious	serious ^a	serious ^b	none	16/150 (10.7%)	29/160 (18.1%)	RR 0.59 (0.34 to 1.03)	74 fewer per 1,000 (from 120 fewer to 5 more)		CRITICAL
Length of hospital stay												
4	randomised trials	not serious	serious ^c	serious ^a	serious ^b	none	150	160	-	MD 0.96 higher (3.84 lower to 1.92 higher)		CRITICAL
Length of ICU stay												
2	randomised trials	not serious	not serious	serious ^a	serious ^b	none	57	59	-	MD 1.35 higher (0.12 lower to 2.83 higher)		CRITICAL
Need for mechanical ventilation												
3	randomised trials	not serious	not serious	serious ^a	serious ^b	none	28/132 (21.2%)	31/134 (23.1%)	RR 0.93 (0.60 to 1.44)	16 fewer per 1,000 (from 93 fewer to 102 more)		CRITICAL
Adverse events												
2	randomised trials	not serious	serious ^d	serious ^a	serious ^e	none	17/78 (21.8%)	0/50 (0.0%)	RR 36.43 (2.25 to 589.34)	0 fewer per 1,000 (from 0 fewer to 0 fewer)		CRITICAL

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

a. Adult patients enrolled

b. Confidence interval crosses the null value

c. I² = 71%

d. Variability in patient population: outpatient and severe

e. Wide confidence interval (all on the side of harm)

Appendix 5. Forest Plots (from Tiu, Milan, Tolosa, and Infantado 2021 [9])

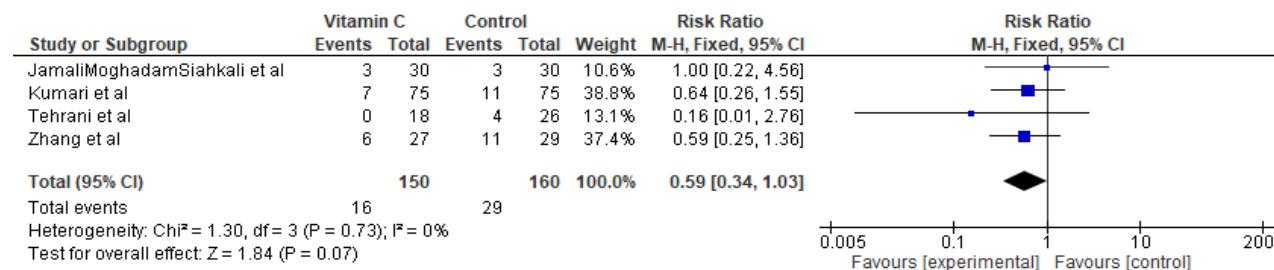


Figure 1. Mortality Outcome

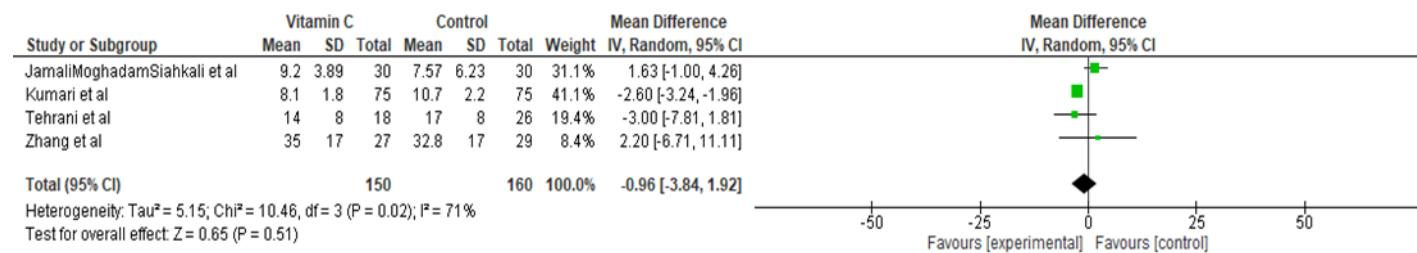


Figure 2. Length of hospital stay

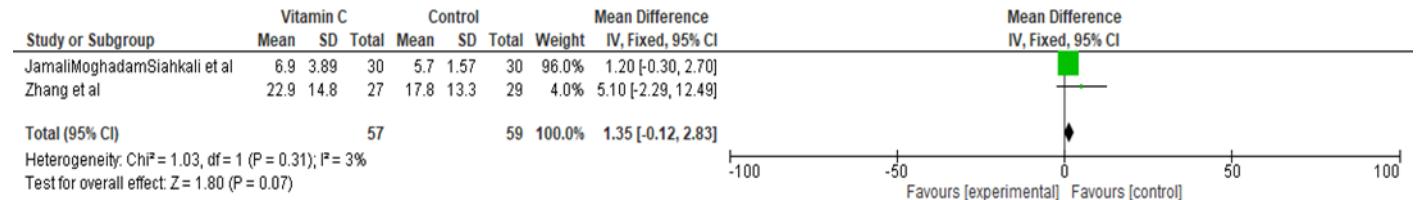


Figure 3. Length of ICU stay

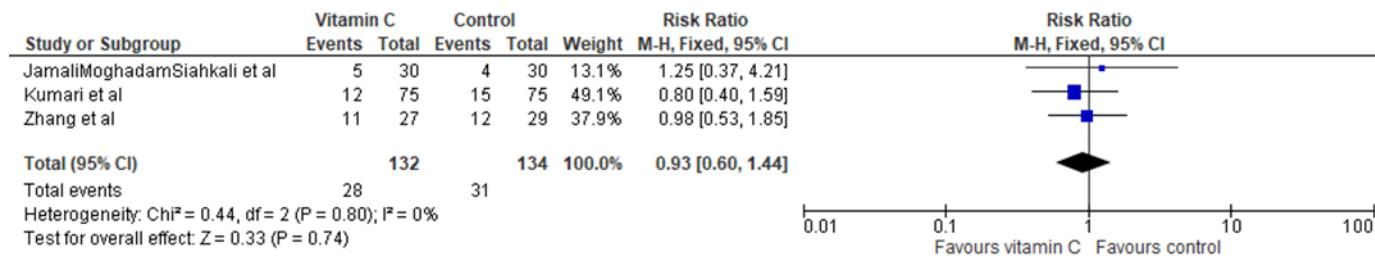


Figure 4. Need for mechanical ventilation

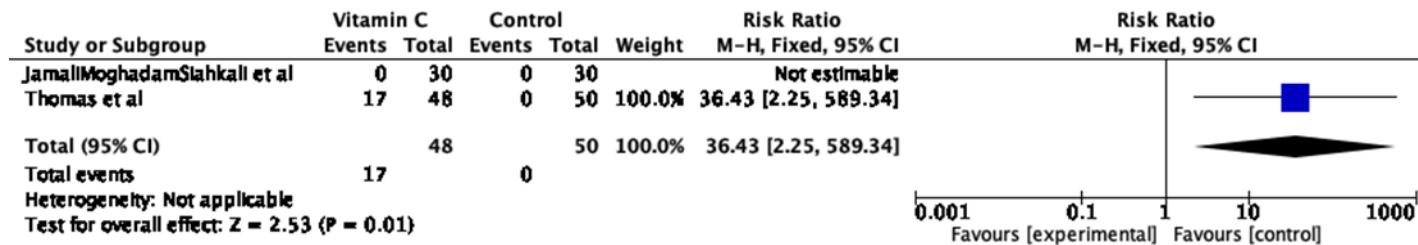


Figure 5. Adverse events

Appendix 6. Table of Ongoing Studies

Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome	Estimated Date of Completion
NCT04682574 Role of Mega Dose of Vitamin C in Critical COVID-19 Patients	Open label RCT	China	COVID-19 patients (children and adult)	Vitamin C 30g/day (10 grams TID) for 2 days with standard treatment	Primary Outcome: Partial pressure of Oxygen in arterial blood to fraction of inspired Oxygen (P/F ratio) Secondary Outcome: Duration of hospital stay	Jan 10, 2021 Status still recruiting
NCT043235 14 Use of Ascorbic Acid in Patients With COVID 19	Single group assignment, open label	Italy	COVID-19 patients (children and adult)	Vitamin C 10g IV with conventional therapy	Primary Outcome: In-hospital Mortality Secondary Outcomes: PCR levels, lactate clearance, hospital stay, symptoms, positive swab, tomography imaging	Mar 13, 2021 Status still recruiting

Appendix 7. Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 10)

FACTORS		JUDGEMENT (N = 10)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS	
Problem	No (1)	Yes (5)		Varies (2)		Uncertain (2)			
Benefits	Large	Moderate (1)	Small (2)	Trivial (1)	Varies (1)	Uncertain (5)		<ul style="list-style-type: none"> Indirect evidence from adult studies show trend towards benefit in terms of mortality. There was no significant benefit and inconclusive results for length of hospital stay, length of ICU stay and need for mechanical ventilation. 	
Harm	Large	Moderate	Small (6)	Trivial	Varies (1)	Uncertain (3)		<ul style="list-style-type: none"> No adverse events from intravenous vitamin C [12] Adverse events noted with oral preparation: flushing, headache, vomiting, stomach pain [16] 	
Certainty of evidence	High	Moderate		Low (1)		Very low (9)		<ul style="list-style-type: none"> Rated very low due to imprecision, inconsistency and indirectness 	
Balance of effects	Favors drug	Probably favors drug (1)	Does not favor drug or no drug (2)	Probably favors no drug	Favors no drug	Varies (3)	Uncertain (4)		
Values	Important uncertainty or variability	Possibly important uncertainty or variability (2)		Probably no important uncertainty or variability (5)		No important uncertainty or variability (3)			
Resources required	Uncertain (1)	Varies (2)	Large costs	Moderate costs (6)	Negligible costs or savings	Moderate savings	Large savings (1)	<ul style="list-style-type: none"> IV vitamin C: Php 110.00/10 ampules of 500mg/2mL Pp 28.19/amp 	
Certainty of evidence of resources required	No included studies		Very low (8)	Low (2)	Moderate	High			
Cost-effectiveness	No included studies (8)	Varies (1)	Favors the comparison	Probably favors the comparison	Does not favor the comparison or the intervention (1)	Probably favors the intervention	Favors the intervention		
Equity	Uncertain (7)	Varies	Reduced (1)	Probably reduced	Probably no impact (2)	Probably increased	Increased		
Acceptability	Uncertain (5)	Varies (1)	No	Probably no	Probably yes (4)	Yes			
Feasibility	Uncertain (5)	Varies (1)	No	Probably no	Probably yes (4)	Yes			

Additional Comments

- Most Filipino children have low dietary vitamin C intake and would need supplementation for this reason.
- Availability and accessibility in far-flung areas needs to be considered since the route of administration discussed in the evidence is intravenous.

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.

Evidence Summary

Key Findings

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.

Introduction

Zinc can inhibit the enzymatic activity and replication of SARS-CoV RNA polymerase through its effect on the virus attachment, infection, and uncoating. Zinc also stabilizes the cell membrane contributing to the prevention of virus entry into the cell. It was also demonstrated that Zinc may enzymatically inhibit viral replication through alteration of the proteolytic processing of replicase polyproteins and RNA-dependent RNA polymerase, potentially reducing the risk of viral respiratory tract infections, including SARS-CoV-2, and shorten the duration and severity of illness [1-3].

Zinc is also an essential co-factor element that may also modify the host's response to an infection. It has an essential role in immune and airway function, wound healing and tissue repair through protection from oxy-radicals which plays a vital role in the delay of recovery from viral respiratory illnesses [4]. It also plays a role in immunological response, through diminishing excessive inflammation and risk for cytokine storm by decreasing the activity of nuclear factor kappa B, through negative feedback mechanism [5].

Zinc deficiency is also often linked to impaired functions of all immune cells and is related to susceptibility by at least 16% to various respiratory infection worldwide, implying a crucial link between zinc deficiency and the risk of infections, higher complication rates, prolonged hospital stay and higher mortality rate from COVID-19 hence suggesting the benefits of zinc supplementation [6].

The results of the studies regarding the utility of adjunctive zinc for children with pneumonia are conflicting, with several studies failing to show benefit of the use of adjunctive zinc supplementation on treatment failure or time to recovery [7,8]. A study in India of 700 infants (7 to 120 days old) with serious bacterial infections (pneumonia, sepsis, and diarrhea) suggested a beneficial effect of adjunctive zinc. Infants who were also treated with zinc (5 mg twice daily by mouth) had significantly less treatment failure (defined as a need to change antibiotics), as compared with those treated with placebo (10 versus 17) or a need for intensive care, or death at any time within 21 days. The absolute risk reduction for treatment failure was at 6.8 percent (95% CI 1.5-12.0) [9].

Five RCTs done among children with Lower Respiratory tract infection (ALRI) showed significant decrease on the hours of stay in the hospital among those treated with Zinc with a mean difference of -9.54 between Zinc and standard of care with 95% CI of -13.21 and -5.86 and a p value of <0.00001 [10-14]. Treatment failure was also evaluated wherein four RCTs showed that more patients on the standard of care compared to Zinc group necessitated change of antibiotics to a broader spectrum either due to lack of improvement or worsening of clinical status with an odds ratio of 0.81 with 95% CI of 0.38 and 2.24 but there was no noted statistical significance with a p value of 0.59 [17-18,21-22].

This review aims to determine the efficacy and safety of zinc as adjunctive treatment of COVID-19 among pediatric patients.

Review Methods

We comprehensively searched different electronic databases that included MEDLINE via PubMed, Cochrane Library, ClinicalTrials.gov, PubMed Clinical Queries, medRxIV, bioRxIV, WHO Clinical Trials Registry, WHO Therapeutics and COVID 19 Living Guidance, WHO Institutional Repository for Information Sharing and HERDIN Plus until January 7, 2022. Free search on Google was also performed. The following keywords were used: “zinc”, “zinc gluconate”, and “zinc sulfate” in free text and MeSH terms for “Zinc” and pediatric COVID-19 (Appendix 2). The table below shows our inclusion criteria.

Table 1. PICO criteria for zinc as adjunctive treatment of COVID-19 among pediatric patients

Population	Children with COVID-19
Intervention/Exposure	Zinc, zinc sulfate, zinc gluconate
Comparison	Standard of care
Outcomes	Need for hospitalization, mortality, recovery, clinical improvement, mechanical ventilation and duration of hospital and ICU stay

We searched for randomized controlled trials, observational studies, systematic reviews and meta-analyses. The risk of bias of included studies was assessed using guide questions derived from Painless Evidence-Based Medicine for RCTs. Certainty of evidence was assessed using the GRADE evidence profile. Review Manager 5.4.1 was used for meta-analysis.

Results

There are no published studies on the use of Zinc among pediatric patients with Covid-19. This review uses indirect evidence from studies on adults with COVID-19 for the use of Zinc as adjunctive treatment.

We found a total of six RCTs wherein adult patients with COVID-19 were given zinc as an adjunct treatment for COVID-19. Among the six, four studies used zinc as the sole adjunctive treatment; the remaining two used it in combination with another adjunct. The studies were also done in different settings: two as outpatient and four in hospital settings and across all severities [15-20]. The overall certainty for each outcome was rated low. Downgrading occurred due to indirectness (from differences in population), and imprecision.

The studies of Abd Eisalam et al. [15] and Patel et al. [16] reported fewer mortalities among those given Zinc (7/111) than those who received standard of care (8/113). The study of Abd elsalam used Zinc with Hydroxychloroquine (control: hydroxychloroquine) while that of Patel used high dose zinc (control: placebo). The pooled result for the outcome of mortality yielded inconclusive results (RR 0.92; 95% CI 0.35,2.44). The certainty of evidence was low because of indirectness (the studies enrolled adult patients) and imprecision.

The study of Thomas [17] and Kaplan [18] reported the outcome of hospitalization among ambulatory patients. The results were not pooled since the study by Kaplan et al. used other adjunctive agents in addition to zinc (i.e., resveratrol). The said study reported one hospitalization from each study arm. In the study of Thomas, which used high dose Zinc versus standard of care, there were inconclusive results for the outcome of hospitalization (RR 1.44; 95% CI 0.36, 5.71).

The study of Patel [16] and Thomas [17] reported significantly more adverse events in the zinc group (13/73) compared to Standard of care (0/68) (RR 13.62 95%CI 1.78, 104.43). The direct adverse effect noted on the study of Patel is infusion site irritation. In the study of Thomas there were ten noted adverse events in the Zinc group.

The study by Darban et al. [19] reported that there is no difference between the length of hospital stay among those given with high-dose vitamin C, melatonin, and zinc compared to standard of care in patients with severe COVID infection. (15 ± 3.3 days vs 14.1 ± 4.2 days; $p = 0.7$).

The study of Abdelmaksoud [20] reported that there is no difference in the duration of recovery among those who received zinc (MD 12 days, range = 8-17) and those who did not (MD 12 days, range = 8-20).

Other Considerations (Evidence to Decision)

Zinc Sulfate is available in drugstores and health outlets, as well as online shopping sites, which show one price at P101 for a 27.5mg/mL (10mg elemental zinc) per 15mL bottle and P107.5 per 60mL bottle. [21,22] The 2021 Philippine Drug Price Reference Index

(DPRI) shows the mean price of P 34.75 for a 27.5mg/mL (10mg elemental zinc) 15ml oral drops and P 38.00 for a 55mg/5mL (20mg elemental zinc) 60mL syrup [23].

Zinc gluconate is also available in the market as a 70mg/tab chewable tablet P10.34 each containing 10mg of elemental Zinc per tablet [24]. No available data on the 2021 Philippine Drug Price Reference Index (DPRI).

Recommendations from Other Groups

The US-NIH COVID-19 Treatment Guidelines Panel recommends against using zinc supplementation due to insufficient evidence for or against the use of zinc for the treatment of COVID-19 [25]. Currently, there are no recommendations from CDC [26], WHO [27], and the American Pediatric Academy [28] on the use of zinc as an adjunct treatment in pediatric-COVID-19.

Research Gaps

As of January 2022, there are no ongoing trials investigating the effectiveness of zinc as adjunctive treatment for pediatric COVID-19. There are eight ongoing studies among adults.

