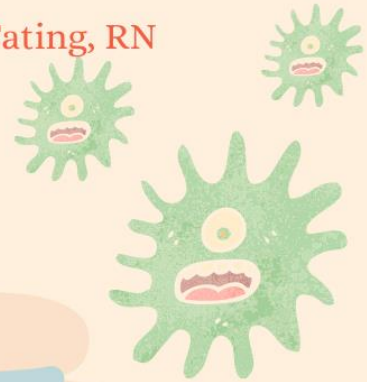
PHILIPPINE COVID-19 LIVING CLINICAL PRACTICE GUIDELINES

as of June 30, 2021

Project Leader:
Marissa M. Alejandria, MD, MSc

Project Co-Leader:
Leonila F. Dans, MD, MSc

Project Manager:
Dan Louie Renz P. Tating, RN



Implementing Agency:
Institute of Clinical Epidemiology, National Institutes of Health
University of the Philippines Manila

Cooperating Agency:
Philippine Society for Microbiology and Infectious Diseases

Funding Agency:
Department of Health, through the Philippine Council for Health Research and Development

Disclaimer

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

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.

Acknowledgements

The Philippine COVID-19 Living CPG was funded by the Department of Health's (DOH) AHEAD Program through the Philippine Council for Health Research and Development (PCHRD). The support of the following people from DOH and PCHRD were most valued: Dr. Gloria Nenita Velasco (Medical Officer IV, Health Policy Development and Planning Bureau, DOH), Ms. Maylene M. Beltran, MPA, CESO III (Former Director IV, Health Policy Development and Planning Bureau, DOH), Mr. Jay Vee C. Bartolome (Junior Project Manager, PCHRD), Ms. Claridel H. Sanchez (Senior Science Research Specialist, PCHRD), and Dr. Jaime C. Montoya, MSc, PhD (Executive Director, PCHRD).

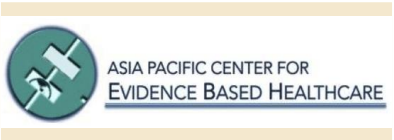
This project was implemented under the Institute of Clinical Epidemiology, National Institutes of Health (NIH), University of the Philippines Manila (UPM). The following provided administrative support during the six-month project: Ms. Krystian Kashe S. Ty and Ms. Maria Lourdes Q. Hipolito (Research Grants Administration Office, UPM), Ms. Lailanie Ann C. Tejuco (Institute of Clinical Epidemiology, NIH, UPM). The leadership of Dr. Carmencita D. Padilla, MAHPS (Chancellor, UPM) and Dr. Eva Maria Cutiongco-Dela Paz (Executive Director, NIH, UPM) gave the project much encouragement.

The project was completed with the valuable contribution of each of the 102 people involved in this CPG project, including the Steering Committee, Evidence Reviewers, Consensus Panelists, Expert Facilitators, Technical Coordinators, Technical Writers, Copy Editors, and Project Associate Staff.

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

Ad Majorem Dei Gloriam.

Participating Professional Societies and Institutions



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Executive Summary

Coronavirus disease 2019 (COVID-19) has grown into a pandemic and global crisis affecting multiple sectors of society. Over 170 million confirmed COVID-19 cases have been reported globally, with 1.24 million of these cases from the Philippines as of June 2021. Despite the national strategies implemented to curtail the health and economic impact of COVID-19 in the country, epidemiologic projections have yet to point to a foreseeable end to the pandemic, especially with the recent rise of variants with increased transmissibility. Thus, the Philippine COVID-19 Living CPG aimed to provide up-to-date, evidence-based recommendations on the management of COVID-19 among adults with or at risk for COVID-19. Thematic areas included in this CPG were screening and diagnosis, treatment, critical care and respiratory management, non-pharmacologic interventions, vaccines and prophylactic interventions, and adjunct interventions for COVID-19. This document also serves as an update of the PSMID-PCP-PCCP-PCHTM-PRA July 2020 Interim Guidance.

Following the standard CPG development process outlined in the DOH Manual for CPG Development and the GRADE methodology, 90 evidence summaries and 136 recommendations were generated by 47 consensus panelists representing 20 health organizations and institutions. With the living CPG model, the 11 evidence summaries were updated within the 6-month project duration. A summary of the recommendations is presented here.