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Evidence Summary Appendices

Appendix 1. Search Yields and Results

Database	Search terms	Yield	Hits
Pubmed	((("pediatric COVID-19" [Supplementary Concept] OR "COVID-19" [Supplementary Concept] "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 epidemic 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 (((((((zinc [tiab]) OR (zinc gluconate [tiab])) OR (zinc sulfate [tiab])) OR (zinc supplement [tiab])) OR (antioxidant [tiab])) OR (supplement [tiab])) OR (zinc* [tiab])) OR (zinc[MeSH Terms])) OR (zinc gluconate [MeSH Terms])) OR (zinc sulfate [MeSH Terms])) OR (Zinc supplement [MeSH Terms])) OR (antioxidant[MeSH Terms])) OR (supplement[MeSH Terms]))	1735	6
Cochrane	((zinc):ti,ab,kw OR Zinc* OR MeSH descriptor: [Zinc] explode all trees) AND (COVID-19 OR SARS-CoV-2 OR MeSH descriptor: [COVID-19] explode all trees)	120	4
	((zinc):ti,ab,kw OR Zinc* OR MeSH descriptor: [Zinc] explode all trees) AND (pediatric COVID-19 OR SARS-CoV-2 OR MeSH descriptor: [COVID-19] explode all trees)	120	0
clinicalTrials.gov	"zinc" and "pediatric covid"	55	0
	"zinc" and "covid"	55	0
MedRxiv	title "zinc" (match all words) and abstract or title "zinc" (match all words) and full text or abstract or title "zinc" (match whole all)	265	0
CovidNMA	Zinc	3	3
WHO International Clinical Trials Registry platform	"Zinc" and "pediatric COVID 19"	0	0
HERDIN	"Zinc" and "pediatric COVID 19"	0	0
Google Scholar	"Zinc" and "pediatric COVID 19"	16,600	1
China Knowledge Resource integrated database	"Zinc" and "pediatric COVID 19"	48	0

Appendix 2. Characteristic of Included Studies: Randomized Control Trials

Study author	Population	Intervention	Control	Outcome
Abd-Elsalam 3 tertiary care centers in Assiut, Tanta and Cairo EGYPT	N= 191 Confirmed RT-PCR positive in three egyptian tertiary care centers from June 23 to August 23,2020 Divided into mild, moderate, severe and critical based on WHO classification	Zinc sulfate 220mg (elemental zinc 50mg) BID HCQ (400mg BID D1, then 200mg BID x 5 days) Standard of care	HCQ (400mg BID D1, then 200mg BID x 5 days) Standard of care	Recovery within 28 days Death Need for mechanical ventilation Duration of Hospital stay (days)
Thomas Multiple outpatient settings in Ohio and Florida USA	N=214 Patients > 18 years old who were newly diagnosed by RT- PCR in an outpatient setting From April 27 to October 14, 2020	Zinc gluconate (50mg OD at bedtime) x 10 days n=58 (20 did not complete follow-up: 11 lost, 9 discontinued intervention) *58 zinc + ascorbic acid x 10 days (11 did not complete: 3 lost, 8 discontinued)	Standard of care only (n=50) *ascorbic acid (8000mg over 2-3x/day) N=48 (14 did not complete, 7 lost, 7 discontinued)	Days required to reach 50% reduction in symptoms Death Hospitalization Serious Adverse Events
Kaplan (Lancet Preprint: no peer review) Outpatient Phase ½ clinical trial USA	N=30 Mild to Moderate COVID	Zinc methionine/ cysteine (Life Extension) 150 mg daily total (50 mg capsules orally three times daily and resveratrol (Mega Resveratrol) 2000 mg orally twice daily for five days.	Placebo Capsule	Primary outcome: Reduction in viral shedding Secondary outcomes: - Reduction of symptoms - Adverse events - Incidence of hospitalization - Length of hospitalization - Days on ventilator support - Time until the 4- symptom score is zero - Composite score at Day 5 - Hospitalization - Deaths
Patel et al In Hospital setting AUSTRALIA	N=33 Hospitalized patients -severe -critical 2021	Zinc Chloride IV at 0.5mkd (elemental Zn 0.24mkd)	Placebo	Death Continuing Hospitalization

Study author	Population	Intervention	Control	Outcome
Darban Single center active controlled open label parallel group setting IRAN	N=20 Severe COVID 2021	Oral zinc sulfate (220 mg containing 50 mg elemental zinc, q6hr) for 10 days (5-7) IV vitamin C (2g, q6hr), oral melatonin (6 mg, q6hr) plus standard of care	Standard cares were azithromycin (250 mg/day), lopinavir/ritonavir (100mg/25mg/day), glucocorticoids and necessary oxygen	Primary outcome: changes in severity of hypoxemia ($\text{PaO}_2/\text{FiO}_2$ ratio) Other outcomes included inflammatory markers (LDH, ESR, ferritin, CRP at baseline, days 5 and 10 after treatment initiation)
Abdelmaksoud Quarantine department hospitals EGYPT	N = 134 2021	Zinc therapy (220 mg zinc sulfate equivocal to 50 mg elemental zinc twice daily [33]) plus the Egyptian protocol of treatment of COVID-19	Egyptian protocol of COVID-19 treatment without zinc therapy	Mean serum zinc levels, median duration of recovery of gustatory/ olfactory function, median duration of complete recovery among those who had anosmia/hyposmia

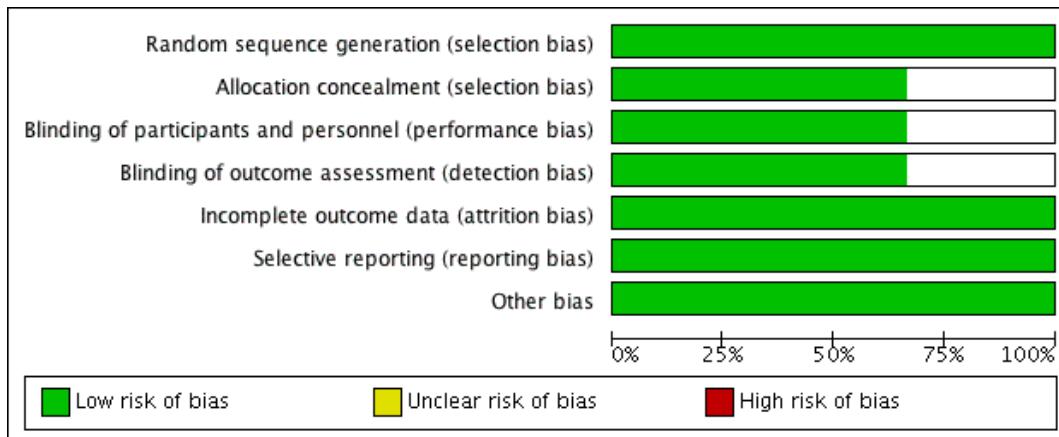
Appendix 3. Detailed Study Appraisal

Directness	Abd-Elsalam	Thomas	Kaplan	Patel	Darban	Abdelmaksoud
	Yes, it had similar outcomes, but different population (adult) and interventions (Zinc as add on to HCQ vs HCQ, which is not standard of care currently) P= Patients with COVID (mild, moderate, severity) I=Zinc+HCQ vs HCQ O=Duration of hospital stay, recovery	Yes, similar intervention and outcome but different population P= Adults diagnosed with COVID I= Zinc, ascorbic acid, ascorbic acid with zinc, standard of care O= Reduction in severity or duration of symptoms	Yes similar outcomes but population is similar Adult COVID patients, but the intervention (Zinc + resveratrol) and primary outcomes are different (reduction in viral shedding)	Yes similar outcome but the population, intervention(high-dose IV Zinc) and primary outcome are different (lowest oxygen saturation for non-ventilated and worst PaO ₂ / FiO ₂ for ventilated)	Yes similar outcome but different population (Adult COVID severe), intervention (standard of care vs standard of care with oral melatonin, oral zinc, IV vit C), and different outcome (changes in hypoxemia)	Yes, similar intervention (zinc) and outcome but different population (Adult Patients with COVID of various severities), similar
Validity						
Randomly assigned to treatment groups	Yes RCT	Yes RCT Open label trial	Yes RCT	Yes RCT	Yes RCT	Yes RCT
Allocation Concealment	Not mentioned	No Open label	Yes	Yes	No	Not mentioned
Similar Baseline characteristic	Yes No significant difference	Yes No significant difference	Yes	Yes	Yes	Yes
Patient blinding	Not mentioned	No	Yes	Yes	No	Not mentioned
Caregiver blinding	Not mentioned	No	Yes	Yes	No	Not mentioned
Outcome assessor blinding	Not mentioned	No	Yes	Yes	No	Not mentioned
Analyzed to group originally randomized	Yes	Yes	Yes	Yes	Yes	Yes
Adequate follow up	Yes	Yes	Yes	Yes	Yes	Yes
RESULTS						
Treatment Effect	Mean Hospital Stay	50% reduction of symptoms,	Reduction in viral shedding	In-hospital mortality (28-day outcome): Zinc: 2/ 15 (14.3%)	PaO ₂ /FiO ₂ at day 10	Serum zinc level: Mild: 0.67 ± 0.18 Common: 0.62 ± 0.14

	Zinc: 13.51 ± 5.34 days Zinc + HCQ: 14.01 ± 6.26 days $p=0.553$ Hospital mortality , Risk difference: n 0.05 (-0.06, 0.06)	Zinc: 5.9 (4.9) days Std: 6.7 (4.4) days $p=0.38$	-no statistically significant difference ($p=0.7$) In-hospital mortality: Zinc: 0/14 Placebo: 0/16 2 were admitted-one each for the interventions. LOS Zn: 46-day LOS with 30 days in the ICU Placebo: 11-day LOS with 5 days in the ICU	Control: 3/18 (16.7%)	Placebo: 222.2 ± 65 Zn: 230.1 ± 59.1 , $p=0.2$ Length of ICU stay: Placebo: 15 ± 3.3 days Zn: 14.1 ± 4.2 days $p = 0.3$	Severe: 0.73 ± 0.18 Extremely severe: 0.72 ± 0.22 $p= 0.084$ Mean duration of recovery of olfaction: Zinc arm: 7 days (range 5-9 days) Control: 18 days (range 14-22 days) Duration of complete recovery Zinc arm: Median 12 (range 8–17 days) Control: Median 12 (range 8–20 days)
Precision	Length of hospital stay: Zn: 13.51, 5.34 days 95% CI: 12.47 to 14.594 Zn+HCQ: 14.01, 6.26 days 95% CI: 12.734 to 15.286 days MD: 0.500 (-1.16, 2.16), $p=0.55$ In-hospital mortality Zinc: 5/96 (5.21%) HCQ: 5/95 (5.26%) <i>Risk difference:</i> 0.05 (-0.06, 0.06) NS	Zn: 95% CI: 0.40 (-1.77 to 2.58) AA: 95% CI 0.40 (-1.99 to 2.80) Zn+AA: 95% CI: 0.07 (-1.94 to 2.09)	N/a	N/a		
APPLICABILITY						
Biologic Issues	None	None	None	None	None	None
Socioeconomic Issues	None	None	None	None	None	None

Appendix 4. Risk of Bias

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abd Eisalam 2021	+				+	+	+
Abdelmaksoud 2021	+				+	+	+
Darban 2021	+	+	+	+	+	+	+
Kaplan 2021	+	+	+	+	+	+	+
Patel 2021	+	+	+	+	+	+	+
Thomas 2020	+	+	+	+	+	+	+



Appendix 5. GRADE Evidence Profile

Author(s): Joanna Marie Tan, MD DPPS, Maria Teresa Tolosa, MD D Clin Epi, FPDS , Ma. Lucila Perez MD MSc FPPS

Question: **Should Zinc be used as an adjunctive treatment for COVID-19 in children?**

Setting: General pediatric population, in-patient and out-patient

Bibliography: Abd Eisalam 2020, Patel 2021, Thomas 2020, Darban 2021, Abdelmaksoud 2021

Certainty assessment							Nº of patients		Effect		Certainty	Importance	
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zinc	Standard of care	Relative (95% CI)	Absolute (95% CI)			
In Hospital Mortality													
2	randomised trials	not serious	not serious	serious ^a	serious ^b	none	7/111 (6.3%) 8/113 (7.1%)	8/113 (7.1%)	RR 0.92 (0.35 to 2.44)	5 fewer per 1,000 (from 41 fewer to 91 more)		CRITICAL	
Hospitalization among Ambulatory patients													
1	randomised trials	not serious	not serious	serious ^c	serious ^b	none	5/58 (8.6%)	3/50 (6.0%)	RR 1.44 (0.36 to 5.71)	26 more per 1,000 (from 38 fewer to 283 more)		CRITICAL	
Adverse Events													
2	randomised trials	not serious	not serious	serious ^c	serious ^d	none	13/73 (17.8%)	0/68 (0.0%)	RR 13.62 (1.78 to 104.43)	0 fewer per 1,000 (from 0 fewer to 0 fewer)		CRITICAL	
Length of Hospitalization													
1	randomised trials	not serious	not serious	serious ^c	serious ^b	none	In the study of Darban the use of High dose Vitamin C+Melatonin and Zinc (15 days) compared to Standard of Care (14.1 days) showed no significant difference in the length of hospital stay.						CRITICAL
Duration of Recovery													
1	randomised trials	not serious	not serious	serious ^c	serious ^b	none	In the study of Abdelmaksoud there is no difference in the duration of activity among those who received Zinc (12 days) compared to those who received standard of care (12 days).						CRITICAL

CI: confidence interval; RR: risk ratio

Explanations

- a. studies used Adult patients with COVID-19
- b. the confidence interval crossed the line of unity
- c. study used was done among Adult patients with COVID-19
- d. the confidence interval is wide

Appendix 6. Forest Plots

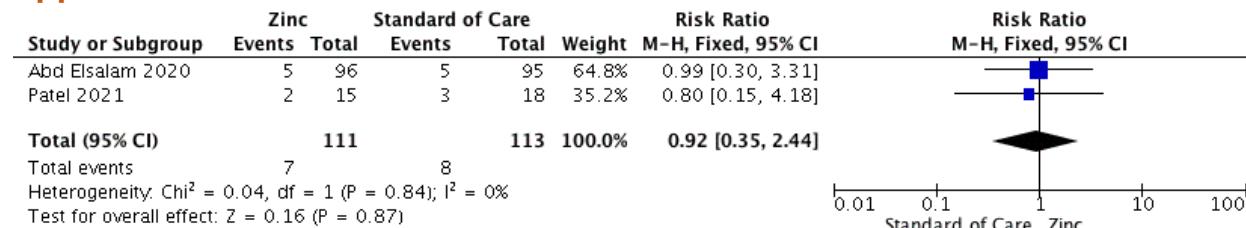


Figure 1. In-hospital mortality

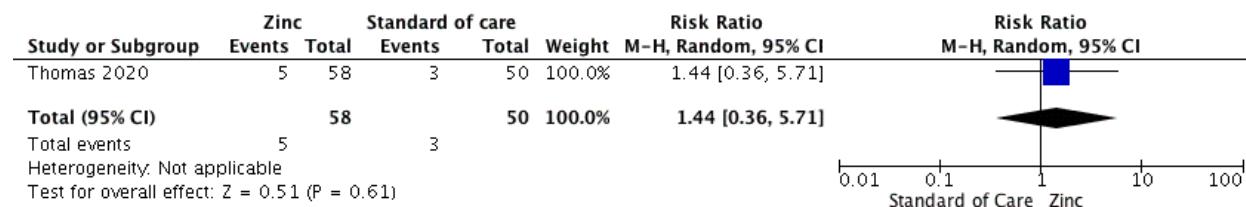


Figure 2. Hospitalization among ambulatory patients

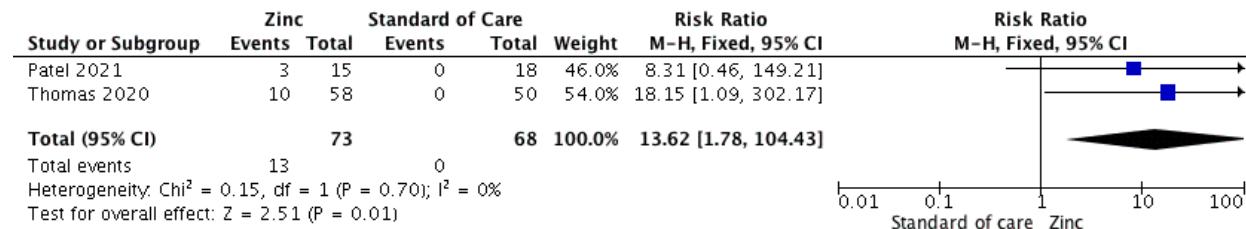


Figure 3. Adverse events

Appendix 7. Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 11)

FACTORS		JUDGEMENT (N = 11)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS	
Problem	No	Yes (10)		Varies		Uncertain (1)			
Benefits	Large	Moderate	Small (2)	Trivial	Varies (1)	Uncertain (8)		<ul style="list-style-type: none"> Inconclusive results for in-hospital mortality, duration of recovery, length of hospital stay, hospitalization among ambulatory patients 	
Harm	Large	Moderate (4)	Small (4)	Trivial	Varies (2)	Uncertain (1)		<ul style="list-style-type: none"> Adverse events significantly higher in the intervention group compared to control 	
Certainty of evidence	High	Moderate			Low (11)	Very low		<ul style="list-style-type: none"> Rated low due to indirectness, risk of bias, imprecision 	
Balance of effects	Favors drug	Probably favors drug	Does not favor drug or no drug (2)	Probably favors no drug (5)	Favors no drug (2)	Varies	Uncertain (2)		
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (4)			Probably no important uncertainty or variability (5)	No important uncertainty or variability (1)			
Resources required	Uncertain (1)	Varies (1)	Large costs	Moderate costs (5)	Negligible costs or savings (3)	Moderate savings (1)	Large savings	<ul style="list-style-type: none"> Zinc sulfate 27.5mg/mL: Php 101.00/15mL bottle Zinc sulfate 27.5mg/mL: Php 107.50/60mL bottle Zinc gluconate 70mg/tab: Php 10.34/tab 	
Certainty of evidence of resources required	No included studies (4)		Very low (1)	Low (2)	Moderate (4)	High			
Cost-effectiveness	No included studies (10)	Varies	Favors the comparison	Probably favors the comparison	Does not favor the comparison or the intervention (1)	Probably favors the intervention	Favors the intervention		
Equity	Uncertain (8)	Varies (1)	Reduced (1)	Probably reduced	Probably no impact (1)	Probably increased	Increased		
Acceptability	Uncertain (7)	Varies	No	Probably no (1)	Probably yes (3)	Yes			
Feasibility	Uncertain (6)	Varies	No (1)	Probably no (1)	Probably yes (2)	Yes (1)			

Additional Comments

- Zinc treatment may be beneficial to Filipino children who are zinc-deficient.

E.Non-Pharmacologic Interventions for COVID-19 in Children

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.

Evidence Summary

Key Findings

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.

Introduction

The World Health Organization (WHO) conceptualizes mental health as a “state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community”. The COVID-19 pandemic has impacted not only the healthcare delivery system and the global economy but also the educational set-up of all institutions around the world. Despite being less afflicted by the first wave of the COVID-19 pandemic, the pediatric population was not spared by the psychosocial impact of the school closures and community lockdowns. A systematic review done by Viner et al (2022) utilized 25 studies across 10 countries. It revealed that there was an association between school closures during broader social lockdown and mental health, health behaviors, and well-being (emotional, behavioral, and problems with inattention) and above risk threshold for symptoms of anxiety and depression [1]. Ferguson et al (2021) elucidated in their cross-sectional study the themes of feelings and emotions that adolescents had during the COVID pandemic which include socio-spatial and temporal disconnections, emotional toll of the pandemic, and positives amid the pandemic [2]. Coping strategies employed by the respondents in the above study include connecting online and outdoors, and leisure with health-promoting activities.

This review aims to determine the efficacy and safety of supportive strategies to optimize mental health among children and adolescents during the COVID-19 pandemic.

Review Methods

The reviewers performed a comprehensive, systematic search for relevant literature until Jan 12, 2022 in PubMed, Cochrane Library, Google Scholar, COVID NMA, and ClinicalTrials.gov. Preprints were searched using medRxiv, chinaXiv and bioRxiv. The following table shows the inclusion criteria.

Table 1. PICO criteria of mental health among children and adolescents during the pandemic.

Population	Children during the Covid 19 pandemic
Intervention/Exposure	Supportive strategies for mental health
Comparison	Without supportive strategies for mental health
Outcomes	Anxiety, depression, resilience, life satisfaction, mindfulness, perception of overall well-being
Methodological filter	Randomized controlled trials (RCTs), Systematic reviews, Observational studies (including Qualitative studies)

The search terms for both Free text and MeSH, used for the subjects were “pediatric,” “children,” and “adolescent.”, “COVID-19,” “SARS-CoV-2,” “nCOV-19;” for the intervention, “mental health,” “coping,” and for the outcome, anxiety level, depression level, resilience, life satisfaction, mindfulness, and overall well-being index. Freehand search using Google was also done to check for other sources of information. There was no limit as to the date, language and country of publication. Filter was utilized to include randomized

controlled trials, systematic reviews, observational studies, and meta-analyses. Websites for pediatric organizations were also searched. Case reports, case series and letters to the editor were excluded.

The JAMA user's guide was used to appraise the articles and a systematic review and narrative synthesis were done to summarize the evidence for the question regarding supportive strategies for the mental well-being of children and adolescents during the COVID-19 pandemic. Pooling of the estimates, while planned, was not carried out due to heterogeneity of intervention arms and outcome measures; hence, meta-analysis was not possible. GRADE was used to assess the certainty of evidence.

Results

A total of 124 related articles were found using Medline, Google Scholar and other relevant medical databases. Initially the reviewers found 10 Observational Studies, 5 Clinical Trials, 6 Systematic Reviews, 3 Qualitative Studies and several articles on prevalence of mental health disorders. After the inclusion and exclusion criteria, 7 articles were found relevant to answer the research question. 5 articles with Randomized Clinical Trial Design and 2 articles which did Qualitative Study design (Appendix 1).

This review includes a total of five randomized controlled trials and two qualitative studies. All of the studies included the pediatric population, particularly the school age and adolescent age groups, across an age range of 10-19. The subjects have all experienced the advent of the COVID-19 pandemic and its consequences on societal set up including, but not limited to, community lockdowns, disease/infection containment measures leading to social contact restrictions, school closures, and reduced opportunities for recreation [1,3].