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

Severity Classification of COVID-19

The Philippine COVID-19 Living CPG used the following definitions for the spectrum of severity of COVID-19, adapted from the WHO COVID-19 Living Guidance (January 2021):

Non-severe COVID-19

Mild COVID-19 – no pneumonia or hypoxia, acute onset of fever and cough or any three 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

a. With pneumonia, no difficulty of breathing, RR < 30 breaths/min, oxygen saturation >/= 94%

b. Without pneumonia but with risk factors for progression: elderly and/or with comorbidities

Severe COVID-19 – with pneumonia and signs of respiratory distress, oxygen saturation < 94%. RR >30 breaths/minute, requiring oxygen supplementation

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

Summary of Recommendations on Screening and Diagnosis

Recommendation	Strength of Recommendation	Certainty of Evidence
We suggest an initial screen for COVID-19 by checking for any influenza-like illness symptoms and typical COVID-19 symptoms* within the past 14 days in apparently healthy adults. **Symptoms include fever, cough, sore throat, runny nose, myalgia, headache, fatigue/malaise, diarrhea, nausea/vomiting, anosmia, ageusia, shortness of breath/dyspnea.*	Conditional	Low
We recommend the use of the following specimens as alternative specimens to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 among symptomatic and asymptomatic patients suspected of COVID-19 in hospital and outpatient settings: • oropharyngeal swab • saliva drool/spit and oral saliva • nasal swab/wash • throat swab **SARS COV-2 RT-PCR of nasopharyngeal swabs remains the diagnostic test of choice to confirm the diagnosis of COVID-19 among suspected individuals.*	Strong	 Moderate Moderate Moderate Low
We suggest the use of saliva swab and posterior oropharyngeal saliva specimens as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 among symptomatic and asymptomatic patients with suspected COVID-19 in hospital and community/outpatient settings.	Conditional	Low
We recommend against the use of sputum as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19.	Strong	Very Low

Recommendation	Strength of Recommendation	Certainty of Evidence
There is no evidence to recommend the use of bronchoalveolar lavage as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19.	-	-
We recommend the use of rapid antigen test in patients suspected of COVID-19 infection meeting all the following conditions: (Moderate quality of evidence; Strong recommendation) • Symptomatic AND • Early phase </=7 days from onset of symptoms AND • Specific brands that demonstrated sensitivity ≥80% and have very high specificity (≥97-100%))	Strong	Moderate
We recommend against the use of saliva as specimen for rapid antigen test in patients suspected of COVID-19 infection.	Strong	Moderate
We recommend against the use of rapid antigen test alone in asymptomatic patients suspected of COVID-19 infection.	Strong	Moderate to High
We suggest the use of pooled RT-PCR testing in targeted* low-risk and low-prevalence populations using a pool size of 5 in individuals suspected of COVID-19 infection. **Target population refer to the list of PSP and DOH*	Conditional	Moderate
We suggest repeating RT-PCR testing when the initial RT-PCR test is negative among symptomatic patients highly suspected to have COVID-19 infection.	Conditional	Low
We recommend the use of both clinical risk assessment and RT-PCR* to screen for COVID-19 among asymptomatic individuals scheduled for non-emergency surgery. **Use high-risk PPE regardless of RT-PCR or Ag-RDT test results in areas with prevalence of 1% or higher.*	Strong	Very Low
We recommend the use of both clinical risk assessment and Antigen-Rapid Diagnostic Test (Ag-RDT)** to screen for COVID-19 among asymptomatic individuals scheduled for non-emergency surgery	Strong	Very Low

Recommendation	Strength of Recommendation	Certainty of Evidence
when RT-PCR testing is not available or when prolonged turnaround time is considered. ***Ag-RDT should have a Sn of 80% and Sp of 97%*		
We suggest using laboratory-based antibody tests with high sensitivity and specificity (e.g., total antibody or IgG assays, ELISA, ECLIA) to determine COVID-19 seroprevalence among adults.	Conditional	Very Low
We recommend against using antibody tests detecting IgM only to determine COVID-19 seroprevalence among adults.	Strong	Very Low
We recommend against using rapid antibody tests (e.g., Lateral flow immunoassays) to determine COVID-19 seroprevalence.	Strong	Very Low
We recommend against the use of SARS-CoV-2 Ab testing to diagnose presumptive COVID-19 reinfection among symptomatic patients previously diagnosed with COVID-19*. **NAAT (RT-PCR) and Genomic sequencing are the recommended diagnostic tests to confirm COVID-19 reinfection.*	Strong	Very Low
We recommend the use of symptom-based strategy for the discontinuation of isolation and return to work clearance of the following: 1. Asymptomatic adults who are not severely immunocompromised if they fulfill the following: • remained asymptomatic throughout their infection • 10 days have passed from the first positive viral diagnostic test (RT-PCR or rapid antigen) 2. Adults who had mild to moderate COVID-19 who are not severely immunocompromised if they fulfill the following: • Afebrile for at least 24 hours without use of antipyretic medications • Respiratory symptoms have improved (cough, shortness of breath) • 10 days have passed from symptom onset	Strong	Very Low