The study of Jianpeng Zhang et al. investigated 335 participants of "research-based psychological counseling" on the mental health of adolescents during the COVID-19 pandemic. Researchers enrolled a total of 160 students from five middle schools in China, who were screened using the Self-rating Anxiety Scale (SAS) and Self-rating Depression Scale (SDS) and were found to have anxiety symptoms. They were then divided equally into experimental and control groups. The control group received the "routine in-campus education of health knowledge related to the epidemic." The experimental group received this plus psychological counseling combined with outdoor exercise. Outcomes of interest included SAS and SDS scores within and between the groups, as well as sleep quality (assessed using the Pittsburgh Sleep Quality Index) and psychological resilience (measured using the Healthy Kids Resilience Assessment). The study reported that scores of the experimental group for both anxiety and depression are lower (improved) than those of the control group, and the differences are statistically significant ($P<0.05$). The study also concluded that there was statistically significant improvement in sleep quality and psychological resilience in the experimental group compared to control.

The Self-rating Anxiety Scale (SAS) and Self-rating Depression Scale (SDS) developed by Zung in 1971 are standard norm-referenced screeners for anxiety and depression

levels, respectively. Cut off scores include: < 50 (normal), 50–60 (mild anxiety), 61–70 (moderate), >70 (severe) for SAS and <50 points (normal), 50–59 (mild depression), 60–69 (moderate depression), and ≥70 (severe depression) for SDS [1].

Yingfeng Zheng e. al (2021) recruited 954 grade 7 students (12-14 years old) from 12 schools in Zhaoqing, China. They studied the effects of a peer-to-peer livestreaming application called REAP (Recess and Exercise Advocacy Program) on self-reported anxiety levels using the Spence Childrens' Anxiety Scale— Child (primary outcome) as well as eye strain and sleep quality (secondary outcome). The REAP allows users to capture short videos and photographs with their smartphones related to their physical exercise or eye relaxation activities. The SCAS – Child is a 45-item self-report scale used by Zheng et al to assess severity of anxiety symptoms in children. This tool is validated for children aged 8-15 years and assesses six domains of anxiety namely Separation Anxiety, Social Phobia, Obsessive Compulsive Problems, Panic/Agoraphobia, Generalized Anxiety/Overanxious Symptoms, and Fears of Physical Injury. The study randomly divided the population into control group (n=469) who received online health information sessions (comparator) and the experimental group (n=485) who received the comparator + REAP. Change in anxiety score was seen in Zheng et al (2021) to be significantly greater in the intervention group compared to the controls (difference -0.36, 95% CI -0.63 to -0.08; P=.02). Other outcomes investigated in the study were eye strain and sleep disturbance and they showed that change in self-reported eye strain significantly greater in the intervention vs the control group while changes in sleep disturbance did not differ significantly between study groups.

Jun Chen et al (2021) explored the intervention effect of the integration model on the negative emotions of adolescents during the COVID-19 epidemic. Research Tools for Outcome Measures were, the Self-rating Anxiety Scale, Positive and Negative Affect Scale, and Psychological Well-Being Scale. The study population included 69 adolescents with moderate and severe anxiety symptoms (SAS >/= 61). The subjects were randomly divided into the experiment group (35) and the control group (34) with the intervention and comparison time lasting for eight weeks. The control group was given routine health education support (comparator) while the experimental group received an Integration model intervention consisting of aerobics exercise course and mindfulness meditation training plus the comparator. They reported that the decrease in the SAS score was higher for the experiment group than for the control group (P<0.01). The positive emotion score was higher in the experiment group than in the control group; and the negative emotion score was lower in the experiment group than in the control group. (p<0.01). No significant difference occurred in the emotional index and life satisfaction between the two groups (P>0.05) The study concluded that the integration model intervention significantly reduced negative emotions such as anxiety, increase positive emotions, and improve the overall well-being of adolescents during the epidemic period.

Shuai Shao (2021) investigated the effect of Satir Model-based dance therapy on the mental health of adolescents with depression during the COVID-19 epidemic. A total of 62 adolescents with depression symptoms using Symptom Checklist 90 (SCL-90) were enrolled. The SCL-90 is a self-report questionnaire that briefly assesses symptoms in 9 dimensions namely somatization, obsessive-compulsive disorder, interpersonal

sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. The experimental group (32) received group psychological intervention and dance therapy based on the Satir Model, whereas the control group (30) was not given any intervention. Outcomes measured were levels of anxiety, depression, psychological resilience, and life satisfaction. Shao reported that post-intervention, life satisfaction level/score of the experiment group was significantly higher than that of the control group ($p<0.01$), depression/anxiety levels of the experiment group was significantly lower than that of the control group and significantly lower than that prior to the intervention ($p<0.01$). The study concluded that the combination of group intervention and dance therapy based on the Satir Model is a feasible method to alleviate adolescents anxiety and depression, promote their life satisfaction and psychological resilience, and thus improve their mental health.

The Anxiety and Depression Subscale of Achenbach Youth Self-Report compiled by Achenbach and revised by Liu Xianchen was used for measurement by Shao et al and it contains 16 items that are rated from 0 (never) to 4 points (often).

A pilot study on art and its impact on mental health by Catherine Malboeuf-Hurtubise et al (2021) was done to compare the impact of an emotion-based directed drawing intervention (experimental) and a Mandala drawing intervention (control), on anxiety, depression, inattention and hyperactivity symptoms in elementary school children, in the context of the COVID-19 pandemic. Both interventions were group-based and delivered online and remotely for 5 weeks. There were 14 children in the Intervention group and 8 in the comparator group. Outcomes were measured using the Behavior Assessment System for Children (BAS-C) and Spence Children's Anxiety Scale – Child, which is a 45-item self-report scale used to assess severity of anxiety symptoms in children. Post-intervention, children in the emotion-based directed drawing group showed lower inattention scores at post-test, compared to participants in the mandala group. Post-hoc sensitivity analyses showed significant decreases in pre-to-post scores for levels of hyperactivity of the total study population. However, for the primary outcomes of anxiety and depression levels, they found no impact of the type of intervention group. The BAS-C, which is a set of rating scales and forms designed to inform understanding of the behaviors and emotions of children and adolescents, was utilized in this study but only select questions for the anxiety, depression, inattention, and hyperactivity domains were used.

A qualitative, cross-sectional study by Kendra Nelson Ferguson et al (2021) explored the feelings and emotions adolescents experienced during the first wave of the COVID-19 pandemic. They identified coping strategies adolescents employed to manage those emotions. Participants living in Canada aged 13–19 years were recruited through social media platforms and youth-serving organizations. There were 2 open-ended questions: “What feelings and emotions have you experienced around the pandemic?” and “What coping strategies have you used during the pandemic?” There were a total of 1164 open-ended responses from Canadian adolescents ($n = 851$; mean age 15.6, standard deviation 1.7, yr) that were analyzed. Three major themes identified within the category of feelings and emotions associated with the pandemic: (1) sociospatial and temporal

disconnections, (2) emotional toll of the pandemic and (3) positives amid the pandemic. The major themes identified within the category of coping strategies were: (1) connecting online and outdoors, and (2) leisure and health-promoting activities. Despite the emotional toll of the first wave of the COVID-19, participants in the study adopted various positive coping strategies to mitigate their distress, including physical activity, safe peer interactions and hobbies. The study highlighted the importance of accessible mental health resources for those experiencing psychological distress.

Janise S. Parker et al (2021) reported in their phenomenological study the effects of the COVID-19 pandemic on marginalized groups. They investigated Black adolescents' perceptions of their experiences with COVID-19, including the challenges they encountered, the coping strategies they employed, and their use of religious/spiritual and school-based support. Twelve Black youth between the ages of 12 and 18 years were interviewed regarding their struggles with adjusting to the changes in their daily routines, navigating virtual learning, and facing the emerging mental health difficulties such as anxiety. Problem-focused coping strategies identified were religious/spiritual practices and social support from the family, school personnel, and religious community.

In summary, outcome measures for the 5 RCTs included in this review were heterogeneous but across studies, measurement of anxiety levels was common. Two studies, that of Zhang et al and Shao et al, measured levels of depression. One RCT measured resilience status (Zhang et al), life satisfaction (Shao, 2021), mindfulness (Malboeuf-Hurtubise et al), and overall well-being (Chen et al).

Specific outcomes measured by the RCTs included were as follows: Zhang et al showed a decrease in SDS and SAS scores (mean difference) ($p<0.05$), decrease in Pittsburgh Sleep Quality Index (PSQI) ($p<0.05$), and increase in psychological resilience score ($p<0.05$). Shao et al (2021) found post-intervention that Life satisfaction level/score of the experiment group is significantly higher than that of the control group, depression/anxiety level of the experiment group is significantly lower than that of the control group and significantly lower than that prior to the intervention. Change in anxiety score was seen in Zheng et al (2021) to be significantly greater in the intervention group compared to the controls, change in self-reported eye strain significantly greater in the intervention vs the control group, but changes in sleep disturbance score ($P=.23$), screen time ($P=.84$), and reading time ($P=.47$) during the 2-week follow-up did not differ significantly between study groups. Decrease in the SAS score in Chen et al (2021) was higher for the experiment group than for the control group ($P<0.01$). The positive emotion score is higher in the experiment group than in the control group; negative emotion score is lower in the experiment group than in the control group. ($p<0.01$). No significant difference occurred in the emotional index and life satisfaction between the two groups ($P>0.05$) was noted. Malboeuf-Hurtubise (2021) found no impact of the type of art intervention on levels of anxiety, depression, hyperactivity or mindfulness.

The overall quality of evidence was rated low because of serious risk of bias. Meta-analysis was not carried out due to heterogeneity of studies in terms of interventions and tools used for the outcome measures. (Appendix 2) There are no ongoing RCT studies

found after the comprehensive literature search but several observational studies on the prevalence of mental health disorder during this pandemic period were available.

The qualitative studies elucidated examples of coping strategies that were deemed effective by the adolescents. Overall, they include connecting with peers online and outdoors, leisure and health-promoting activities, personal and spiritual coping, and social support from the household and sectors of the community. (Appendix 2).

Other Considerations (Evidence to Decision)

Resource Use and Cost Effectiveness	For professional psychological counseling-- will it be reimbursable to Philhealth/HMOs
Availability/Equity	No issues on availability
Patient's Values or Preferences; Social Impact	No available evidence
Factors to Impact Acceptability or Compliance/ Feasibility	Due to ongoing pandemic, many of the proposed interventions will be done online via video conferencing or mobile applications. Digital and online activities are generally acceptable to children and adolescents; however, access to internet/mobile data might be a major factor that will affect compliance to interventions.

Recommendations from Other Groups

As of December 2021, the American Academy of Pediatrics issued an interim guidance on supporting the emotional and behavioral health needs of children, adolescents and families during the COVID-19 pandemic. Recommended supportive strategies include:

- Mindfulness, relaxation, and focusing on the present moment can help the entire family build coping skills to deal with uncomfortable and frightening feelings
- Building networks of social support have also been found to be central to promoting resilience
- Participating in volunteer opportunities to help the community, can help children and caregivers feel less vulnerable and
- Building networks of social support have also been found to be central to promoting resilience.

In the Philippines, there are currently no local guidelines or recommendations on mental health strategic interventions for the pediatric population during the COVID-19 pandemic.

Research Gaps

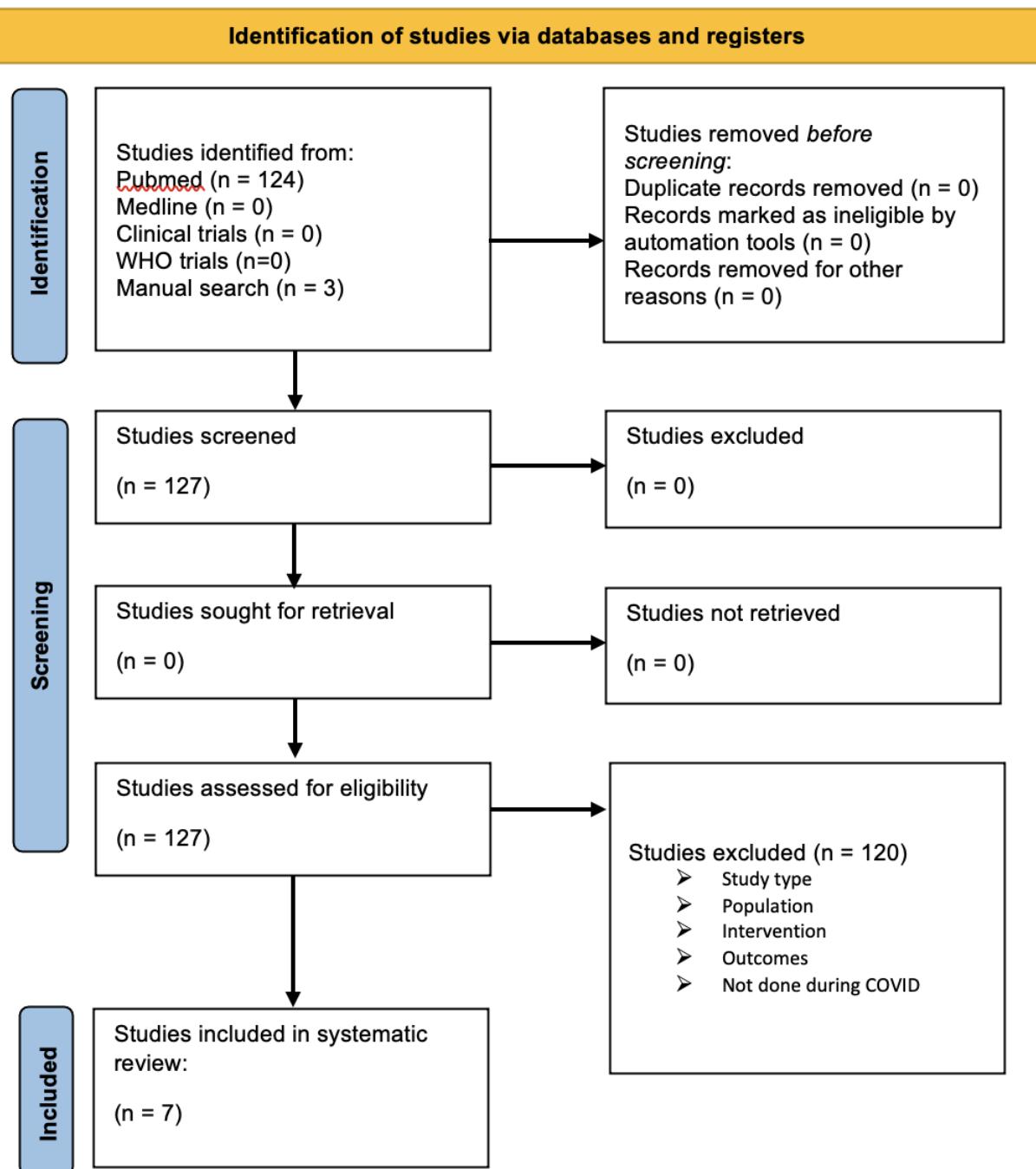
Majority of studies found in the recommended coping strategies found to optimize mental health were done in the adolescent age group. There was no study found on effective coping strategies for the younger age group.

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Evidence Summary Appendices

Appendix 1. Search Yield & Results.



Appendix 2. Characteristics of Included Studies

Title/Author/ Country	Study Design	Population	Interventi on	Comparis on	Outcomes																																									
					ANXIETY		DEPRESSION		RESILIENCE		OTHER KEY FINDINGS																																			
INTERVENTI ON EFFECT OF RESEARCH- BASED PSYCHOLO GICAL COUNSELIN G ON ADOLESCEN TS' MENTAL HEALTH DURING THE COVID- 19 EPIDEMIC, Zhang, et al., 2021 China	RCT	School children aged 12-18 with SDS and SAS score >=50 (N = 153, Exp=76 C=77) Anxiety: Score of >50 Depression : Score of ≥50	Research- based psychologi cal counseling model and outdoor exercise + Comparat or 8 weeks	Routine community health education (public health, personal health, disease prevention)	In E, Decr SAS(MD) (p<0.05)		In E, Decr in SDS (MD) (p<0.05)		In E, Incr psychological resilience score (p<0.05)		In E, Dec in Pittsburgh Sleep Quality Index (PSQI) (p<0.05)																																			
					<table border="1"> <thead> <tr> <th></th> <th>Before</th> <th>After</th> </tr> </thead> <tbody> <tr> <td>E</td> <td>64.03 ±9.96</td> <td>56.83± 10.96</td> </tr> <tr> <td>C</td> <td>64.05 ±9.45</td> <td>60.81± 9.51</td> </tr> </tbody> </table>		Before	After	E	64.03 ±9.96	56.83± 10.96	C	64.05 ±9.45	60.81± 9.51		<table border="1"> <thead> <tr> <th></th> <th>Before</th> <th>After</th> </tr> </thead> <tbody> <tr> <td>E</td> <td>62.91±6. 69</td> <td>54.91 ±9.00</td> </tr> <tr> <td>C</td> <td>64.16±7. 21</td> <td>60.01 ±8.87</td> </tr> </tbody> </table>		Before	After	E	62.91±6. 69	54.91 ±9.00	C	64.16±7. 21	60.01 ±8.87	<table border="1"> <thead> <tr> <th></th> <th>Before</th> <th>After</th> </tr> </thead> <tbody> <tr> <td>E</td> <td>82.54±8. 14</td> <td>100.05±7.</td> </tr> <tr> <td>C</td> <td>85.04±10. .46</td> <td>91.09±9.5</td> </tr> </tbody> </table>		Before	After	E	82.54±8. 14	100.05±7.	C	85.04±10. .46	91.09±9.5	<table border="1"> <thead> <tr> <th></th> <th>Before</th> <th>After</th> </tr> </thead> <tbody> <tr> <td>E</td> <td>8.84± 3.47</td> <td>6.21±3.86</td> </tr> <tr> <td>C</td> <td>8.45± 3.73</td> <td>7.64±4.01</td> </tr> </tbody> </table>		Before	After	E	8.84± 3.47	6.21±3.86	C	8.45± 3.73	7.64±4.01	
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INTERVENTION ON EFFECT OF DANCE THERAPY BASED ON THE SATIR MODEL ON THE MENTAL HEALTH OF ADOLESCEN TS DURING THE COVID-19 EPIDEMIC. Shao 2021 China	RCT	Adolescents aged 15.98 +/- 0.11 with depression symptoms based on SCL-90 (n=62) N = 62, Exp= 32 C= 30 (SCL-90) The factor higher than 3 = used as the criterion for judging mental disorders.	Group psychological intervention (7 weeks) and dance therapy (8 weeks)	No intervention																							
					ANXIETY	DEPRESSION	RESILIENCE	OTHER KEY FINDINGS																			
					Anxiety level of the E group is significantly lower than that of the control group and significantly lower than that prior to the intervention. <table border="1"> <thead> <tr> <th></th> <th>Before</th> <th>After</th> </tr> </thead> <tbody> <tr> <td>E</td> <td>2.09±0.21</td> <td>1.55±0.33</td> </tr> <tr> <td>C</td> <td>3.00±0.20</td> <td>2.99±0.20</td> </tr> </tbody> </table>		Before	After	E	2.09±0.21	1.55±0.33	C	3.00±0.20	2.99±0.20	Depression level of the E group Depression is significantly lower than that of the control group and significantly lower than that prior to the intervention.	The psychological resilience level of the control group after the intervention is significantly higher than that prior to the intervention.	Life satisfaction level/score of the experiment group is significantly higher than that of the control group	<table border="1"> <thead> <tr> <th></th> <th>Before</th> <th>After</th> </tr> </thead> <tbody> <tr> <td>E</td> <td>2.01±0.36</td> <td>5.46±0.45</td> </tr> <tr> <td>C</td> <td>1.97±0.42</td> <td>2.93±0.38</td> </tr> </tbody> </table>		Before	After	E	2.01±0.36	5.46±0.45	C	1.97±0.42	2.93±0.38
	Before	After																									
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A Peer-to-Peer Live-Streaming Intervention for Children During COVID-19 Homeschooling to Promote Physical Activity and Reduce Anxiety and Eye Strain: Cluster Randomized Controlled Trial, Zheng, et al., 2021 China	RCT	Grade 7 students, aged 12-13 (N=954 Exp=485 C=469)	Recess and Exercise Advocacy Program (live-streaming platform) allows users to capture short videos and photographs with their smartphones related to their physical exercise or eye relaxation activities + Comparator	Online health information session	ANXIETY		OTHER KEY FINDINGS										
					Change in anxiety score was significantly greater in the intervention group compared to the controls (difference -0.36, 95% CI -0.63 to -0.08; P=.02)												
					<table border="1"> <thead> <tr> <th></th><th>Before</th><th>After</th></tr> </thead> <tbody> <tr> <td>E</td><td>3.72 (3.69 to 3.76)</td><td>3.49 (3.46 to 3.52)</td></tr> <tr> <td>C</td><td>3.67 (3.64 to 3.70)</td><td>3.79 (3.76 to 3.83)</td></tr> </tbody> </table>		Before	After	E	3.72 (3.69 to 3.76)	3.49 (3.46 to 3.52)	C	3.67 (3.64 to 3.70)	3.79 (3.76 to 3.83)			
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E	3.72 (3.69 to 3.76)	3.49 (3.46 to 3.52)															
C	3.67 (3.64 to 3.70)	3.79 (3.76 to 3.83)															
							Change in self-reported eye strain significantly greater in the intervention vs the control group (difference -0.15, 95% CI -0.26 to -0.03; P=.02)										
							<table border="1"> <thead> <tr> <th></th><th>Before</th><th>After</th></tr> </thead> <tbody> <tr> <td>E</td><td>1.21 (1.19 to 1.23)</td><td>1.13 (1.11 to 1.15)</td></tr> <tr> <td>C</td><td>1.08 (1.06 to 1.10)</td><td>1.15 (1.12 to 1.18)</td></tr> </tbody> </table>		Before	After	E	1.21 (1.19 to 1.23)	1.13 (1.11 to 1.15)	C	1.08 (1.06 to 1.10)	1.15 (1.12 to 1.18)	
	Before	After															
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							Changes in sleep disturbance score (P=.23), screen time (P=.84), and reading time (P=.47) during the 2-week follow-up did not differ significantly between study groups.										
							<table border="1"> <thead> <tr> <th></th><th>Before</th><th>After</th></tr> </thead> <tbody> <tr> <td>E</td><td>2.51 (2.50 to 2.52)</td><td>2.57 (2.56 to 2.58)</td></tr> <tr> <td>C</td><td>2.53 (2.53 to 2.54)</td><td>2.55 (2.54 to 2.56)</td></tr> </tbody> </table>		Before	After	E	2.51 (2.50 to 2.52)	2.57 (2.56 to 2.58)	C	2.53 (2.53 to 2.54)	2.55 (2.54 to 2.56)	
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INTERVENTION ON EFFECT OF THE INTEGRATION MODEL ON NEGATIVE EMOTIONS OF ADOLESCENTS DURING THE OUTBREAK OF CORONA VIRUS DISEASE 2019 , Chen, et al., 2021 China	RCT	Adolescents with SAS >/= 61 (moderate to severe) (N=69 Exp=35 C=34)	Integration intervention: aerobics exercise course and mindfulness meditation training + Comparator x 8 weeks	Routine health education support	ANXIETY		EMOTION SCORE		OTHER KEY FINDINGS																																																							
					Decrease in the SAS score higher for the experiment group than for the control group (P<0.01)																																																											
					<table border="1"> <thead> <tr> <th></th><th>Before</th><th>After</th></tr> </thead> <tbody> <tr> <td>E</td><td>66.8±8.1</td><td>50.8±9.3</td></tr> <tr> <td>C</td><td>67.7±8.2</td><td>57.1±8.9</td></tr> </tbody> </table>		Before	After	E	66.8±8.1	50.8±9.3	C	67.7±8.2	57.1±8.9		<table border="1"> <thead> <tr> <th></th><th>Before</th><th>After</th></tr> </thead> <tbody> <tr> <td>E</td><td>27.3±7.3</td><td>32.7±6.1</td></tr> <tr> <td>C</td><td>27.2±8.4</td><td>29.2±8.1</td></tr> </tbody> </table>		Before	After	E	27.3±7.3	32.7±6.1	C	27.2±8.4	29.2±8.1	<table border="1"> <thead> <tr> <th></th><th>Before</th><th>After</th></tr> </thead> <tbody> <tr> <td>E</td><td>24.5±5.9</td><td>19.5±4.2</td></tr> <tr> <td>C</td><td>24.1±6.7</td><td>22.3±6.3</td></tr> </tbody> </table>		Before	After	E	24.5±5.9	19.5±4.2	C	24.1±6.7	22.3±6.3	<p>The positive emotion score is higher in the experiment group than in the control group; negative emotion score is lower in the experiment group than in the control group. (p<0.01).</p> <p>Positive Emotion</p> <table border="1"> <thead> <tr> <th></th><th>Before</th><th>After</th></tr> </thead> <tbody> <tr> <td>E</td><td>7.6±2.0</td><td>9.5±1.9</td></tr> <tr> <td>C</td><td>7.8±2.3</td><td>8.3±2.7</td></tr> </tbody> </table> <p>Negative Emotion</p> <table border="1"> <thead> <tr> <th></th><th>Before</th><th>After</th></tr> </thead> <tbody> <tr> <td>E</td><td>24.5±5.9</td><td>19.5±4.2</td></tr> <tr> <td>C</td><td>24.1±6.7</td><td>22.3±6.3</td></tr> </tbody> </table>		Before	After	E	7.6±2.0	9.5±1.9	C	7.8±2.3	8.3±2.7		Before	After	E	24.5±5.9	19.5±4.2	C	24.1±6.7	22.3±6.3	<p>After the intervention, no significant difference occurred in the emotional index and life satisfaction between the two groups (P>0.05), but the difference in the overall well-being index is statistically significant (P=0.040)</p> <p>Overall well-being index</p> <table border="1"> <thead> <tr> <th></th><th>Before</th><th>After</th></tr> </thead> <tbody> <tr> <td>E</td><td>7.6±2.0</td><td>9.5±1.9</td></tr> <tr> <td>C</td><td>7.8±2.3</td><td>8.3±2.7</td></tr> </tbody> </table>		Before	After	E	7.6±2.0	9.5±1.9	C	7.8±2.3	8.3±2.7
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Online art therapy in elementary schools during COVID-19: results from a randomized cluster pilot and feasibility study and impact on	RCT	Grade 4-5 students (N=22 Exp=14 C=8)	Emotion-based directed drawing intervention 5 weeks	Mandala drawing intervention	<table border="1"> <thead> <tr> <th colspan="2">ANXIETY</th> <th colspan="2">DEPRESSION</th> <th colspan="2">MINDFULNESS</th> <th colspan="2">OTHER KEY FINDINGS</th> </tr> </thead> <tbody> <tr> <td colspan="8">No impact of type intervention group on levels of anxiety, depression, hyperactivity or mindfulness.</td> </tr> <tr> <td>Before</td><td>After</td><td>Before</td><td>After</td><td>Before</td><td>After</td><td>Before</td><td>After</td> </tr> </tbody> </table>	ANXIETY		DEPRESSION		MINDFULNESS		OTHER KEY FINDINGS		No impact of type intervention group on levels of anxiety, depression, hyperactivity or mindfulness.								Before	After	Before	After	Before	After	Before	After	No impact	<table border="1"> <thead> <tr> <th></th><th>Before</th><th>After</th></tr> </thead> <tbody> <tr> <td>E</td><td>24.5±5.9</td><td>19.5±4.2</td></tr> <tr> <td>C</td><td>24.1±6.7</td><td>22.3±6.3</td></tr> </tbody> </table>		Before	After	E	24.5±5.9	19.5±4.2	C	24.1±6.7	22.3±6.3	<p>INATTENTION</p> <p>Emotion- based directed drawing group showed lower inattention scores at post-test (Mpost,</p>																							
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mental
health,
Malboeuf-
Hurtubise , et
al, 2021
Canada

E	3.71 (1.48)	3.5 (1.70)		E	2.46 (1.71)	2.07 (1.49)
C	3.25 (2.05)	2.87 (.83)		C	2.62 (1.84)	2.62 (1.50)

E	2.27 (0.83)	2.04 (0.85)
C	2.30 (0.81)	2.03 (0.77)

adjusted for
baseline=1.32), when
compared to
participants in the
mandala group (Mpost,
adjusted for
baseline=1.97).

	Before	After
E	1.38 (1.32)	1.23 (1.23)
C	1.75 (1.83)	2.12 (1.24)

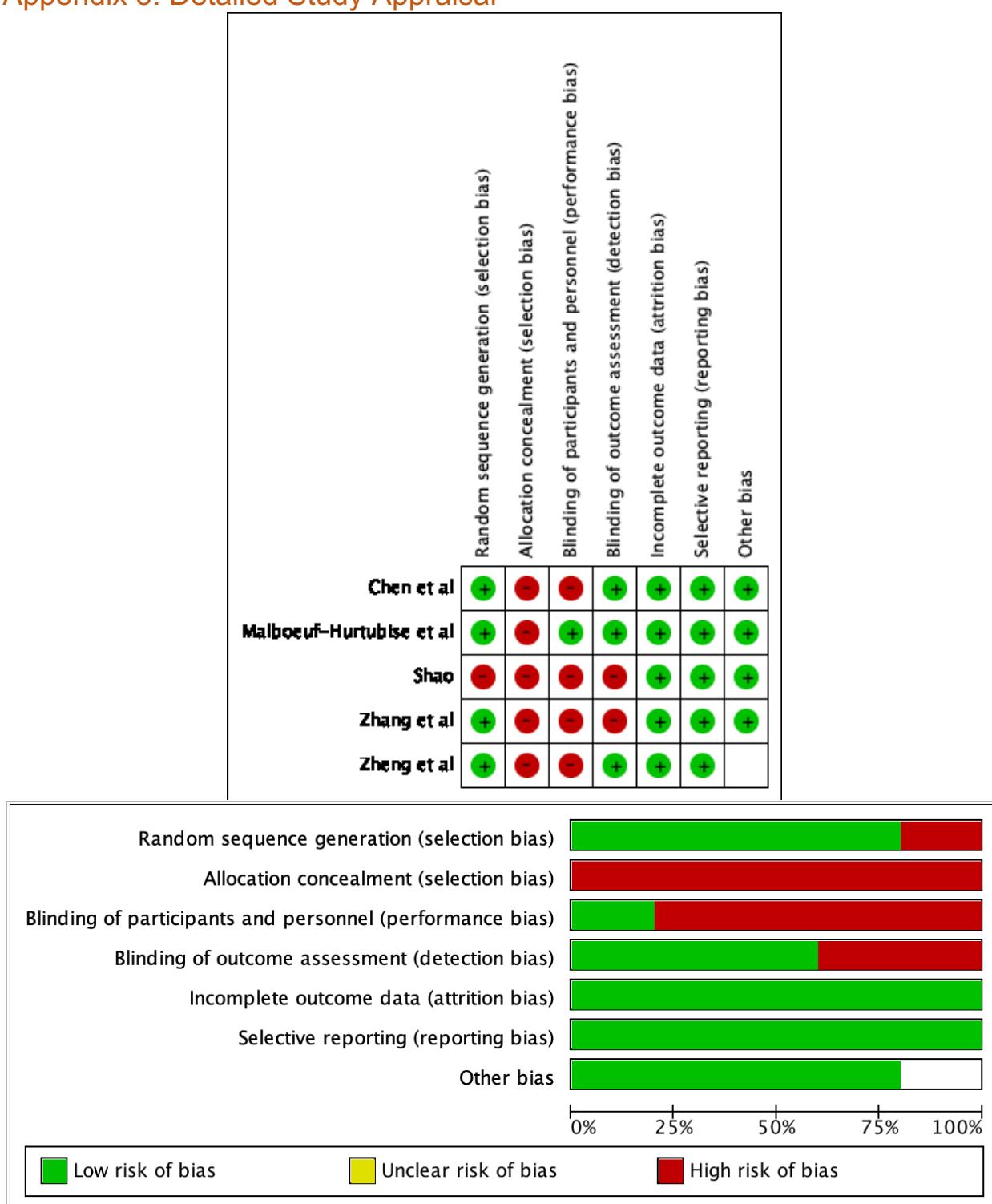
HYPERACTIVITY
Significant decreases in
pre-to-post scores for
levels of hyperactiv- ity
($t(21) = 2.01, p = 0.05$)
for the complete
sample

	Before	After
E	2.21 (1.25)	1.78 (1.57)
C	1.37 (1.4)	2.00 (1.3)

<p>The mental well-being and coping strategies of Canadian adolescents during the COVID-19 pandemic: a qualitative, cross-sectional study, Ferguson, et al., 2021 Canada</p>	<p>Qualitative, Cross sectional</p>	<p>Canadian adolescents (13-19 y/o) 1164 open-ended responses</p>	<p>Open ended questions: “What feelings and emotions have you experienced around the pandemic?” and “What coping strategies have you used during the pandemic?” 4months</p>	<p>None</p>	<p>3 major themes within the category of <u>feelings and emotions</u> associated with the pandemic: sociospatial and temporal disconnections, emotional toll of the pandemic and positives amid the pandemic. Within the category of <u>coping strategies</u> used during the pandemic, 2 major themes were identified:</p> <ol style="list-style-type: none"> 1. Connecting online and Outdoors -video calls, texting, playing video games together, and social media. Outdoor playing games, going for walks or just hanging out, visits with friends or family outdoors to connect and socialize, while following physical distancing 2. Leisure and health-promoting activities. Incorporating exercise into daily routines, going for walks, working on sport-specific skills. Finding activities and new hobbies to keep busy video gaming, cooking and baking, arts (i.e., crafts, music and dance), reading, and watching television or movies.
<p>Black Adolescents' Perceptions of COVID-19: Challenges, Coping, and Connection to Family, Religious, and School Support, Parker et al., 2021 USA</p>	<p>Qualitative Phenomenological</p>	<p>African American 12-17 y/o (n=12)</p>	<p>Interview 2months Q: (a) the challenges they experienced as a result of COVID-19, (b) how religious/spiritual practices helped them cope with COVID-related challenges, (c) additional coping strategies they</p>	<p>None</p>	<p>Experiences as particularly challenging due to COVID-19: (a) loss of normalcy due to a change in their routine and limited social interactions, (b) online learning, and (c) mental health and trauma-related experiences.</p> <p>Coping Strategies:</p> <p>1. Personal Coping: reading, listening to music, personal grooming (room cleaning, painting nails, doing hair, etc.), completing “artsy” based projects (e.g., painting and coloring), and exercising. Learn new skills and learn more about themselves. Had opportunities to rest, spend time with family, improve health, and focus on school.</p> <p>Religious and Spiritual Coping. Having a strong faith and trust in God helped participants cope with COVID-19 and reconcile the negative feelings they experienced.</p> <p>2. Social support: Family, Religious community, and School personnel</p> <p>Family Support. time spent with family members in their households as fun and as a chance to reconnect.</p> <p>School-Based Support. Schools provided both instrumental (“giving lunch to those who needed it,” “handing out computers” (i.e., laptops) for students to complete virtual school, and providing academic support for students) and emotional support (teachers initiated more explicit discussions about the students’ social-emotional well-being by seeking student input, offering encouragement and reassurance, and providing brief-check-ins)</p>

			used to manage their response to COVID-19, (d) how their school supported them in the early stages of COVID-19 (from March to June 2020 when school was still in session), and (e) their perceptions of the school and religious/spiritual-based support they received.		<p><u>Religious Community Support</u>. Youth leaders provided social and emotional check-ins, which included having mentors and youth directors facilitate individual and group meetings to check on the youths' well-being.</p>
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Appendix 3. Detailed Study Appraisal



1. APPRAISAL FORM FOR THERAPY - Zhang,China

APPRAISING DIRECTNESS	
Does the study provide a direct enough answer to your clinical question in terms of type of patients (P), exposure/ intervention (E) and outcome (O)?	<p>What are the supportive strategies to optimize mental health among children during the COVID-19 pandemic?</p> <p>P 0-18 yrs I supportive strategies C none O optimized MH Intervention Effect of Research-based Psychological Counseling on Adolescents' Mental Health during the COVID-19 Epidemic P -12-18 yrs I - routine community health education, research-based psychological counseling model and outdoor exercise. C- routine community health education O - Resilience Assessment, Pittsburgh Sleep Quality Index (PSQI)</p>
APPRAISING VALIDITY	
Were the patients randomly assigned to treatment groups?	Yes
Was allocation concealed?	No
Were baseline characteristics similar at the start of the trial?	Yes
Were patients blinded to treatment assignment?	No
Were caregivers blinded to treatment assignment?	No
Were outcome assessors blinded to treatment assignment?	No

Were all patients analyzed in the groups to which they were originally randomized?	7 drop outs Censored analysis was done Orig:160 Exp=76 C=77 (153)
Was follow-up rate adequate?	yes
APPRAISING RESULTS	
How large was the treatment effect?	Comparison of anxiety and depression: Decreases were noted in the scores of both groups in anxiety and depression after the intervention, and the differences are statistically significant ($P<0.001$). Comparison of sleep quality: Decreases were noted in the PQSI score of both groups after the intervention, and the differences are statistically significant ($P<0.001$). Comparison of psychological resilience: Increases were noted in the scores of both groups in psychological resilience and its five dimensions after the intervention, and the differences are statistically significant ($P<0.001$)
How precise was the estimate of the treatment?	precise

Intervention Effect of Research-based Psychological Counseling on Adolescents' Mental Health during the COVID-19 Epidemic

[Jianpeng Zhang](#) 1, [Zixiang Zhou](#), [Wei Zhang](#)

2. APPRAISAL FORM FOR THERAPY -Shao,China

I. APPRAISING DIRECTNESS	
Does the study provide a direct enough answer to your clinical question in terms of type of patients (P), exposure/intervention (E) and outcome (O)?	<p>What are the supportive strategies to optimize mental health among children during the COVID-19 pandemic?</p> <p>P 0-18 yrs I supportive strategies C none O -optimized MH</p> <p>INTERVENTION EFFECT OF DANCE THERAPY BASED ON THE SATIR MODEL ON THE MENTAL HEALTH OF ADOLESCENTS DURING THE COVID-19 EPIDEMIC</p> <p>P – adolescent age grp I – dance therapy with grp psycho intervention C- none O – promote MH</p>
II. APPRAISING VALIDITY	
1. Were the patients randomly assigned to treatment groups?	No
2. Was allocation concealed?	No
3. Were baseline characteristics similar at the start of the trial?	Yes
4. Were patients blinded to treatment assignment?	No
5. Were caregivers blinded to treatment assignment?	No
6. Were outcome assessors blinded to treatment assignment?	No

7	Were all patients analyzed in the groups to which they were originally randomized?	yes Orig:62 Exp=32 C=30
8	Was follow-up rate adequate?	yes
III APPRAISING RESULTS		
.		
1.	How large was the treatment effect?	life satisfaction between two groups: life satisfaction level of the experiment group is significantly higher than that of the control group depression/anxiety between two grps: life depression/anxiety level of the experiment group is significantly lower than that of the control group and significantly lower than that prior to the intervention. psychological resilience between two groups: level of the experiment group in psychological resilience and its dimensions is significantly higher than those of the control group
2.	How precise was the estimate of the treatment?	precise

INTERVENTION EFFECT OF DANCE THERAPY BASED ON THE SATIR MODEL ON THE MENTAL HEALTH OF ADOLESCENTS DURING THE COVID-19 EPIDEMIC
Shuai Shao

3. APPRAISAL FORM FOR THERAPY -Yingfeng Zheng, China

I. APPRAISING DIRECTNESS	
Does the study provide a direct enough answer to your clinical question in terms of type of patients (P), exposure/intervention (E) and outcome (O)?	<p>What are the supportive strategies to optimize mental health among children during the COVID-19 pandemic?</p> <p>P 0-18 yrs I supportive strategies C none O -optimized MH</p> <p>A Peer-to-Peer Live-Streaming Intervention for Children During COVID-19 Homeschooling to Promote Physical Activity and Reduce Anxiety and Eye Strain: Cluster Randomized Controlled Trial</p> <p>P – Grade 7 (12-13 yrs) I – health education information promoting exercise and ocular relaxation, and access to a digital behavior change intervention, with live streaming and peer sharing of promoted activities REAP app C- health education information only O – primary outcome: self-reported anxiety score. Secondary outcomes- eye strain and sleep quality</p>
II. APPRAISING VALIDITY	
1. Were the patients randomly assigned to treatment groups?	YES
2. Was allocation concealed?	No
3. Were baseline characteristics similar at the start of the trial?	Yes
4. Were patients blinded to treatment assignment?	No