Recommendation	Strength of Recommendation	Certainty of Evidence
3. Adults who had severe to critical COVID-19 who are not severely immunocompromised if they fulfill the following: • Afebrile for at least 24 hours without use of antipyretic medications • Respiratory symptoms have improved (cough, shortness of breath) • 21 days have passed from symptom onset *A repeat negative RT-PCR test is no longer needed for discharge of immunocompetent patients with probable or confirmed COVID-19 regardless of severity, because, in most cases, it results in prolonged isolation of patients who continue to shed detectable SARS-CoV-2 RNA but are no longer infectious.*		
We suggest test-based strategy using RT-PCR for the discontinuation of isolation and return to work clearance of the following: 1. Severely immunocompromised adults* 2. Health care workers If they fulfill the following: • Afebrile for at least 24 hours without use of antipyretic medications • Respiratory symptoms have improved (cough, shortness of breath) • With at least one negative RT-PCR test of a respiratory specimen **Severely immunocompromised: Ongoing chemotherapy for cancer, or within one year from receiving a hematopoietic stem cell or solid organ transplant; untreated HIV infection with CD4 count < 200, combined primary immunodeficiency disorder, and receipt of prednisone >20mg/day for more than 14 days, may cause a higher degree of immunocompromise and require actions such as prolonging the duration of work restrictions. Other less immunocompromising conditions include advanced old age, DM, CKD. The degree of immunocompromise is determined by the health care provider, and preventive actions are adapted to each individual and situation.*	Conditional	Very Low
We suggest against the use of chest x-ray to diagnose COVID 19 infection among asymptomatic individuals.	Conditional	Very Low

Recommendation	Strength of Recommendation	Certainty of Evidence
We suggest chest x-ray to facilitate rapid triage, infection control and clinical management among any of the following: • patients with mild features of COVID 19 at risk for progression • patients with moderate to severe features of COVID 19 • patients with symptoms of at least 5 days duration	Conditional	Very Low
We suggest against the routine use of CT scan for diagnosing COVID-19 among suspected patients with COVID-19 presenting at the emergency department if RT-PCR testing is readily available with timely results.	Conditional	Very Low
If RT-PCR test is not available, we suggest using non-contrast chest CT scan for symptomatic patients suspected of having COVID-19 to guide early triage and management under the following conditions: • patients with mild COVID-19 who are at risk for progression (elderly, with comorbidities) • patients with moderate to severe COVID-19	Conditional	Very Low
We suggest against the use of lung ultrasound alone in diagnosing patients with suspected COVID-19 infection.	Conditional	Low
<u>To guide the decision to admit patients with COVID-19 to the hospital:</u> We suggest the use of the following scoring systems: • Age, BUN, number of Comorbidities, CRP, SpO2/FiO2 ratio, Platelet count, Heart rate (ABC2-SPH) risk score, • Confusion Urea Respiration Blood Pressure (CURB-65) severity score, • Risk Stratification in the Emergency Department in Acutely Ill Older Patients (RISE-UP) score, and • Rapid Emergency Medicine Score (REMS)	Conditional	Low
<u>To guide in the expectant monitoring of hospitalized patients:</u> We suggest the use of the 4C Deterioration model. There is insufficient evidence to recommend the use of the Modified Early Warning Score (MEWS) and	Conditional -	Low Very low

Recommendation	Strength of Recommendation	Certainty of Evidence
National Early Warning Score 2 (NEWS2) scoring systems.		
There is insufficient evidence to recommend the use of breath test in detecting COVID-19 infection.	-	High
There is insufficient evidence to recommend the use of specific cut-off values of CRP, LDH and Ferritin to guide immunotherapy in COVID-19.	-	Very Low
We suggest the use of D-dimer to guide anticoagulation of patients with COVID-19, because of its significant association with mortality, thromboembolism, and worsening severity of disease.	Conditional	Low