5.	Were caregivers blinded to treatment assignment?	yes
6.	Were outcome assessors blinded to treatment assignment?	yes
7	Were all patients analyzed in the groups to which they were originally randomized?	Orig: 954 included in the intention-to-treat analysis. Exp =485 C=469 Completed:896 children Exp=467 C=429
8	Was follow-up rate adequate?	yes
III APPRAISING RESULTS		
.		
1.	How large was the treatment effect?	anxiety scores was greater in the intervention (-0.23 , 95% CI -0.27 to -0.20) vs control group (0.12 , 95% CI 0.09 - 0.16 ;
2.	How precise was the estimate of the treatment?	precise

A Peer-to-Peer Live-Streaming Intervention for Children During COVID-19

Homeschooling to Promote Physical Activity and Reduce Anxiety and Eye Strain: Cluster Randomized Controlled Trial Yingfeng Zheng, MD, PhD,^{#1,2,3} Wei Wang, MD, PhD,^{#1}, et al

4. APPRAISAL FORM FOR THERAPY -Chen,China

I. APPRAISING DIRECTNESS	
Does the study provide a direct enough answer to your clinical question in terms of type of patients (P), exposure/intervention (E) and outcome (O)?	<p>What are the supportive strategies to optimize mental health among children during the COVID-19 pandemic?</p> <p>P 0-18 yrs I supportive strategies C none O -optimized MH</p> <p>INTERVENTION EFFECT OF THE INTEGRATION MODEL ON NEGATIVE EMOTIONS OF ADOLESCENTS DURING THE OUTBREAK OF CORONA VIRUS DISEASE 2019</p> <p>P-adolescents I-routine health education support + integration model (aerobics exercise course and mindfulness meditation training) C - routine health education support O Changes in the psychological anxiety levels and negative emotions of the both groups before and after the intervention were compared</p>
II. APPRAISING VALIDITY	
1. Were the patients randomly assigned to treatment groups?	YES
2. Was allocation concealed?	No
3. Were baseline characteristics similar at the start of the trial?	Yes
4. Were patients blinded to treatment assignment?	No
5. Were caregivers blinded to treatment assignment?	yes

6.	Were outcome assessors blinded to treatment assignment?	yes
7	Were all patients analyzed in the groups to which they were originally randomized?	Orig: 72 E=36 C=36 Completed: Exp= 34 C=35
8	Was follow-up rate adequate?	Yes LOST: 2- control group 1-experiment group
III APPRAISING RESULTS		
1.	How large was the treatment effect?	<p>anxiety scores: After one month of intervention, the SAS scores of the two groups decreased, and the differences in their respective SAS values before the intervention are statistically significant ($P<0.01$). After the intervention, the SAS of the experiment group was lower than that of the control group, and the decrease in the SAS score is higher for the experiment group than for the control group. The differences are statistically significant ($P<0.01$)</p> <p>positive and negative emotion scores: After one month of intervention, the positive emotion scores of the two groups both increased, while the negative emotion scores both decreased after the intervention ($P<0.01$). The difference between their respective values before the intervention are statistically significant ($P<0.01$). After the intervention, the positive emotion score is higher in the experiment group than in the control group, and the negative emotion score is lower in the experiment group than in the control group. The variances in the positive and negative emotion scores are higher in the experiment group than in the control group ($P<0.01$).</p> <p>overall well-being index: After one month of intervention, the scores for emotional index, life satisfaction, and general well-being index increased in both groups.</p>

	After the intervention, no significant difference occurred in the emotional index and life satisfaction between the two groups ($P>0.05$), but the difference in the overall well-being index is statistically significant ($P=0.040$).
2. How precise was the estimate of the treatment?	precise

Intervention Effect of the Integration Model on Negative Emotions of Adolescents during the Outbreak of Corona Virus Disease 2019

Jun Chen 1, Guoqiang Sang, Yu Zhang, Aifeng Jiang

5. APPRAISAL FORM FOR THERAPY -Hurtubise,Canada

APPRAISING DIRECTNESS	
Does the study provide a direct enough answer to your clinical question in terms of type of patients (P), exposure/intervention (E) and outcome (O)?	<p>What are the supportive strategies to optimize mental health among children during the COVID-19 pandemic?</p> <p>P 0-18 yrs I supportive strategies C none O -optimized MH</p> <p>Online art therapy in elementary schools during COVID-19: results from a randomized cluster pilot and feasibility study and impact on mental health P- elementary school children I-emotion-based directed draw[1]ing intervention (directed) C- mandala drawing intervention (not directed) and more attention-focused O-anxiety, depression, inattention and hyperactivity symptoms</p>
APPRAISING VALIDITY	
Were the patients randomly assigned to treatment groups?	YES
Was allocation concealed?	No
Were baseline characteristics similar at the start of the trial?	Yes
Were patients blinded to treatment assignment?	yes

Were caregivers blinded to treatment assignment?	yes
Were outcome assessors blinded to treatment assignment?	yes
Were all patients analyzed in the groups to which they were originally randomized?	Orig: E=14 C=8
Was follow-up rate adequate?	Yes No attrition
APPRAISING RESULTS	
How large was the treatment effect?	<p>INATTENTION</p> <p>Participants in the emotion[1]based directed drawing group showed lower inattention scores at post-test (M_{post}, adjusted for baseline=1.32), when compared to participants in the mandala group (M_{post}, adjusted for baseline=1.97). However, sensitivity analyses using paired t-tests did not show significant pre-to-post changes in inattention scores in participants from each group ($p_{emotion-based}=0.43$; $p_{mandala}=0.35$). We found no impact of type intervention group on levels of anxiety, depression, hyperactivity or mindfulness. Post-hoc sensitivity analyses showed significant decreases in pre-to-post scores for levels of hyperactiv[1]ity ($t(21)=2.01$, $p=0.05$) for the complete sample. It thus seems that participants from both groups showed a decrease in scores from pre-intervention (M_{pre} total sample[1]ple=2.22) to post-intervention (M_{post} total sample=1.86).</p>

7. How precise was
the estimate of the
treatment?

precise

Appendix 4: GRADE Evidence Profile

Author(s): Galindez, Milan, et al

Question: Supportive mental health strategies compared to standard of care for pediatric population during COVID 19 pandemic

Setting: Philippines

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	supportive mental health strategies	standard of care	Relative (95% CI)	Absolute (95% CI)		

Anxiety level (follow-up: mean 7.4 weeks; assessed with: SAS, SCAS, ADS, BAS-C)

1 (n=153)	Randomized trial (Zhang et al , 2021)	serious ^{a,b,c}	not serious	not serious	not serious	none	76	77	-	MD 3.98 lower (7.22 lower to 2.23 lower)	 Moderate	IMPORTANT
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1 (n=62)	Randomized trial (Shao, 2021)	very serious ^{a,b,c,d}	not serious	not serious	not serious	none	32	30	-	MD 1.44 lower (1.58 lower to 1.31 lower)	 Low	IMPORTANT
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1 (n=954)	Randomized trial (Zheng et al, 2021)	serious ^{a,b}	not serious	not serious	not serious	none	485	469	-	MD 0.3 lower (0 to 0)	 Moderate	IMPORTANT
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1 (n=69)	Randomized trial (Chen et al, 2021)	serious ^{a,b}	not serious	not serious	not serious	none	35	34	-	MD 6.3 lower (10.59 lower to 2 lower)	 Moderate	IMPORTANT
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1 (n=22)	Randomized trial	serious ^b	not serious	not serious	not serious	none	14	8	-	MD 3.63 higher (0 to 0)	 Moderate	IMPORTANT
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	(Malboeuf-Hurtubise et al, 2021)										
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Depression level (follow-up: mean 8 weeks; assessed with: SDS, Achenbach Youth Self-report)

1 (n=153)	Randomized trial (Zhang et al , 2021)	serious ^{a,b,c}	not serious	not serious	not serious	none	76	77	-	MD 5.1 lower (7.93 lower to 2.27 lower)	 Moderate	IMPORTANT
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1 (n=62)	Randomized trial (Shao, 2021)	very serious ^{a,b,c,d}	not serious	not serious	not serious	none	32	30	-	MD 1.44 lower (1.58 lower to 1.31 lower)	 Low	IMPORTANT
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Resilience (follow-up: mean 8 weeks)

1 (n=62)	Randomized trial (Shao, 2021)	very serious ^{a,b,c,d}	not serious	not serious	not serious	none	32	30	-	MD 8.96 higher (6.18 higher to 11.74 higher)	 Low	IMPORTANT
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Life Satisfaction (follow-up: 8 weeks)

1 (n=62)	Randomized trial (Shao, 2021)	very serious ^{a,b,c,d}	not serious	not serious	not serious	none	32	30	-	MD 2.53 higher (2.32 higher to 2.74 higher)	 Low	IMPORTANT
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Mindfulness (follow-up: mean 5)

1 (n=22)	Randomized trial (Malboeuf-Hurtubise et al, 2021)	serious ^b	not serious	not serious	not serious	none	14	8	-	MD 0.01 higher (0 to 0)	 Moderate	IMPORTANT
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Overall well-being (follow-up: mean 8 weeks)

1 (n=69)	Randomized trial (Chen et al, 2021)	serious ^{a,b}	not serious	not serious	not serious	none	35	34	-	MD 1.2 higher (0.11 higher to 2.29 higher)	 Moderate	IMPORTANT
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CI: confidence interval; MD: mean difference

Explanations

- a. Subjects are difficult to blind to interventions
- b. No mention of allocation of concealment
- c. No mention of blinding of outcome assessors
- d. No mention of randomization

Appendix 5. Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 9)

FACTORS			JUDGEMENT (N = 9)				RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS	
Problem	No	Yes (9)			Varies		Uncertain	
Benefits	Large (1)	Moderate (1)	Small (1)	Trivial	Varies	Uncertain (6)		
Harm	Large	Moderate	Small (1)	Trivial (1)	Varies	Uncertain (7)		
Certainty of evidence	High	Moderate (1)		Low (7)		Very low (1)		
Balance of effects	Favors intervention (1)	Probably favors intervention (2)	Does not favor intervention or no intervention	Probably favors no intervention	Favors no intervention	Varies	Uncertain (6)	
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (1)		Probably no important uncertainty or variability (6)		No important uncertainty or variability		
Resources required	Uncertain (8)	Varies	Large costs	Moderate costs	Negligible costs or savings (1)	Moderate savings	Large savings	
Certainty of evidence of resources required	No included studies (9)		Very low	Low	Moderate	High		
Cost-effectiveness	No included studies (6)	Varies (2)	Favors the comparison	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention	Favors the intervention (1)	
Equity	Uncertain (5)	Varies	Reduced	Probably reduced (2)	Probably no impact (1)	Probably increased	Increased (1)	
Acceptability	Uncertain (6)	Varies	No	Probably no	Probably yes (2)	Yes (1)		
Feasibility	Uncertain (7)	Varies	No	Probably no	Probably yes (1)	Yes (1)		

Additional Comments

While the preliminary data is encouraging, the training of manpower may be difficult and demands closer evaluation.

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

RECOMMENDATION
<p>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)</p> <p><i>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).</i></p> <p>Consensus Issues</p> <p>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 ways to ensure that there is adequate air exchange in enclosed spaces.</p>

Evidence Summary

Key Findings

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.

Introduction

Nearly 2 years into the COVID-19 pandemic, schools in around 30 countries remain fully closed from February to May 2021 [5]. In the Philippines, as of January 20, 2022, schools have been closed for 61 weeks [6], with 24.9 million pre-primary to upper secondary students having missed three-fourths or almost all classroom instruction time from March 2020 to September 2021 [5]. Because several studies have shown the negative effects of limited in-person instruction on learning, mental and emotional well-being [7], ways by which schools can open safely are of paramount concern.

Although the association between the use of NPIs such as personal protective measures and physical distancing and the reduction of the incidence of COVID-19 have been suggested by systematic reviews and meta-analyses [8], there is a lack of studies investigating the impact of NPIs used in school settings on transmission of COVID-19 in schools and among students, teachers and staff. This review was done to determine the evidence for interventions that could be used for the safe opening of schools.

Review Methods

Search for existing clinical trials, systematic reviews, clinical practice guidelines (WHO, UNICEF, UNESCO, NICE, CENTRAL) and observational studies on COVID-19 databases, publications (PubMed, Google Scholar, HERDIN), pre-print databases (bioRxiv.org, medRxiv.org) and trial registries (WHO, ICTRN, EU) was done. The following keywords were used in MeSH and free text search: “school reopening”, “Return to school”, “kindergarten”, “daycare,” “pre-school”, “K-12”, “return of students,” “primary school,” “secondary school,” mitigation strategies,” “systematic reviews,’ “clinical trials,” “RCT,” and COVID-19 related terms in the search strategy, without language restrictions. Hand search and cross-referencing were also done. [last search January 21, 2022]. Reference lists were reviewed for inclusion. Two reviewers independently screened titles and abstracts initially then selected and retrieved the eligible full text articles.

Included were studies that dealt with school opening or reopening among the pediatric age group in school settings, i.e. early childhood education, primary, secondary and high school or K-12 levels, and those which implemented NPIs. Excluded were studies on modeling, school closures, no NPIs mentioned nor outcomes relevant to mitigating measures. Critical appraisal using the Newcastle Ottawa Scale (NOS) was done. Subgroup analyses were planned for age and for outcomes such as viral load, adverse effects and subgroups. However, no data on these could be obtained from the studies.

Results

Characteristics of Included Studies

There were 17 studies included in this review, 16 cross-sectional studies and one (1) intervention study done in ten (10) countries in Europe, Asia, Australia, Middle East and North America (USA). Populations examined were students, teachers and staff of educational settings – early childhood education and schools (primary and secondary). Of the 17 studies, only three (3) had comparators— number of outbreaks before school closure and after re-opening [9], transmission rates among children and their families who attended school and those who stayed home [10] and incidence rates of COVID-19 in school children and staff and the general population. [11]. (Appendix 3A)

The 17 studies were heterogeneous in terms of NPIs used— with masking, personal hygiene and physical distancing (ex. limited class sizes, cohorting, canceling of extra-curricular activities, distance between desks, physical barriers) common to only seven of the 17 studies. Per individual NPI, physical distancing measures were mentioned in all 17 studies, masking in 12 studies, and personal hygiene in 11 studies. (Appendix 3B, 3C) However, it was uncertain if non-mention of a specific NPI (ex. hand or personal hygiene or masking), meant that it was not being implemented. Other NPIs reported were cleaning and disinfecting, use of HEPA filters, ventilation, daily health reports and symptom monitoring, regular testing for COVID-19, contact tracing (using a proximity tracking device in one study), isolation and quarantine protocols in variable combination with other common NPIs. In England, masks are not required in classrooms and communal areas of schools except for close contacts. [12]

As the studies were done from February to December 2020, with only one study extending to January 2021 [13], vaccination was not included as a preventive measure in any of the studies. The countries covered by the studies all had surveillance, contact tracing and testing as intervention measures as national guidelines.

The studies varied in the outcomes measured – number of primary and secondary cases (n=15), transmission rate (n=12), incidence rate (n=4), number of cases per outbreak (n=2), and number of outbreaks per week, prevalence rate and attack rate in one study each.

Overall Summary of Methodological Quality of the Studies

All studies were assessed to have very low to low certainty of evidence mainly because all were descriptive studies. None of the studies compared the presence of NPIs against no NPIs. Studies also had a high risk of selection and measurement bias. Other reasons are heterogeneity in the exposure variable (NPIs) and outcomes measured, as well as indirectness. There was no measurement of the direct impact of the NPIs on transmission of COVID-19 in school settings except for three (3) studies [10,14,15] which reported the implementation of specific NPIs in the included schools. (Appendix 4B) Other studies reported instead their respective government recommendations on NPIs to use in schools. Therefore, information on the use of NPIs in these studies were obtained at the country level (not school level), whereas the outcomes were measured at the school level.

Summary of Results of Included Studies

Number of Cases

From the 16 studies that measured the number of cases, the median number of cases was 68 (range 1-825 cases). The follow-up period ranged from 1.57 weeks to 30.86 weeks (median = 10.29 weeks). In a 14-week study done in New Jersey, USA [15], only 2/27 (7%) cases were due to on-campus transmission. During the 12-week study in Wisconsin, USA [11], only 7/191 (3.7%) cases among students and staff were actually linked to in-school transmission.

Transmission Rates

Two studies found low transmission of COVID-19 cases in schools despite increased community incidences— 0.7% [13], 2.0% (2/102) [14] transmission rates. Furthermore, a nationwide surveillance study of all educational settings in England [16] and study conducted in two major cities of Norway [17] found that child-to-child transmission was found to be very low at 0.5/100 000 and 0.85% (2/234), respectively.

Secondary transmission was absent in 11 studies. [10,15,18] to very low [4,13,15,16,17,19,20,21,22] However, although the overall transmission was found to be low in Italy [20], transmission in the middle to high school was found to be non-negligible (6.64%). The utility of prompt testing was demonstrated by this study as the possible reasons given for the higher transmission in the middle to high school students were delayed testing and not all classmates of the cases were isolated immediately.

Number of Outbreaks

Two studies done in Germany [9] and England [16] assessed the number of outbreaks in schools and reported 48 and 55 outbreaks, respectively. In these studies, outbreak was defined as the occurrence of at least two cases in the same school. The number of outbreaks, however, was not significantly different from pre-closure outbreak occurrences. [9] The 48 outbreaks in Germany occurred within five months (March to Aug 2020) when the period of reopening schools coincided with relaxing of prevention measures in settings outside of the schools. Some schools were closed for the summer break within the period of the outbreak. The rates of COVID-19 infection and outbreaks were low across all educational settings but an association between outbreaks and regional incidence was found, with the risk increasing by 72% (95%CI: 28— 130) for every 5 cases per 100 000 population increase in community incidence. [16]

Only one study in Israel [3], reported a major outbreak with high attack rates among students (13.2%) and the staff (16.6%) in one high school, ten days after school-reopening. Upon investigation, non-compliance to the NPIs (large classes, no distancing, poorly ventilated classrooms, use of air-conditioners and suspension of masking policy) was seen as contributors to the SARS-CoV-2 transmission. This resulted in the school's closure.

Prevalence Rate

The study done in Switzerland [23], found very low prevalence of COVID-19 in children at 0-0.2%.

Incidence Rates

Four studies, which were done in counties in the US— Missouri, New Jersey, Wisconsin— and England showed lower incidence rates in schools than in the community. The 2-week pilot investigation done in Missouri [14], approximated the incidence of COVID-19 in schools to be 8/100 000 persons, when the community incidence ranged from a high 711-996/100 000 persons. The study done in New Jersey [15] did twice weekly testing for 14 weeks. In a 7-day period, the incidence of COVID-19 ranged from 74-300/100,000, lower than the county incidence of 17-402/100 000 persons. In Wisconsin [11], the study

showed that the incidence rate in schools was 37% lower than that in the community for a period of nearly 13 weeks. Weekly COVID-19 incidence was 72-699 cases per 100,000 students and staff versus 34-1,189 per 100,000 persons in the community. The England [16] survey, done in 7 weeks, showed that staff had higher incidence than students, 27 cases/100 000 per day compared with 18 cases in early years students, 6.0 cases in primary schools students, and 6.8 cases in secondary school students.

Other Considerations (Evidence to Decision)

There were no studies that reported cost of resources, i.e. NPIs used, including surveillance and screening. One study [15] adopted biweekly screening and the use of proximity tracing devices to monitor strict adherence to physical distancing rules. It commented that these additional measures may not be as feasible in other settings. No studies provided evidence of acceptability of NPIs to the students, teachers and staff. Only one study investigated non-compliance by the school with NPIs after an outbreak. [3].

The WHO, UNICEF, UNESCO and World Bank developed checklists and essential actions for reopening schools and possible resurgences and recommended that the interventions used should be based on the countries' analysis of context-specific risks and benefits, financial capacity and logistics and implemented in all levels, national, subnational and school levels. [24,25,26]

Recommendations from Other Groups

Table 1. Summary of recommendations from other groups

CDC (updated Feb 7, 2022) [33]	<ul style="list-style-type: none"> • The use of multiple prevention strategies, including indoor face masking, is emphasized, regardless of vaccination status. • Forgo quarantine for those with completed vaccine series (even without boosters) to minimize disruption of in-person learning.
WHO [24]	<ul style="list-style-type: none"> • Plans to reopen schools should be based on assessments and analyses of context-specific risks and benefits and should be for the best interests of the students and public health considerations. Checklist has 38 essential actions for reopening and potential resurgences, 15 should be implemented at school level reopening. (See Appendix 8 : Glossary of NPIs)
UNICEF [25]	<ul style="list-style-type: none"> • Six key dimensions used to assess the state of readiness of identified schools for reopening: policy, financing, safe operations, learning, reaching the most marginalized and wellbeing/protection.
UNESCO – World Bank Framework [26]	<ul style="list-style-type: none"> • Implement context-appropriate health and hygiene protocols based on capacity and resources, to consider cost implications and include symptom screening, handwashing, use of protective equipment and cleaning procedures for facilities.

UK [32]	<ul style="list-style-type: none"> None mentioned on preparing for school reopening. Does NOT recommend wearing of masks or face covering in classrooms and communal areas of school, except for close contacts. Daily testing of close contacts for 5-7 days or until tested positive.
AUSTRALIA [27]	<ul style="list-style-type: none"> Schools should open and remain open whenever possible. Multiple interventions can reduce the likelihood of infection in school. When there is increased community transmission, screen students and teachers before attendance.
DOH [28-30]	<ul style="list-style-type: none"> DepEd-DOH JMC No. 01 adopts the UNESCO-UNICEF-World Bank Framework for Reopening Schools and DepEd Shared Responsibility Principle. Schools to set up physical structures, wash facilities and supplies, health and safety protocol, and adjusted class programs.
PSMID- Philippine Adult Living Clinical Practice Guidelines [31]	<p>Recommend against use of:</p> <ul style="list-style-type: none"> Ionizing air filters, UV lamps, foot baths and misting tents, face shields in addition to face masks in non-health settings. (Low to very low QoE; Strong Recommendation) <p>Recommends use of the following:</p> <ul style="list-style-type: none"> Well-fitted cloth mask or medical mask in the community setting, preferably ≥ 2 layers of cloth mask.(Very low CoE, Strong) HEPA filter in indoor spaces with inadequate ventilation.(Low CoE, Conditional) Face shields by the general public in areas with sustained community transmission.(Very low CoE, strong recommendation) Protective physical barriers in areas where physical distancing cannot be adhered to. Very low CoE, Conditional) Cleaning and disinfection surfaces $\geq 3x$ a day, especially high touch high traffic areas. (Very low CoE, strong recommendation) Carbon dioxide (CO₂) monitors in enclosed space to guide actions to improve ventilation. (Moderate CoE, strong recommendation)

* Details of the recommendations above can be seen in Appendix 7 with corresponding links to the actual documents.

Research Gaps

There are no reported ongoing or registered clinical trials on the adoption of NPIs in preventing COVID-19 in schoolchildren. There is a protocol of a systematic review published by Lopez-Junior, et al on school reopening and the risks accelerating the COVID-19 pandemic, which will include school children of all educational levels.

Issues to be addressed by future studies are: 1) direct impact of use of the NPIs by the schools on COVID-19 transmission rates in schools; 2) adherence of schools to the NPIs; 3) comparison of specific NPIs, on top of the minimum health protocols, in reducing transmission; 4) comparison of attack rates in schools that are open during low community transmission periods versus high community transmission periods and 5) effect of NPIs in transmission in schools, considering the vaccination rates in children and adolescents

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Evidence Summary Appendices

Appendix 1. Glossary of Non-pharmacologic Interventions

Non-pharmacologic interventions (NPIs) for COVID-19, as distinguished from vaccination and treatment, are public health interventions that help prevent the transmission and control the spread of the virus.

The multi-layered approach as recommended by WHO, refers to implementation of prevention measures at different levels – community, school, classroom and individual at high-risk levels. The measures per level are described in the table below:

Community level	<p>Recommended broader community level measures in communities where schools are reopening:³</p> <ul style="list-style-type: none">• Early detection of suspected cases, test suspect cases; identify and trace contacts; quarantine contacts• Investigation of clusters to implement and communicate localized measures to limit gatherings and reduce mobility• Physical distancing of at least 1 metre, hand and other personal hygiene practices and age-appropriate wearing of masks when physical distancing cannot be achieved⁹• Community-led initiatives for risk reduction (e.g. addressing incorrect and misleading information, rumours and stigma) and protection/shielding of vulnerable groups and safe public transportation, including organizing “walking buses” and safe cycling routes• Other PHSM, as appropriate.
School level	<ul style="list-style-type: none">• Administrative policies: setting attendance and entry rules; cohorting (keeping students and teachers in small groups that do not mix, also referred to as bubble, capsule, circle, safe squad); staggering the start of school, breaks, bathroom, meal and end times; alternate physical presence (e.g. alternate days, alternate shifts)• Infrastructure: Reorganization of the physical space or its use, identifying entry/exists and marking direction of walking, handwashing facilities, building environmental design clues (“nudging”) to facilitate appropriate use of space• Maintaining clean environment: frequent cleaning of surfaces and shared objects• Ensuring adequate and appropriate ventilation with priority for increasing fresh outdoor air by opening windows and doors, where feasible, as well as encouraging outdoor activities, as appropriate• The age-appropriate use of masks where physical distancing cannot be maintained; this includes ensuring the availability of masks• Symptom screening by parents and teachers, testing and isolation of suspected cases, as per national procedures; stay-at-home when sick policies• Reorganization of school transportation and arrival/departure times• Clear accessible sharing of information, and feedback mechanisms established with parents, students and teachers• Continuation of essential school-based services such as mental health and psychosocial support, school feeding and nutrition programmes, immunization and other services.
Classroom level	<ul style="list-style-type: none">• Physical distancing where appropriate• Wearing of masks, where recommended• Frequent hand hygiene• Respiratory etiquette• Cleaning and disinfection• Adequate ventilation• Spacing of desks or grouping of children if required.
Individuals at high-risk	<ul style="list-style-type: none">• Identification of students and teachers at high-risk of severe illness – those individuals with pre-existing medical conditions; develop appropriate strategies to keep these individuals safe• Adoption of a coordinated and integrated approach to ensure vulnerable children’s holistic needs (protection, mental health and psychosocial support, rehabilitation, nutrition and other issues)• Maintenance of physical distancing and use of medical masks• Frequent hand hygiene and respiratory etiquette.

Physical distancing

At school and between groups

- Administrative measures to keep groups apart:
 - Cohorting - no or reduced mixing of classes^{2,3}
 - Phased reopening -- school re-opening is done on a staggered schedule, with different grade levels going back to school at different dates, more commonly re-opening earlier for higher grade levels ex. started with graduating classes only of secondary schools, then grad classes of primary schools before all classes.⁴⁻⁶
 - Staggering of schedules of classes and breaks - includes breaktime/recess is scheduled at different times for different grade levels^{3,7}
 - Hybrid learning - educational approach where the online components are intended to replace a portion of face-to-face class time. Instructors and facilitators teach remote and in-person learners at the same time using technology like video conferencing.^{8,9}
 - Blended learning – Educational strategy where face-to-face class sessions are accompanied by online materials and activities--essentially a “blend” of both live and online learning. A fundamental component is that these online materials are not intended to “replace” face-to-face class time; rather, they are meant to supplement and build upon the content discussed in the classroom.⁹
 - Limiting class sizes – classes in the study of Krieger limited students to 10/class and Falk’s study 11-20 students, without reference to the regular (normal) class sizes.^{2,8}
 - Limit mixing of classes and after-school activities - only students from 1 grade level and mixing of students from different grade levels is avoided as much of possible by measures such as suspension of extra-curricular activities, sports and having staggered mealtimes.^{2,3}
 - Suspension of extra-curricular activities,
 - Crowd control during drop-off and pick-up periods,
 - Identification of entry and exit points, marked directions for walking

Individual physical distancing¹

- Maintaining a distance of at least 1 meter between all individuals, outside and inside the classroom

Masking¹

- Risk-based approach to required use of mask: based on age and where physical distancing is not feasible

Ventilation¹

- Either natural ventilation by opening windows or use of air-conditioning systems coupled with regular inspection, maintenance (especially of filters) and cleaning

Hygiene¹

- Personal hygiene: frequent hand hygiene, respiratory etiquette, use of mask
- Regular cleaning of school environment with water and soap/detergent and disinfectant, including frequently touched surfaces
- Respiratory and hand hygiene and physical distancing measures in transportation, e.g school buses

Screening and management of sick students, teachers and staff¹

- “Stay at home if unwell” policy
- Daily symptom screening/monitoring
- Quarantine of contacts
- Notification of public health authorities in case of positive COVID-19
- Contact tracing (use of clear protocols to notify, interview, and advise close contacts to patients with confirmed or probable COVID-19).
- Early testing to identify current infections with clinical manifestations of COVID-19, or asymptomatic with recent close exposure to SARS-CoV-2

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Appendix 2. Search Yield and Results

Search number	Query	Sort By	Filters	Search Details	Results	Time
5	#1 AND #2 AND #3		Systematic Review	(("Schools"[MeSH Terms] OR "school*"[Title/Abstract] OR "nurser*"[Text Word] OR "kindergarten"[Text Word] OR "preschool"[Text Word] OR "pre school"[Text Word] OR "day care"[Text Word] OR "daycare"[Text Word]) AND ("SARS-CoV-2"[MeSH Terms] OR "SARS CoV2"[Text Word] OR "SARS"[Text Word] OR "severe acute respiratory syndrome"[Text Word] OR "coronavirus*"[Text Word] OR "coronavirus infections"[Text Word] OR "2019-nCoV"[Text Word] OR "SARS-CoV-2"[Text Word])) AND ("Child"[MeSH Terms] OR "child*"[Title/Abstract] OR "infant"[Text Word] OR "pediatric"[Text Word])) AND (systematic review[Filter])	94	21:59:10
4	#1 AND #2 AND #3			("Schools"[MeSH Terms] OR "school*"[Title/Abstract] OR "nurser*"[Text Word] OR "kindergarten"[Text Word] OR "preschool"[Text Word] OR "pre school"[Text Word] OR "day care"[Text Word] OR "daycare"[Text Word]) AND ("SARS-CoV-2"[MeSH Terms] OR "SARS CoV2"[Text Word] OR "SARS"[Text Word] OR "severe acute respiratory syndrome"[Text Word] OR "coronavirus*"[Text Word] OR "coronavirus infections"[Text Word] OR "2019-nCoV"[Text Word] OR "SARS-CoV-2"[Text Word])) AND ("Child"[MeSH Terms] OR "child*"[Title/Abstract] OR "infant"[Text Word] OR "pediatric"[Text Word])	4,858	21:36:10
3	"Child"[Mesh] OR child*[tiab] OR infant[tw] OR pediatric[tw]			"Child"[MeSH Terms] OR "child*"[Title/Abstract] OR "infant"[Text Word] OR "pediatric"[Text Word]	3,150,270	21:35:28
2	"SARS-CoV-2"[Mesh] OR "SARS CoV2"[tw] OR SARS[tw] OR "severe acute respiratory syndrome"[tw] OR coronavirus*[tw] OR "coronavirus infections"[tw] OR 2019-nCoV[tw] OR SARS-CoV-2[tw]			"SARS-CoV-2"[MeSH Terms] OR "SARS CoV2"[Text Word] OR "SARS"[Text Word] OR "severe acute respiratory syndrome"[Text Word] OR "coronavirus*"[Text Word] OR "coronavirus infections"[Text Word] OR "2019-nCoV"[Text Word] OR "SARS-CoV-2"[Text Word]	182,473	21:34:52
1	"Schools"[Mesh] OR school*[tiab] OR nurser*[tw] OR kindergarten[tw] OR preschool[tw] OR "pre school"[tw] OR "day care"[tw] OR daycare[tw]			"Schools"[MeSH Terms] OR "school*"[Title/Abstract] OR "nurser*"[Text Word] OR "kindergarten"[Text Word] OR "preschool"[Text Word] OR "pre school"[Text Word] OR "day care"[Text Word] OR "daycare"[Text Word]	1,336,578	21:34:09

Search number	Query	Sort By	Filters	Search Details	Results	Time
	clinicaltrials.gov			COVID-19 AND school reopening OR return to school OR re-entry OR restart	Jan 22, 2022 6:54:30	0
	https://covid-nma.com/			COVID-19 AND school reopening OR return to school OR re-entry OR restarting school	Jan 22, 2022, 9:05:00	0
	COAP Living Evidence on COVID-19			((school reopening) OR (return to school) AND (COVID-19))	4	Jan 22, 2022, 9:12:00
	CDC			COVID-19 and school guideline to open	1	Dec 30, 2021; 17:05:00 GMT+8
	UNICEF			COVID-19 and guideline for school reopening	1	Dec 30, 2021; 17:20:00 GMT+8
	Australian HPPC			COVID-19 and guideline for school reopening	1	Dec 30, 2021; 17:32:22 GMT+8
	UK			COVID-19 and guideline for school reopening	1	Dec 30, 2021; 18:00:00 GMT+8
	UNESCO https://planipolis.iiep.unesco.org/		by continent	COVID-19 and guideline for school reopening	60	Dec 30, 2021; 20:50:00 GMT+8

Appendix 3A. Characteristics of Included Studies

Author, Year	Study Design	Setting	Population	Intervention	Comparison	Outcome/s
Kriemler, 2021	Cross-sectional	Switzerland	N = 641 students and 66 teachers of 14 Primary and secondary schools; randomly selected Students and teachers	masks for teachers and children >12- years-old tapering of school breaks no mixing of classes ban of group gatherings such as excursions and camps beyond class units, no parents on school grounds (varies among schools) keep children at home when sick Facemasks for adults in the school from October 19 and for children of secondary schools (>12-years- old) from October 29, 2020.	none	No. of cases in children and teachers No. of students and teachers with symptoms Prevalence of COVID-19 in children and teachers
Yung et al, 2021	Cross-sectional	Singapore	1 Pre-school, 1 Secondary school	Terminal cleaning of the schools Suspension of extracurricular or sports activities Staggered recess breaks	none	No. of Primary cases No. of contacts that become symptomatic No. of secondary cases Transmission rate
Kriger et al, 2020	Cross-sectional	Israel	Alternative primary school for children 3- 12 y/o of HCW; 70 attended school vs 30 stayed at home	Small class size, daily disinfecting and temperature check, face mask used by staff, handwashing	none	No. of cases and transmission rate among children and their families who attended school and those who stayed home

Author, Year	Study Design	Setting	Population	Intervention	Comparison	Outcome/s
Stein-Zamir et al, 2020	Cross-sectional	Israel	N= 1,161/1,190 students (12-18 y.o); 152/162 staff member	Masks, personal hygiene, social distancing daily health reports	none	No. of index cases No. of secondary cases Transmission rate, students and staff
Yoon et al, 2020	Cross-sectional	S Korea	N > 13 000 diagnosed COVID-19 cases students and staff; (K-12)	Masks, personal hygiene, restricting class size, staggered breaks, plastic barriers, symptom monitoring, online classes	none	No. of primary and secondary cases among students
Kampe et al, 2020	Cross-sectional	Germany	Diagnosed COVID-19 cases among schoolchildren 6-20 y/o and contacts	Masks, personal hygiene, restricting class size, staggered timetables	before school closure	No of cases before school closure and after re-opening No of school outbreaks per week No of cases per outbreak per week
Ehrhardt 2020	Cross-sectional	Germany	Cases and contacts of primary and secondary schools, and Emergency child care facilities	Phased opening; Face masks, Hand hygiene, reduced class size, Disinfecting, Physical distancing, cohorting, cancellation of activities (sports and music), cleaning ventilation	none	No. of primary and secondary cases among students Transmission rate

Author, Year	Study Design	Setting	Population	Intervention	Comparison	Outcome/s
Larosa et al, 2020	Cross-sectional	Italy	COVID-19 cases in 36 schools with possible contact exposures in school; 0-19 y/o; N=1 248 contacts (only 1,200 were tested)	Masks, social distancing, physical distancing	none	No of primary and secondary cases among students and teachers Transmission rate (primary, secondary and overall)
Macartney, 2020	Cross-sectional	NSW, Australia	4 600 ECEC 3 103 primary and secondary schools ~ 143 084 school staff ~1.2M enrolled students 633/1448 contacts tested	Physical distancing (cohorting) Surveillance tracing	none	No of primary and secondary cases among students and teachers/staff Transmission rate
National Center for Immunization Research and Surveillance (NCIRS), 2020	Cross-sectional	NSW, Australia	Students and staff of ECE, primary and secondary schools	Surveillance of close contacts Physical distancing, hand hygiene, phased reopening cleaning, surveillance tracing	none	No of primary and secondary cases among students and teachers, per school term Transmission rate
Ismail 2020	Cross-sectional	England	ECE, K-12 N = median 928 000 (630 000 – 1 230 000) daily student attendance; 38 000 (IQR 35 500 – 41 500) ECEs, 15 600 (13 450 – 17 300) primary schools; 4000 (3700 – 4200) secondary schools	Smaller classes separated into bubbles; physical distancing and hand washing [Bubble setting (staff and children performing activities together without interaction with other bubbles); outbreak 2 linked cases within 14 days]	none	Event rates, case rates, transmission rate, Outbreaks

Author, Year	Study Design	Setting	Population	Intervention	Comparison	Outcome/s
Brandal 2021	Cross-sectional	Norway	Index cases aged 5-13 y/o in 2 counties of Norway with highest incidence of C19 13 cases and 292 school contacts	Preventive measures physical distancing, strengthened hygiene measures, stay home if symptomatic; no face masks	none	Child to child and child to adult transmission rate
Dawson 2021	Prospective	Missouri, USA	N=21 342 in-person students from Springfield (22 schools) and St Louis/Springfield (57 : 12 SL and 45 Sf)	Face masks, physical distancing, ventilation, contact tracing, hand washing or sanitizer; isolation	none	No. of Primary and secondary cases
Volpp 2021	Cross-sectional	NJ, USA	G9-12 boarding school N=520 resident and 255 commuter students, 405 faculty/staff	Masking, testing, ventilation, physical distancing, proximity tracing devices, limit class, quarantine, isolation protocols with 2x weekly screening, webinars/sanctions/motivational contracts	none	no of primary and secondary cases among students and faculty
Falk 2020	Cross-sectional	Wisconsin, USA	17 rural K-12 schools 4,876 students, 654 faculty/staff	Masking within 6 feet outdoors and at all times indoors; cohorting; social & physical distancing (no mixing of classes, small class size, limit time in shared indoor spaces, distance of 6 ft from each other); classes and lunch periods held indoors	general population of the county	no. of cases/study pop'n Incidence rate in schools vs incidence rate in county

Author, Year	Study Design	Setting	Population	Intervention	Comparison	Outcome/s
Hershaw 2021	Cross-sectional	Utah, USA	20 elementary schools 10,171 students 1,214 faculty/staff	Masking, physical distancing, restriction of school-related extra-curricular activities & large group gatherings, non-essential extracurricular activities (e.g. sports, assemblies, performance, field trips) held virtually, cohorting, staggered lunch, gym classes, special activities (e.g. library use, art classes), mixed classes by grade levels during recess in some schools	none	no. of index and primary cases 2 ^o attack (transmission) rate
Zimmerman 2021	Intervention (no unexposed group; no pre-intervention outcomes)	North Carolina, USA	11 school districts >90,000 students, faculty/staff	Program: (1) education of leaders, staff and community; 2) peer-to-peer support for public health prevention measures, with sharing of lessons; 3) evaluation of secondary transmission 3Ws: wear mask, wait 6 ft apart, wash hands; daily screening, staggered classes cleaning, daily symptom screening	none	no. of primary and secondary cases case clustering

Appendix 3B. Summary of Non-Pharmacologic Interventions and corresponding outcomes based on Countries Included in 17 observational studies

Countries	Context	Non-pharmacologic interventions	Outcomes	Management of outbreak / resurgence
Switzerland (Kriemler, 2021)	Closed from March 16 – May 10, 2020 Continuous operation, Aug 17 – end of 2020 Study done when incidence rate for SARS-CoV-2 was high for Zurich	Masks for teachers and children >12-years-old Physical distancing rules Tapering of school breaks No mixing of classes Ban of group gatherings such as excursions and camps beyond class units No parents on school grounds Requirement to keep children at home if sick	Even in a setting of high incidence of SARS-CoV-2 infections, unrecognized virus spread within schools was very low.	N/A
Singapore (Yung, 2021)	Schools not routinely closed Opened until April 8, then closed due to outbreak	Terminal cleaning of the schools Suspension of extracurricular or sport activities Staggered recess breaks	No evidence of SARS-CoV-2 transmission among children in schools SARS-CoV-2 transmission in children is significantly lower than that observed for other respiratory viruses	All close contacts quarantined for 14 days; admitted if developed symptoms; Non-close contacts continued classes 1 pre-school closed for 14 days, following increasing number of staff members with COVID-19 detection Single NP swab screening among asymptomatic children attending the school
Israel (^a Kriger, 2020; ^b Stein-Zamir, 2020)	Closed from March 13-May 17, 2020 Opened an alternative primary school for HCWs of a medical center, during the 9-week lockdown Outbreak on May 26, 2020	• Small class size, daily disinfecting and temperature check; face mask used by staff; frequent handwashing • Masks; personal hygiene; social physical distancing; daily health reports	• No evidence of increased infection in those who attended school and those who stayed • Outbreak occurred due to non-compliance with protocols [large classes of 35-38 students; no distancing in poorly ventilated classrooms were likely contributors to spread; air conditioners used b/c. of heat wave (Min. of Health exempted school children from facemasks for 3 days)]	• Isolated children exposed to positive teacher; did PCR testing twice (7 th & 14 th day from exposure); none tested positive to PCR; return to school after 14 days • School Isolating Testing of the school community
South Korea (Yoon, 2020)	Closed until April 6, 2020 Stepwise opening for online and off-line learning, depending on grade level	Masks Personal hygiene Restricting class size Staggered breaks Online classes for Music Plastic barriers between desks Symptom monitoring	No significant school-related outbreak from school closure to online and off-line opening	N/A
Germany (^c Kampe, 2020; ^d Erhardt, 2020)	Closed from March 16 to April 19, 2020 Phased reopening for secondary and primary levels	Phased reopening Face masks Hand hygiene Reduced class size	^c Only few and small school outbreaks occurred ^d low child to child transmission	School closure not deliberate, happened because of summer break during June to Aug (part of study period).