Summary of Recommendations on Treatment

Recommendation	Strength of Recommendation	Certainty of Evidence
We recommend against the use of hydroxychloroquine/chloroquine, with or without azithromycin among patients with COVID-19 infection.	Strong	Moderate
We recommend against the use of azithromycin among patients with COVID-19 infection.	Strong	Moderate
There is insufficient evidence to recommend the use of favipiravir among patients with COVID-19.	-	Very low
We suggest against the use of remdesivir in patients with COVID-19 infection who have O2 saturation ≥94% and do not require oxygen supplementation.	Conditional	Low
We suggest the addition of remdesivir to dexamethasone in patients with COVID-19 infection who have O2 saturation < 94% and/or requiring oxygen supplementation.	Conditional	Low
We suggest against the use of remdesivir in patients with COVID-19 infection who are already on invasive mechanical ventilation or ECMO. **For patients who progress to invasive mechanical ventilation while on remdesivir, the drug can be continued.*	Conditional	Low
We recommend the addition of tocilizumab to systemic steroids in patients with elevated biomarkers of inflammation (CRP), showing rapid respiratory deterioration and/or requiring high doses of oxygen (high-flow nasal cannula, noninvasive or invasive mechanical ventilation).	Strong	Moderate
We recommend against the use of tocilizumab in patients with COVID-19 infection who do not require oxygen supplementation.	Strong	Very low
We recommend against the use of convalescent plasma among patients with COVID-19 infection.	Strong	Moderate
We recommend against the use of ibuprofen as treatment among patients with COVID-19 infection.	Strong	Very low

Recommendation	Strength of Recommendation	Certainty of Evidence
There is no evidence to recommend the use of VCO as treatment among patients with COVID-19 infection.	-	-
We recommend against the use of Lianhua as treatment among patients with COVID-19 infection.	Strong	Very low
We suggest against the use of ivermectin for the treatment of patients with mild-to-moderate COVID-19. We recommend against the use of ivermectin for the treatment of patients with severe COVID-19. We suggest against the use of ivermectin combined with doxycycline for the treatment of patients with COVID-19.	Conditional Strong Conditional	Very low Very low Very low
We suggest against the use of colchicine in the treatment of COVID-19.	Conditional	Low
We suggest against the use of interferon in the treatment of hospitalized patients with moderate to critical COVID-19.	Conditional	Very low
We suggest the use of baricitinib in combination with remdesivir in hospitalized COVID-19 patients who cannot take corticosteroids and require oxygen supplementation. There is insufficient evidence to recommend the use of baricitinib in combination with remdesivir and corticosteroids in hospitalized COVID-19 patients. There is no evidence to recommend the use of baricitinib alone in hospitalized COVID-19 patients.	Conditional	Low Very low
There is insufficient evidence to recommend the use of inhaled corticosteroids as treatment for non-hospitalized patients with mild to moderate COVID-19 infection.	-	Very low
We recommend against the use of lopinavir/ritonavir as treatment for COVID-19 infection.	Strong	Moderate

Recommendation	Strength of Recommendation	Certainty of Evidence
There is insufficient evidence to recommend the use of casirivimab plus imdevimab as treatment for COVID-19 infection.	-	Low
There is insufficient evidence to recommend the use of leronlimab as treatment for COVID-19.	-	Very low
We recommend against the use of steam inhalation alone in the treatment of COVID-19.	Strong	Very low
We suggest against the use of baloxavir as treatment for patients with COVID-19 infection.	Conditional	Very low
We recommend against the use of oseltamivir as treatment for patients with COVID-19 infection.	Strong	Very low
We suggest against the use of intravenous immunoglobulin as treatment for moderate to severe COVID-19.	Conditional	Very low
There is insufficient evidence to recommend using umbilical cord-derived mesenchymal stem cell therapy among adults with severe COVID-19.	-	Very low
We suggest against the use of famotidine in the treatment of COVID-19.	Conditional	Very low

Summary of Recommendations on Critical Care and Respiratory Management

Recommendation	Strength of Recommendation	Certainty of Evidence
We recommend the use of dexamethasone in patients with COVID-19 infection who require supplemental oxygenation (i.e., including high-flow device, non-invasive, invasive mechanical ventilation and ECMO).	Strong	High
We recommend against the use of systemic corticosteroids among patients with COVID-19 infection who do not require oxygen supplementation.	Strong	Moderate to high
We suggest the use of prophylactic anticoagulation among hospitalized patients with COVID-19 infection, unless with contraindications.	Conditional	Very low
We suggest the use of prophylactic dose anticoagulation rather than therapeutic anticoagulation in critically ill patients with COVID-19 infection.	Conditional	Low
We recommend against the routine use of antibiotics in patients with severe and critical COVID-19 infection, unless with suspicion of secondary bacterial co-infection. For patients on empiric antibiotics, they should be assessed daily for the need for discontinuation, continuation or deescalation based on clinical and laboratory parameters.	Strong	Very low
There is insufficient evidence on the use of hemoperfusion among patients with COVID-19 infection.	-	Very low
We suggest the use of conservative fluid management rather than liberal fluid management strategy in mechanically ventilated adult COVID-19 patients with acute respiratory distress syndrome who have been adequately resuscitated*. **without tissue hypoperfusion and fluid responsiveness*	Conditional	Low
We suggest self-proning to improve oxygenation status of non-intubated hospitalized patients with COVID-19 infection requiring oxygen supplementation.	Conditional	Very low
We suggest the use of high-flow nasal cannula oxygenation rather than non-invasive ventilation (e.g.,	Conditional	Very low