		Disinfecting Physical distancing Cohorting Cancellation of activities (sports and music)		
Italy (Larosa, 2020)	Closed from March 10 2020 Reopened Sept 15, 2020	Masks Suspension of extracurricular activities Dividing into class groups (alternate attending school and remote learning) Single desks Physical distancing bet. Students Separate school entrance and exits	Non-negligible transmission, particularly in 10-18 years old	Prompt isolation Investigation Testing of contacts
Australia (Macartney, 2020; NCIRS, 2020)	Schools kept open March 23, 2020 – online learning implemented April 29 – schools reopened May 25 – full face-to-face teaching	Enhanced Surveillance of close contacts Early testing Hand hygiene Physical distancing Phased reopening Cleaning	Limited transmission in educational settings	N/A
England (Ismail, 2020)	Closed from Mar 20, 2020 Reopened June 1, 2020 for summer school. Study done during summer half term (Jun 1 – Jul 17) Public health England initiated national surveillance in educational settings 1.6M/ 8.9M attended in-school that summer	Small classes separated into distinct social bubble (do not mix with other bubbles) Physical distancing Handwashing Masking not mentioned	Rates were low across all educational settings with highest risk in primary schools. There was strong association between outbreaks and regional C19 incidence, with risk increasing by 72% for every 5 cases /100 000 pop'n increase in community incidence, even during a period of low community incidence. Very little transmission between students noted.	Strengthen infection control measures at 2 levels : adult staff to be more vigilant for exposure outside of educational settings; and stringent infection control between staff. Real time reporting, risk assessment and national initiatives.
Norway (Brandal, 2020)	Study done when cases were highest in Oslo and Viken during 28 Aug to 11 Nov, 2020.	Strengthened hygiene measures Physical distancing Stay home if symptomatic NO face masks	Minimal child-to-child (0.9%) and child-to-adult (1.7%) transmission Household transmission is a considerable source of infection in children. Teachers are not at higher risk for C19 compared with other professions.	Strengthened hygiene measures Physical distancing Stay at home if symptomatic Adjust IPC measures according to community transmission level rather than closing schools.

^a Krieger et al, 2020

^b Stein-Zamir et al, 2020

^c Kampe et al, 2020

^d Ehrhardt et al, 2020

USA

Counties	Context	Non-pharma interventions	Outcomes	Mgt of outbreaks/ resurgence
Wisconsin (Falk, 2020)	For whole of US: only ½ of students receiving online instruction since March 2020 For Wood County, at time of study (Aug 31-Nov 29, 2020): only ~12.4% of children were attending virtually Widespread community transmission (7-40% positivity rates) Masking compliance = 92.1 to 97.4%	Masking within 6 feet outdoors and at all times indoors Cohorting Physical distancing (no mixing of classes, small class size, limit time in shared indoor spaces, distance of 6 ft from) All classes and lunch periods held indoors No systematic screening done in school or in community	No in-school transmission between separate classroom cohorts	Infection source
Utah (Hershaw, 2020)	Aug 4, 2020, reopened for in-person learning High community transmission (290-670 cases/1000) Mask use = 86% Median distance bet. students' seats = 3 ft Dec 17, 2020: change in definition of school contact for quarantine (only quarantined when index case or contact did not wear a mask during the interaction vs previously, all school contacts regardless of mask use, were quarantined After change in quarantine rules: 158 contacts continued school	Masking Restriction of school-related extra-curricular activities & large group gatherings; non-essential extracurricular activities (e.g. sports, assemblies, performance, field trips) held virtually Cohorting Staggered lunch, gym classes, special activities (e.g. library use, art classes) Some schools mixed classes by grade levels during recess	School-associated SARS-CoV-2 transmission is low No school. Related outbreaks Tertiary transmission in households of school-associated cases	Contact tracing Quarantine Testing Investigation of NPI compliance (social and physical distancing and masking)
North Carolina (Zimmerman 2020)	March 14, 2020: Closed pre-kindergarten to Grade 12 public schools, to in-person instruction July 15, 2020: re-opened via remote or hybrid learning	ABC Science Collaborative Program: (1) education of leaders, staff and community; 2) peer-to-peer support for public health prevention measures, with sharing of lessons; 3) evaluation of secondary transmission 3Ws: wear mask, wait 6 ft apart, wash hands Daily screening Staggered classes (50% in-person, 2 days each week; other 50% on different days) Cleaning Daily symptom screening Transparency in public reporting of cases	773 community-acquired SARS-CoV-2 infections 32 infections in contacts 3 clusters of cases (5 cases of within-school transmission): causes: exemptions of mask wearing in pre-kindergarten; eating together in close proximity Extremely limited within-school secondary transmission No instance of child-to-adult transmission	Contact tracing Testing encouraged but not required Quarantine Closing of schools with cluster of cases (5 cases of within-school transmission) Developed policies: 1) use of face shields if wearing of masks not feasible; 2) specialized plans for lunch and breakfast: outdoor eating, distancing, food preparation before taking masks off, limiting

		<p>Close collaboration with health dept.</p> <p>Regular updates with principals and staff to encourage adherence to NPIs and report secondary transmission and breaches in safety protocols</p>		mask-off time to 15 minutes for eating, no talking while eating and while masks are off
Missouri (Dawson, 2020)	<p>December 7-18, 2020; at the time, the cumulative community incidence at St Louis was 711/100 000 and 996 / 100 000 at Springfield</p> <p>57 K-12 schools with all but one offering full- or part-time virtual learning</p> <p>70% (21 342/ 30 558) students attended in-person school at least part-time</p> <p>Modified quarantine policy adopted by Springfield, MO allowing student close contacts ≤ 18 y/o of C19+ students with proper mask requirements to continue in-person learning</p>	<p>100% mask mandate</p> <p>Desk spacing ≥ 3-6 ft apart</p> <p>Physical barriers between students and teachers</p> <p>Hand washing or hand sanitizing stations at school entrances, dining areas, restrooms and classrooms</p> <p>Increased ventilation (open windows or doors, fans, reduced occupancy, 5% updated heating/air con systems and ventilation)</p>	<p>56 confirmed C19+ persons with 270 school-based exposure contacts = 326</p> <p>193 (59%) agreed to participate (37 primary and 156 contacts) 24/37 (65%) and 137/156 (88%) of which were students</p> <p>Only 102/156 contacts agreed to testing. 2% (2/102) tested C19+</p> <p>None of those who underwent modified quarantine had C19+ results</p> <p>2-week school incidence is 8/100 000 or < 1% of the average community incidence</p>	<p>Follow CDC-recommended mitigation measures on isolation and quarantine guidance</p> <p>Contact tracing</p>
New Jersey (Volpp, 2021)	<p>During fall 2020, many K-12 schools closed to limit in-school transmission</p> <p>Aug 20-Nov 27, 2020, a private boarding school implemented comprehensive mitigation strategy for all incoming students and staff members for the SY. Included 2-week quarantine for all arriving students, upon arrival and</p> <p>At time of study, 7-day community incidence ranged from low 17 (late Aug) to 402 /100 000 (Nov 24)</p>	<p>Included 2-week quarantine for all arriving students, upon arrival and a (-) RT PCR w/in 10 days of arrival.</p> <p>Isolation protocols</p> <p>Universal masking</p> <p>Testing, mandatory biweekly screening</p> <p>Upgraded air-handling equipment to improve ventilation</p> <p>Physical distancing ≥ 6 ft</p> <p>Contact tracing :</p> <p>(In Nov, the definition of closed contacts was changed to include persons within 15 minutes (before 10 mins) of cumulative exposure within 6 ft of a C19+ person during the 48 hours before testing.)</p> <p>Proximity tracing devices to be worn at all times on campus</p> <p>"Strike" system : consequences for students who do not comply</p>	<p>8 995 saliva specimen from 405 faculty/staff</p> <p>12 494 nasal swab from 775 students</p> <p>4% of Faculty/staff and 1% students were C19+, 7 mild, no hospitalizations, rest asymptomatic</p> <p>93% (25/27) were infected by off-campus contacts</p> <p>Despite the increased incidence by Nov, the school did not experience any epidemiologically linked cases leading to clusters or outbreaks.</p>	<p>Persons with newly identified cases should be rapidly isolated to reduce transmission.</p> <p>Strict regimen of physical distancing and universal masking</p> <p>Behavioral reinforcement</p> <p>Improved air filtration and frequent testing</p>

Appendix 3C. Table of Non-Pharmacologic Interventions per Study

Non-Pharmacologic Interventions (NPIs)	Total count	Norway	Germany	BW, Germany	Italy	Switzerland	England	NC, USA	MI, USA	UT, USA	WI, USA	NJ, USA	SMC, Israel	Jerusalem, Israel	NSW, Australia	NCIRS, NSW, Australia	Singapore	SKorea
Classification based on DOH-DEPED Guidelines on Safe Reopening (JMC No. 1) ¹	TOTAL PER NPI	Primary schools in Oslo and Viken, Norway	National surveillance of school outbreaks fr Jan to Aug 2020	0-19 y/o +COVID -19	41 classes in 36 educ'l settings (~31 000)	15 of 55 schools nested from Ciao Corona study	National surveillance in all educational settings : med 928 000 (630 000 - 1 230 000)	> 90 000 students & staff of 11/56 school districts	K-12 schools in St. Louis and Springfield, MI	20 K-6 schools in Salt Lake, UT	4476 K-12 students in 17/18 schools in Wood County, WI	775 Gr 9-12 and 405 staff of boarding school	435 3-12 y/o children of HCW working in Sheba MC	1190 students (12-18 y/o) and 162 staff of a public HS	3103 PS to HS schools & 4600 ECEC in NSW (N > 1 375 451)	10 educational settings (1 ECEC, 6 PS, 3 HS)	National surveillance of preschool to secondary schools	K-12 cases from the Korean CDC
I. SAFE OPERATIONS																		
Physical Distancing ²	17	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Masking ³	12	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓
Face Shields ⁴	0																	
Single desks ⁵	1					✓												
Reduced class size ⁶	7		✓	✓			✓		✓		✓		✓					✓
No / reduced mixing of Classes	7					✓	✓	✓	✓	✓	✓	✓						✓
Ventilation ⁷	5		✓	✓					✓	✓			✓					
HEPA filters	1												✓					
CO2 Monitoring devices ⁸	0																	
Separate entry/exits	1					✓												
No parents/guardians on school grounds	1						✓											
Sanitizing stations	1										✓							
Respiratory etiquette	2		✓	✓														
Personal Hygiene	11	✓	✓	✓				✓	✓	✓			✓	✓	✓	✓	✓	✓
Disinfection ⁹	6		✓	✓					✓				✓					✓
Daily screening	2								✓			✓						
Daily symptom monitoring/ health report	4								✓	✓				✓				✓
Contact tracing ¹⁰	7						✓		✓		✓	✓	✓	✓	✓	✓		
School Cleaning ¹¹	2													✓	✓	✓		
Hybrid Learning ¹²	3		✓	✓								✓						
Cohorting ¹³	4		✓					✓			✓	✓						
II. ENSURING TEACHING AND LEARNING																		
Phased reopening ¹⁴	3		✓	✓														✓
Staggered/tapered school breaks, i.e. lunch	6		✓					✓		✓	✓						✓	✓
Suspend/reduce school-related extracurricular activities, i.e. excursion, gym, PE, music	5			✓	✓	✓					✓							✓
Early testing ¹⁵	1																	✓
III. WELL-BEING AND PROTECTION																		
Temperature checks	3								✓				✓					✓
Stay home when sick	5	✓	✓	✓	✓		✓											✓
Surveillance of close contacts	3						✓					✓						
Quarantine and isolation protocols	3								✓	✓			✓					
Proximity devices ¹⁶	1												✓					
Plastic Barriers	2								✓									✓

LEGEND:

BW= Baden-Wurttemberg, NC= North Carolina, MI= Missouri, UT=Utah, WI= Wisconsin, NJ=New Jersey, SMC=Sheba Medical Center, NCIRS= National Center for Immunization Research and Surveillance, NSW=New South Wales ECEC= Early Childhood Education and Care, PS=primary schools, HS=high school.

¹Categories are based on the DOH-DEPED Joint Memorandum Circular No. 1: Operational Guidelines on the Implementation of Limited Face-to-Face Learning Modality (Sept 27, 2021).

²Physical distancing
Defined as being ≥ 3 to 6 ft apart, depending on study

³Masks
Surgical masks for children at all times except when not tolerated anymore (especially in preschool or elementary)

⁴CO₂ monitors & Face shields
Found in Philippine Adult Living CPG with evidence and recommendations but not mentioned as NPIs in the studies presented.

⁵Single desks
Soaked desks ≥3-6 ft apart

⁶Reduced class size
Germany reported 50% reduction in all levels; S Korea based it on community alert levels reducing by 1/3 or 2/3 of class size and school closure with at least 1 confirmed case.

⁷Ventilation
Includes opening windows and doors, improving A/C circulation, use of fans, upgrading air vents and filters

⁸Disinfection
Surface disinfection in NC, USA

⁹School Cleaning
Done prior to school reopening after being closed due to confirmed +COVID-19 Cases

¹⁰Hybrid learning
Combination of in-person (on-site) school and online (remote) learning days in school

¹¹Cohorting
Group of students and staff who remain together throughout the school year

¹²Phased reopening
Opening of specific levels at different times, i.e. Graduation classes first then regular levels.

¹³Early testing
Case-contact testing where enhanced investigations using surveys, RT-PCR tests and serologic tests are done on close contacts 5-10 days after last case contact

¹⁴Proximity devices
Devices worn by students and staff to monitor physical distancing. Worn in a boarding school in New Jersey, USA

¹⁵Contact tracing
Contact tracing was explicitly mentioned as NPI in 7 studies but transmission rates were reported in 12 studies indicating possible indirect evidence of contact tracing.

Appendix 4. Risk of Bias Assessment for cross-sectional Studies (Newcastle Ottawa Scale)³³

Study	Selection				Comparability based on design and analysis; control of confounders	Outcome		Quality
	Representativeness of sample	Sample size	Non-respondents	Ascertainment of exposure		Assessment	Statistical test	
Kriemler et al, 2021	*	*	*			**	*	poor
Yung et al, 2020	*					*	*	poor
Kriger et al, 2020								poor
Yoon et al, 2020				*				poor
Kampe et al, 2020	*			*			*	poor
Stein-Zamir et al, 2020	*					**		poor
Larosa et al, 2020	*					**		poor
Macartney et al, 2020		*		**		*		poor
Ehrhardt et al, 2020	*			**				poor
NCIRS, 2020	*	*		**		**		poor
Ismail 2021	**	*		**		**		poor
Brandal 2020	*			**		**		poor
Dawson 2020		*		**		**		poor
Volpp 2021	*	*		**		**	*	poor
Falk 2020		*			**	**		poor
Hershaw 2021						**		poor
Zimmerman 2021				**		**		poor

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain

Poor quality: 0 or 1 star in selection domain OR 0 star in comparability domain OR 0 or 1 star in outcome domain

Appendix 5. GRADE Evidence Profile

Author(s): Tapia, Carolina and Eubanas, Gina, Perz, Ma. Lucila, Tolosa, Ma. Teresa

Question: Non-pharmacologic interventions compared to no intervention for decreasing COVID-19 transmission in school settings

Setting: school

References: ¹Yoon, 2020; ²Stein-Zamir, 2020; ³Kriemler, 2020; ⁴Yung, 2021; ⁵Erhardt, 2020; ⁶Larosa, 2020; ⁷Macartney, 2020; ⁸NCIRS, 2020; ⁹Hershaw, 2020; ¹⁰Zimmerman, 2021; ¹¹Falk; ¹²Brandal, 2020; ¹³Dawson; ¹⁴Volpp, 2021; ¹⁵Ismali; ¹⁶Kampe

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPIs	No intervention	Relative (95% CI)	Absolute (95% CI)		
number of cases												
15 ^k	observational studies	serious ^a	serious ^b	serious ^c	not serious ^d	all plausible residual confounding would reduce the demonstrated effect	2711 cases: 50 cases ¹ 180 cases ² 1 case ³ 3 cases ⁴ 15 cases ⁵ 86 cases ⁶ 45 cases ⁷ 119 cases ⁸ 786 cases ⁹ 825 cases ¹⁰ 191 cases ¹¹ 13 cases ¹² 24 cases ¹³ 27 cases ¹⁴ 130 cases ¹⁵ 216 cases ¹⁶	Median: 68 cases (range 1 to 825 cases) only 2 studies provided data on total population: 1/707 = 0.14% ³ 786/11385 = 6.9% ⁹ Duration of follow-up: median = 101.29 weeks (Range 1.57 to 30.86 weeks) Prevalence study (Kriemler, 2021) was excluded due to 2 days of testing only Overall, studies were from Feb 2020-Jan 31 2021 (11 months)	⊕○○○	Very low	CRITICAL	
Transmission rate												
12 ^k	observational studies	not serious ^a	serious ^b	serious ^c	not serious ^e	all plausible residual confounding would reduce the demonstrated effect	0 to 6.64% ⁴⁻¹⁵	0/0	not estimable	⊕○○○	Very low	CRITICAL
number of outbreaks per week												
1 ^l	observational studies	very serious ^f	serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	¹⁶ after reopening: 2.2 outbreaks per week before school closure: 3.2 outbreaks per week	⊕○○○	Very low	CRITICAL		
number of cases per outbreak												

Certainty assessment							No of patients		Effect		Certainty	Importance	
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPIs	No intervention	Relative (95% CI)	Absolute (95% CI)			
2 median of 57 600 schools ¹⁵	observational studies	very serious ^f	serious ^g	not serious ^h	not serious	all plausible residual confounding would reduce the demonstrated effect	¹⁶ after re-opening: 4 cases per outbreak ^{before school closure: 6 cases per outbreak}			¹⁵ Early years 16, Primary 27, Secondary 7		⊕○○○ Very low	IMPORTANT

Incidence Rate

4 3 studies ^{11, 13-14} 71 schools, 28050 participants median of 38,000 early years settings, 4000 secondary schools 600 primary schools ¹⁵ median attendance = 928000 students ¹⁵	observational studies	serious ⁱ	not serious ^b	not serious	not serious ^j	none	3,454/100 000 school children and staff (vs 5,466/100 000 in county) ¹¹ weekly IR: 72-699/100 000 students & staff ¹¹ 8/100,000 ¹³ Students: 74/100 000 ¹⁴ Staff: 300/100 000 ¹⁴ Staff: 27/100 000 per day ¹⁵ Students: 6-18/100 000 ¹⁵	0.0%	not estimable		⊕○○○ Very low	CRITICAL
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Prevalence Rate

1 14 schools; 641 students, 66 teachers ³	observational studies	not serious	not serious	not serious	not serious	none	1 case/641 students = 0.2% no case among teachers			⊕⊕○○ Low	CRITICAL
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Attack rate (assessed with: rates)

1 1 school; 1161 students, 152 staff ²	observational studies	not serious	not serious	not serious	not serious	none	students:152/1161 (13.1%) staff: 25/152 (16.6%)	0.0%	not estimable		⊕⊕○○ Low	CRITICAL
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CI: confidence interval

Explanations

- a. There is a high risk of bias due to selection of sample and measurement bias.
- b. Inconsistency is due to heterogeneity of interventions, and age range of subjects.
- c. There was no assessment of direct impact of the interventions on the outcome.
- d. The number of cases reported in these studies were reported by counties, regions and school districts, with large enough populations. (Kampe, Ehrhardt, Larosa, Yoon, Brandal)
- e. One study (Ismail) was a national surveillance effort involving all educational settings.
- f. There was measurement bias (outcome measured in a different age group).
- g. One study (Kampe) compared outbreaks before and after school closure. The other study (Ismail) studied association between outbreaks and regional C19 incidence.
- h. The definition of an outbreak is the same for both studies.
- i. There was measurement bias from use of google forms to monitor attendance and compliance with NPIs. Only 50% of teachers participated. No surveillance screening; may have missed asymptomatics.
- j. The large population size came from the National surveillance done in England, including all educational levels.

^ktotal number of schools or participants cannot be computed as cases were obtained from national surveillance systems, their contacts traced and tested; in some studies not all contact were tested
^lno mention of total number of schools, students nor teachers/staff

Appendix 6. Table of Ongoing Studies

Author, Year	Title	Study design	Objectives	Population	Exposure	Comparison	Outcome/s
Lopes-Junior, 2021 (Prospero Reg no. CRD42021265 283 PMID: 34788344 DOI: 10.1371/journal.pone.0260189	School reopening and risks accelerating the COVID-19 pandemic : A SRMA protocol	observational studies	synthesize and evaluate the potential risks of accelerating COVID-19 pandemic among children, adolescents, young adults and adults with school opening	infant, child, preschool, adolescents, young adult, adult (MeSH), all sexes, all ethnicity	school reopening	school lockdown	primary : risks accelerating COVID-19 pandemic secondary: viral load among children and teachers; transmission rate

Appendix 7. Detailed Recommendations from Other Groups

CDC (updated Feb 7, 2022)	<ul style="list-style-type: none"> ● Universal indoor masking, regardless of vaccination status. ● Physical distancing (at least 1 meter). If this is not possible, layer it with multiple preventive strategies, i.e. screening, ventilation, handwashing and respiratory etiquette, staying at home when sick, contact tracing, cleaning and disinfection. ● Schools may consider foregoing quarantine for students 12-17 years old who completed their vaccine series (even without boosters) to minimize disruption of in-person learning. ● For Early Care and Education (ECE), use of multiple prevention strategies is emphasized, including universal indoor masking for children ≥ 2 years old, regardless of vaccination status, as well as the other aforementioned preventive strategies. ● Link : https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/index.html#:~:text=CDC%20recommends%20universal%20indoor%20masking,layered%20prevention%20strategies%20in%20place
WHO	<ul style="list-style-type: none"> ● Plans to reopen schools should be based on assessments and analyses of context-specific risks and benefits and should be for the best interests of the students and public health considerations. It should also aim to reduce inequalities and improve educational conditions and health outcomes for the most vulnerable and marginalized. ● There are 38 essential actions in the checklist for reopening and potential resurgences, divided among decision-makers and stakeholders in the national, subnational and school levels. 15 essential actions at the school level should be implemented for reopening. Notable among these are: 1) establishing a school support team who will assess the feasibility of implementing protective measures (physical distancing, outdoor classes; handwashing facilities, staggered set-ups, multiple entrances); 2) promote wearing masks; 3) promoting hand hygiene and respiratory etiquette; 4) adequate ventilation; 5) health education; 6) raise awareness of importance of self-reporting of symptoms; and 6) record students' health status. ● Link : https://www.who.int/publications/item/9789240017467

UNICEF (21 September 2021)	<ul style="list-style-type: none"> • Six key dimensions used to assess the state of readiness of identified schools for reopening, one of which is safe operations. • Provide clear national guidance on parameters for decision making on school opening, beginning with areas with low transmission rates and localized risks, and staging (few days a week, by grades or levels, etc) • Develop detailed protocols on hygiene measures (hand washing, masks cleaning procedures and respiratory etiquette) • Link : https://www.unicef.org/lac/en/guidance-notes-and-guidelines-safe-school-reopening ; <ul style="list-style-type: none"> ◦ Guidelines for Philippines : https://www.unicef.org/hieldsan/reopening-schools-safely ◦ Checklist : https://www.unicef.org/lac/en/media/14591/file
UNESCO-World Bank Framework (June 2020)	<ul style="list-style-type: none"> • With sufficient capacity and resources, schools can successfully implement context-appropriate health and hygiene protocols. These include symptom screening, handwashing, use of protective equipment and cleaning procedures for facilities. • Multiple measures – with varying cost implications- can be used to reduce physical contact and limit transmission. These include improving indoor ventilation, moving classes outdoors, building additional classrooms, staggering start/end times, alternating shifts/days, hiring additional teachers to reduce class size, blending distance and in-person learning, and isolating class groupings from one another. • Link : https://www.wfp.org/publications/framework-reopening-schools-reportunesco-unicef-world-bank-and-world-food-programme
UK updated December 2021 9	<ul style="list-style-type: none"> • None mentioned on preparing for school reopening. • Latest update does not recommend wearing of masks or face covering in classrooms and communal areas of school of secondary schools and colleges, except for close contacts. Daily testing of close contacts for 5-7 days or until tested positive. • Link : https://www.gov.uk/government/collections/guidance-for-schools-coronavirus-covid-19

AUSTRALIA updated November 2021	15	<ul style="list-style-type: none"> • Schools are an essential service and should open and remain open whenever possible. • Multiple interventions can reduce the likelihood of infection in school, including: elimination (remote learning), substitution (screening and isolation); engineering (ventilation, cleaning, physical distancing); administrative (cohorting, altering routines); and PPE (surgical masks for adults and students) • When there is increased community transmission, screen students and teachers before attendance • Link : https://www.health.gov.au/news/hieldsan-health-protection-principal-committee-ahppc-statement-on-covid-19-schools-and-early-childhood-education-and-care
DOH		<ul style="list-style-type: none"> • DepEd-DOH JMC No.01 adopts the UNESCO-UNICEF-World Bank Framework for Reopening Schools and DepEd Shared Responsibility Principle. • Schools to set up physical structures, wash facilities and supplies, PPEs, health and safety protocol, adjusted class programs (blended learning, staggered class hours, etc) as required by the Joint Memorandum Circular between DepEd and DOH. • Other requirements include screening the vaccination records of children (routine immunization), well-fitted face masks and face shields, physical distancing, adequate ventilation, large learning spaces, well-marked entrances, and contact tracing procedures. • Link : https://www.deped.gov.ph/wp-content/uploads/2021/09/DEPED-DOH-JMC-No.-01-s.-2021.pdf

Appendix 8. Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 9)

FACTORS		JUDGEMENT (N = 9)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)		Varies		Uncertain		<ul style="list-style-type: none"> 24.9M students missed ¾ or all face-to-face classroom instruction for more than 60 weeks.
Benefits	Large (3)	Moderate (6)	Small	Trivial	Varies	Uncertain		<ul style="list-style-type: none"> Lower transmission with multi-layered prevention strategies
Harm	Large	Moderate (3)	Small (4)	Trivial (1)	Varies (1)	Uncertain		
Certainty of evidence	High	Moderate		Low (4)	Very low (5)			
Balance of effects	Favors intervention (1)	Probably favors intervention (7)	Does not favor intervention or no intervention	Probably favors no intervention	Favors no intervention	Varies	Uncertain	
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (3)		Probably no important uncertainty or variability (5)		No important uncertainty or variability		<ul style="list-style-type: none"> All studies are done in first world countries.
Resources required	Uncertain (1)	Varies	Large costs (5)	Moderate costs (3)	Negligible costs or savings (1)	Moderate savings	Large savings	
Certainty of evidence of resources required	No included studies (7)		Very low	Low (2)	Moderate	High		
Cost-effectiveness	No included studies (7)	Varies	Favors the comparison	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention (2)	Favors the intervention	
Equity	Uncertain (5)	Varies	Reduced	Probably reduced (1)	Probably no impact	Probably increased (3)	Increased	
Acceptability	Uncertain (2)	Varies (2)	No	Probably no (1)	Probably yes (4)	Yes (1)		
Feasibility	Uncertain (4)	Varies (2)	No	Probably no	Probably yes (2)	Yes (1)		

Additional Comments

- The feasibility and equity will highly depend on whether the schools are in the private or public setting.

V. Discussion

A. 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. Refer to Appendix D for the schedule of panel presentations.

B. 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.

C. 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.

D. 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.

VI. Conclusion

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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VIII. Appendices

- A** Members of the Philippine Pediatric COVID-19 Living CPG Task Force
- B** Decisions of the Oversight Committee – Review of Conflict of Interest
- C** General Search Strategy for COVID-19
- D** Breakdown of Consensus Panel Meetings
- E** AGREE Report Checklist

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Appendix B. Decisions of the Oversight Committee – Review of Conflict of Interest

CPG Panel on COVID – 19 in Children		
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Appendix C. General Search Strategy for COVID-19

Search strategy for COVID-19:

((("COVID-19" [Supplementary Concept] OR "COVID-19 diagnostic testing" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [Supplementary Concept] OR "COVID-19 vaccine" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR "2019-nCoV" OR "2019nCoV" OR "cov 2" OR "Covid-19" OR "sars coronavirus 2" OR "sars cov 2" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus 2" OR "COVID 19" OR "COVID-19" OR "2019 ncov" OR "2019nCoV" OR "corona virus disease 2019" OR "cov2" OR "COVID-19" OR "COVID19" OR "nCov 2019" OR "nCoV" OR "new corona virus" OR "new coronaviruses" OR "novel corona virus" OR "novel coronaviruses" OR "SARS Coronavirus 2" OR "SARS2" OR "SARS-COV-2" OR "Severe Acute Respiratory Syndrome Coronavirus 2") OR ((19[tiab] OR 2019[tiab] OR "2019-nCoV" OR "Beijing" OR "China" OR "Covid-19" OR epidem*[tiab] OR epidemic* OR epidemic 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 coronavirus*[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 Panel Meetings

CONSENSUS PANEL MEETINGS	
Vitamin D (Prophylactic and Adjunct Intervention)	February 23, 2022
Vitamin C (Adjunct Intervention)	
Vitamin C (Prophylactic Intervention)	
Zinc (Adjunct Intervention)	
Zinc (Prophylactic Intervention)	February 28, 2022
Intravenous immunoglobulin (Treatment)	
Corticosteroids (Treatment)	
Tocilizumab (Treatment)	
Remdesivir (Treatment)	March 2, 2022
Anticoagulation (Treatment)	
Monoclonal Antibodies (Treatment)	
Alternate clinical specimens to nasopharyngeal swab for RT-PCR (Screening and Diagnosis)	
Preventive interventions used in school settings to reduce transmission (Non-Pharmacologic Intervention)	March 9, 2022
Supportive strategies to optimize mental health (Non-Pharmacologic Intervention)	

Appendix E. AGREE Report 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 <i>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.</i>	<input checked="" type="checkbox"/> Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) <input type="checkbox"/> Expected benefit(s) or outcome(s) <input checked="" type="checkbox"/> Target(s) (e.g., patient population, society)	6
2. QUESTIONS <i>Report the health question(s) covered by the guideline, particularly for the key recommendations.</i>	<input checked="" type="checkbox"/> Target population <input checked="" type="checkbox"/> Intervention(s) or exposure(s) <input checked="" type="checkbox"/> Comparisons (if appropriate) <input checked="" type="checkbox"/> Outcome(s) <input checked="" type="checkbox"/> Health care setting or context	See relevant sections
3. POPULATION <i>Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.</i>	<input checked="" type="checkbox"/> Target population, sex and age <input checked="" type="checkbox"/> Clinical condition (if relevant) <input checked="" type="checkbox"/> Severity/stage of disease (if relevant) <input checked="" type="checkbox"/> Comorbidities (if relevant) <input type="checkbox"/> Excluded populations (if relevant)	6
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
4. GROUP MEMBERSHIP <i>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.</i>	<input checked="" type="checkbox"/> Name of participant <input type="checkbox"/> Discipline/content expertise (e.g., neurosurgeon, methodologist) <input checked="" type="checkbox"/> Institution (e.g., St. Peter's hospital) <input type="checkbox"/> Geographical location (e.g., Seattle, WA) <input checked="" type="checkbox"/> A description of the member's role in the guideline development group	404–409
5. TARGET POPULATION PREFERENCES AND VIEWS <i>Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.</i>	<input checked="" type="checkbox"/> 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) <input checked="" type="checkbox"/> Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) <input type="checkbox"/> Outcomes/information gathered on patient/public information <input checked="" type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations	12
6. TARGET USERS <i>Report the target (or intended) users of the guideline.</i>	<input checked="" type="checkbox"/> The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators)	7

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	<input checked="" type="checkbox"/> How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	
DOMAIN 3: RIGOUR OF DEVELOPMENT		
7. SEARCH METHODS <i>Report details of the strategy used to search for evidence.</i>	<input checked="" type="checkbox"/> Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) <input checked="" type="checkbox"/> Time periods searched (e.g., January 1, 2004 to March 31, 2008) <input checked="" type="checkbox"/> Search terms used (e.g., text words, indexing terms, subheadings) <input checked="" type="checkbox"/> Full search strategy included (e.g., possibly located in appendix)	9, 412, and other relevant sections
8. EVIDENCE SELECTION CRITERIA <i>Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.</i>	<input checked="" type="checkbox"/> Target population (patient, public, etc.) characteristics <input checked="" type="checkbox"/> Study design <input checked="" type="checkbox"/> Comparisons (if relevant) <input checked="" type="checkbox"/> Outcomes <input checked="" type="checkbox"/> Language (if relevant) <input type="checkbox"/> Context (if relevant)	10 and other relevant sections
9. STRENGTHS & LIMITATIONS OF THE EVIDENCE <i>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.</i>	<input checked="" type="checkbox"/> Study design(s) included in body of evidence <input checked="" type="checkbox"/> Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) <input checked="" type="checkbox"/> Appropriateness/relevance of primary and secondary outcomes considered <input checked="" type="checkbox"/> Consistency of results across studies <input checked="" type="checkbox"/> Direction of results across studies <input checked="" type="checkbox"/> Magnitude of benefit versus magnitude of harm <input checked="" type="checkbox"/> Applicability to practice context	10
10. FORMULATION OF RECOMMENDATIONS <i>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.</i>	<input checked="" type="checkbox"/> Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) <input checked="" type="checkbox"/> Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) <input checked="" type="checkbox"/> How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with	11

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	recommendations and the final vote)	
11. CONSIDERATION OF BENEFITS AND HARMS <i>Report the health benefits, side effects, and risks that were considered when formulating the recommendations.</i>	<input checked="" type="checkbox"/> Supporting data and report of benefits <input checked="" type="checkbox"/> Supporting data and report of harms/side effects/risks <input checked="" type="checkbox"/> Reporting of the balance/trade-off between benefits and harms/side effects/risks <input checked="" type="checkbox"/> Recommendations reflect considerations of both benefits and harms/side effects/risks	See relevant sections
12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE <i>Describe the explicit link between the recommendations and the evidence on which they are based.</i>	<input checked="" type="checkbox"/> How the guideline development group linked and used the evidence to inform recommendations <input checked="" type="checkbox"/> Link between each recommendation and key evidence (text description and/or reference list) <input checked="" type="checkbox"/> Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	See relevant sections
13. EXTERNAL REVIEW <i>Report the methodology used to conduct the external review.</i>	<input checked="" type="checkbox"/> Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) <input checked="" type="checkbox"/> Methods taken to undertake the external review (e.g., rating scale, open-ended questions) <input checked="" type="checkbox"/> Description of the external reviewers (e.g., number, type of reviewers, affiliations) <input checked="" type="checkbox"/> Outcomes/information gathered from the external review (e.g., summary of key findings) <input checked="" type="checkbox"/> 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)	14–15
14. UPDATING PROCEDURE <i>Describe the procedure for updating the guideline.</i>	<input checked="" type="checkbox"/> A statement that the guideline will be updated <input checked="" type="checkbox"/> Explicit time interval or explicit criteria to guide decisions about when an update will occur	18

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	<input checked="" type="checkbox"/> Methodology for the updating procedure	
DOMAIN 4: CLARITY OF PRESENTATION		
15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS <i>Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.</i>	<input checked="" type="checkbox"/> A statement of the recommended action <input checked="" type="checkbox"/> Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) <input checked="" type="checkbox"/> Relevant population (e.g., patients, public) <input checked="" type="checkbox"/> Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) <input checked="" type="checkbox"/> If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	See relevant sections
16. MANAGEMENT OPTIONS <i>Describe the different options for managing the condition or health issue.</i>	<input checked="" type="checkbox"/> Description of management options <input checked="" type="checkbox"/> Population or clinical situation most appropriate to each option	See relevant sections
17. IDENTIFIABLE KEY RECOMMENDATIONS <i>Present the key recommendations so that they are easy to identify.</i>	<input checked="" type="checkbox"/> Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms <input checked="" type="checkbox"/> Specific recommendations grouped together in one section	See relevant sections and Executive Summary
DOMAIN 5: APPLICABILITY		
18. FACILITATORS AND BARRIERS TO APPLICATION <i>Describe the facilitators and barriers to the guideline's application.</i>	<input checked="" type="checkbox"/> Types of facilitators and barriers that were considered <input checked="" type="checkbox"/> 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) <input checked="" type="checkbox"/> 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) <input checked="" type="checkbox"/> How the information influenced the guideline development process and/or formation of the recommendations	399

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19. IMPLEMENTATION ADVICE/TOOLS <i>Provide advice and/or tools on how the recommendations can be applied in practice.</i>	<input checked="" type="checkbox"/> Additional materials to support the implementation of the guideline in practice. For example: <ul style="list-style-type: none"> ○ 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 	15 and 399
20. RESOURCE IMPLICATIONS <i>Describe any potential resource implications of applying the recommendations.</i>	<input checked="" type="checkbox"/> Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) <input checked="" type="checkbox"/> 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.) <input checked="" type="checkbox"/> Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) <input checked="" type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations	400 and other relevant sections
21. MONITORING/ AUDITING CRITERIA <i>Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.</i>	<input checked="" type="checkbox"/> Criteria to assess guideline implementation or adherence to recommendations <input checked="" type="checkbox"/> Criteria for assessing impact of implementing the recommendations <input checked="" type="checkbox"/> Advice on the frequency and interval of measurement <input checked="" type="checkbox"/> Operational definitions of how the criteria should be measured	17 and 400
DOMAIN 6: EDITORIAL INDEPENDENCE		
22. FUNDING BODY <i>Report the funding body's influence on the content of the guideline.</i>	<input checked="" type="checkbox"/> The name of the funding body or source of funding (or explicit statement of no funding) <input checked="" type="checkbox"/> A statement that the funding body did not influence the content of the guideline	18
23. COMPETING INTERESTS <i>Provide an explicit statement that all group members have declared whether they have any competing</i>	<input checked="" type="checkbox"/> Types of competing interests considered <input checked="" type="checkbox"/> Methods by which potential competing interests were sought	18–19 and 410–411

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<i>interests.</i>	<input checked="" type="checkbox"/> A description of the competing interests <input checked="" type="checkbox"/> How the competing interests influenced the guideline process and development of recommendations	

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.agreertrust.org>.