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

Summary of Recommendations on Non-Pharmacologic Interventions

Recommendation	Strength of Recommendation	Certainty of Evidence
We recommend that healthcare workers not directly taking care of COVID-19 patients, and other persons with high risk of exposure to COVID-19 should use properly fitted surgical masks instead of cloth masks.	Strong	Moderate
We suggest using a cloth mask that fits snugly on the face and made of at least two layers of cotton (e.g., t-shirt fabric) or non-woven nylon with aluminum nose bridge for the general public with low risk of exposure to COVID-19 in outdoor or indoor areas to prevent COVID-19 infections.	Conditional	Low
We recommend against the use of ionizing air purifier to reduce COVID-19 transmission in the community.	Strong	Low
We recommend against the use of footbaths for the prevention and control of COVID-19 transmission.	Strong	Very low
We recommend against the use of misting tents or disinfection chambers for preventing and controlling COVID-19 transmission.	Strong	Very low
We recommend against the use of UV lamps or other UV devices in any place outside of a controlled clinic or hospital setting to prevent and control COVID-19 transmission.	Strong	Low
We suggest the use of HEPA filter as an option to improve air quality in indoor spaces with inadequate ventilation.	Conditional	Low
In situations where there is shortage of filtering facepiece respirators (FFR), we suggest the use of Hydrogen Peroxide Vapor (HPV), Ultraviolet Germicidal Irradiation (UVGI), moist heat and peracetic acid dry fogging system (PAF) as options for N95 mask decontamination as recommended by the manufacturer based on their ability to reduce SARS-COV-2 load while still maintaining N95 mask integrity.	Conditional	Low
We recommend against the use of autoclave and alcohol as these methods alter filtering facepiece respirator's (N95) integrity and degrade filtration efficacy.	Strong	Very low

Recommendation	Strength of Recommendation	Certainty of Evidence
We recommend the use of appropriate PPE to include mask (N95 or higher), fluid repellent sealed well-fitting long gown, double gloves, apron, full face shield or goggles or visor, scrub hat, and disposable shoe covers or dedicated closed footwear among surgeons engaged in aerosol generating procedures of suspected or confirmed COVID-19 patients.	Strong	Very low
We recommend the use of at least a surgical face mask and face shield for protection against COVID-19 infection among healthcare workers in the outpatient setting not performing aerosol generating procedures. Additional PPEs such as medical gowns and gloves should be worn as part of standard precautions during the performance of other procedures.	Strong	Very low
We recommend the use of the following PPE: disposable hat, medical protective mask (N95 or higher standard), goggles or face shield (anti-fog), medical protective clothing, disposable gloves and disposable shoe covers or dedicated closed footwear as an effective intervention in the prevention of COVID-19 among health care workers in areas with possible direct patient care of confirmed or probable COVID-19 patients and possible performance of aerosol generating procedures.	Strong	Moderate
We suggest the use of face mask plus protective eyewear in the form of face shield or goggles for the general public in areas with sustained community transmission of SARS-COV2. We recommend using medical face mask plus face shield and standard personal protective equipment among health care workers not directly involved in the care of COVID-19 patients in areas with sustained community transmission of SARS-COV2.	Conditional Strong	Very low Very low
We suggest against the use of protective physical barrier enclosures (ex. aerosol box) for the prevention of COVID-19 among health care providers who perform aerosol generating medical procedures*. *Proper PPEs should be used by health care providers when performing aerosol-generating procedures.	Conditional	Very low

Recommendation	Strength of Recommendation	Certainty of Evidence
We suggest using protective physical barriers in areas where physical distancing cannot be adhered to (e.g., offices, reception desk)**. ** Adequate ventilation, physical distancing, use of facemasks and personal hygiene should still be maintained to prevent COVID-19 infections. Regular cleaning and disinfection of physical barriers should be practiced.	Conditional	Very low
We recommend cleaning and disinfecting surfaces using the appropriate disinfecting chemical agents such as 0.5% sodium hypochlorite solution (bleach) or 70% alcohol to prevent COVID-19 infection. For high touch surfaces and high traffic areas, such as in the workplace, disinfection should be done before shift, intermittently during shift and after the shift. For household disinfection, once daily disinfection of high touch surfaces is recommended.	Strong	Low

Summary of Recommendations on Vaccines and Prophylactic Interventions

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

Recommendation	Strength of Recommendation	Certainty of Evidence
vaccines to prevent SARS-CoV-2 infection in adults who have stable medical comorbidities and are at risk for severe infection.		
We suggest the use of CoronaVac (Sinovac) to prevent SARS-CoV-2 infection in adults who have stable medical comorbidities and are at risk for severe infection.	Conditional	Very low
We recommend the use of BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya), CoronaVac (Sinovac) and Ad26.COV2.S (Janssen/ Johnson&Johnson) vaccines to prevent SARS-CoV-2 infection in immunocompromised patients (i.e., diagnosed with HIV, hepatitis B and C, those with cancer undergoing chemotherapy, transplant patients receiving immune-suppression) after medical clearance from a physician.	Strong	Low
We recommend the use of BNT162b2 (Pfizer/BioNTech)vaccine in children 12 years old and above to prevent SARS-CoV-2 infection.	Strong	Moderate
There is no evidence on the use of mRNA-1273 (Moderna), ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya), Ad26.COV2.S (Janssen/ Johnson&Johnson) and CoronaVac (Sinovac) among children <18 years old to prevent SARS-CoV-2 infection.	-	-
We recommend against the use of these vaccines for those who have known allergies to the contents / excipients of the vaccine, such as polysorbate: (ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya) and Ad26.COV2.S (Janssen/ Johnson&Johnson) and polyethylene glycol or PEG200 DMG (BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna).	Strong	Moderate to high
We recommend against the use of melatonin as prevention for COVID-19 infection.	Strong	Very low
We recommend against the use of Vitamin D supplementation to prevent COVID-19 infection.	Strong	Very low

Recommendation	Strength of Recommendation	Certainty of Evidence
We recommend against the use of zinc supplementation to prevent COVID-19 infection.	Strong	Very low
We recommend against the use of HCQ for pre-exposure prophylaxis in adults who are at high risk of exposure to COVID-19 cases. We recommend against the use of HCQ for post-exposure prophylaxis in adults who are exposed to COVID-19 cases.	Strong Strong	Moderate Low
We recommend against the use of lopinavir/ritonavir for chemoprophylaxis in individuals exposed to COVID-19 patients.	Strong	Very low
There is insufficient evidence to recommend the use of saline nasal irrigation (SNI) to prevent COVID-19 in healthy individuals.	-	Very low
We recommend against the use of steam inhalation in the prevention of COVID-19	Strong	Very low
There is insufficient evidence to recommend the use of antiseptic mouthwash or gargle to prevent COVID-19 in healthy individuals.	-	Very low
We recommend against the use of ivermectin as COVID-19 prophylaxis for the general population. We recommend against the use of ivermectin for COVID-19 as post-exposure prophylaxis for household contacts of confirmed COVID-19 patients. We recommend against the use of ivermectin for COVID-19 as prophylaxis for healthcare workers.	Strong Strong Strong	Very low Very low Very low
We suggest against the use of BCG vaccine for the prevention of COVID-19 infection.	Conditional	Very low
There is insufficient evidence on the use of aspirin as prophylaxis against COVID-19-induced coagulopathy among patients with COVID-19.	-	Very low

Summary of Recommendations on Adjunct Interventions

Recommendation	Strength of Recommendation	Certainty of Evidence
There is insufficient evidence to recommend the use of zinc as adjunct treatment for patients with COVID-19 infection both in the outpatient and in-patient setting.	-	Very low
We suggest against the use of B vitamins as adjunct in the treatment of patients with COVID-19.	Conditional	Very low
There is insufficient evidence to recommend the use of intravenous Vitamin C as adjunct treatment for patients with COVID-19 infection.	-	Low
There is insufficient evidence to recommend the use of Vitamin D supplementation as adjunct treatment for patients with COVID-19 infection.	-	Very low
There is insufficient evidence to recommend the use of melatonin as adjunct treatment for patients with COVID-19 infection.	-	Very low
There is no evidence to recommend the use of virgin coconut oil as adjunct treatment for patients with COVID-19 infection.	-	-
There is insufficient evidence to recommend the use of fatty acid supplements as adjunctive treatment for patients with COVID-19.	-	Low
We recommend against the use of intravenous N-acetylcysteine as adjunct treatment for patients with COVID-19 infection.	Strong	Moderate
We recommend continuing maintenance RAAS blockers for hypertension among patients with COVID-19 infection.	Strong	Moderate
We suggest that ibuprofen may still be used as symptomatic treatment of patients with COVID-19 infection if clinically warranted. Concurrent use of ibuprofen is not associated with worsening of COVID-19 outcomes.	Conditional	Very low

There is insufficient evidence to recommend discontinuation of aspirin as maintenance therapy for underlying medical conditions in patients with COVID-19.	-	Very low

Introduction

Coronavirus disease 2019 (COVID-19) has grown into a pandemic and global crisis affecting multiple sectors of society. As of June 1, 2021, over 170 million confirmed COVID-19 cases have been reported globally [1]. In the Philippines, the number of confirmed cases has rapidly increased to 1.24 million as of June 1, 2021, with 21,012 deaths recorded nationwide [2]. The national strategy towards the new normal is prevention, detection, isolation, treatment, and reintegration [3]. 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 1.7 million fully vaccinated individuals as of June 10, 2021 [4]. Notwithstanding these strategies, none of the epidemiologic projections on COVID-19 in the Philippines point to a foreseeable end of the pandemic, especially with the rise of variants with increased transmissibility.

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

Objectives

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

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

Target Population

This CPG was intended to apply primarily for adult Filipinos aged 18 years old and above diagnosed with, or at risk of COVID-19. The severity of COVID-19 was indicated in several recommendations if it is severity-specific. Other clinical characteristics,

such as comorbidities, that would affect the recommendations were indicated clearly in the wording, as appropriate.

Intended Users

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

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

CPG Development Methodology

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

Overview of Philippine COVID-19 Living CPG Development Process

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

1. **Guideline Preparation** – The Steering Committee identified and convened members of the Living CPG task force: Evidence Review Experts (ERE) or Technical Working Group (TWG) and the Consensus Panel. A total of 21 specialty societies and stakeholders were represented in the task force.

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

2. **Evidence Synthesis** - Evidence Review Experts (ERE) reviewed and appraised existing CPGs, systematic reviews, preprints and published literature, prepared evidence summaries, and drafted evidence-based recommendations. During this stage of development, three technical coordinators with expertise in CPG Development and Evidence-Based Medicine oversaw the retrieval and appraisal of evidence and the creation of the draft recommendations. Three technical writers ensured that the evidence summaries are uniform, concise, and clear. The Steering Committee organized several practice sessions for the ERE to finalize their presentations, and discuss them with other EREs, Steering Committee, and technical experts. Evidence summaries were collated, formatted, and prepared for presentation to the consensus panel.

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

4. **Living CPG Process** – From the base CPG created in the above standard guideline development process, some of the questions were prioritized to a *living* status and updated depending on the following: (1) current priority for

decision making, or (2) new evidence available likely to change existing recommendation [8]. The EREs working on living recommendations performed continual surveillance of literature to update the living systematic review with new evidence and updated the Evidence Summary tables and draft recommendations for the panel discussion. The Steering Committee reviewed the updated evidence summary document and revised draft recommendation. As needed, the Consensus Panel concerned was convened again in an online meeting to discuss the new evidence and any changes in the living recommendation.

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

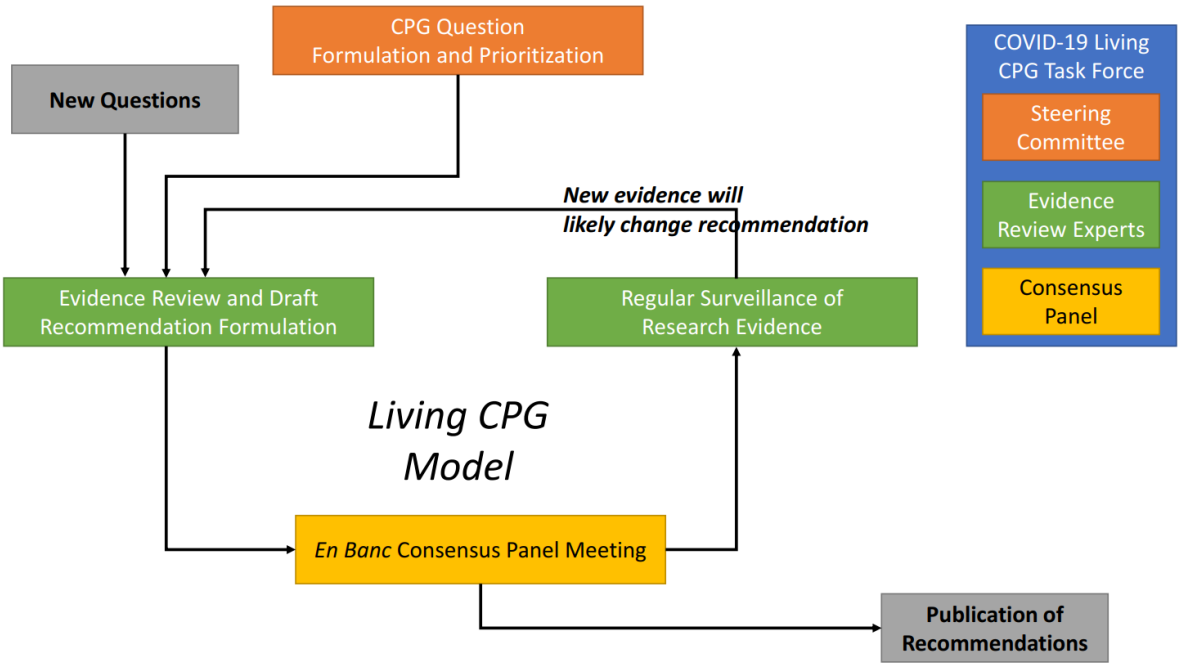


Figure 1. Philippine COVID-19 Living CPG Development Process.

Guideline Preparation

COMPOSITION OF THE GUIDELINE TASK FORCE

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

The Evidence Review Experts (ERE) were composed of members with one or more of the following expertise: methodologists, clinical epidemiologists, evidence-based

medical practitioners. They preferably had previous training and experience in CPG development and evidence synthesis.

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

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

KEY CLINICAL ISSUES AND QUESTIONS

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

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

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

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

Screening and Diagnosis	Treatment
• 14-day COVID-19 symptom-based test • Choice of sample for RT-PCR (including saliva testing) • Pooled sample testing using RT-PCR • Rapid antigen tests • Repeat testing using RT-PCR • Antibody testing for reinfection	• Hydroxychloroquine (HCQ) or Chloroquine (CQ) with or without Azithromycin • Azithromycin • Convalescent Plasma • Favipiravir • Remdesivir • Tocilizumab • Ivermectin

- Antibody tests (LFIA, ECLIA, and ELISA) for seroprevalence
- Clinical risk assessment and RT-PCR testing for patients undergoing surgery
- Return to work after COVID-19 (non HCW and HCWs)
- Chest X-ray in the diagnosis of COVID-19
- CT Scan in the diagnosis of COVID-19
- Chest UTZ in diagnosis
- Prognostic factors of severe disease and mortality
- LDH, CRP, and Ferritin for immunotherapy
- D-dimer for anticoagulation
- Breath test

- Traditional Chinese Medicine (Lianhua capsules)
- Lopinavir/ritonavir
- Interferon
- Colchicine
- Inhalational steroids
- Baricitinib
- Leronlimab
- Regeneron (casirivimab-imdevimab)
- Bamlanivimab-etesevimab
- Mesenchymal stem cell therapy
- Intravenous immunoglobulin
- Ibuprofen
- Famotidine
- Baloxavir
- Oseltamivir
- Virgin coconut oil
- Steam inhalation

Critical Care and Respiratory Management	Non-Pharmacologic Interventions
• Anticoagulation • Systemic corticosteroids • Empiric antimicrobials • Fluid management • Hemoperfusion • High-Flow Nasal Cannula (versus Non-invasive ventilation or Conventional oxygen therapy) for acute hypoxemic respiratory failure • Lung protective ventilation, PEEP, and driving pressure for ARDS patients • Proning in non-intubated COVID-19 patients • Etoposide for cytokine storm • ECMO • Hyperbaric Oxygen Therapy • Rapid sequence intubation versus delayed intubation • Pulmonary rehabilitation for patients with long COVID-19	• Cloth masks • Face masks and protective eyewear (face shield or goggles) • Foot bath • HEPA filter • Ionizing air filters • Methods of decontaminating N95 mask for reuse • Misting tents • UV lamps • PPEs for HCWs in the hospital setting (wards, ICUs, and emergency rooms) • PPEs for HCWs in OPDs in areas with sustained community transmission • Minimum PPE during surgeries • Methods of surface disinfection • Acrylic physical barriers

Vaccines and Prophylactic Interventions	Adjunct Interventions
• COVID-19 Vaccines • Hydroxychloroquine (HCQ) or Chloroquine (CQ) • Lopinavir/ Ritonavir • Melatonin • Nasal saline irrigation • Antiseptic mouthwash/ gargle • Steam inhalation • Vitamin D • Zinc supplements • BCG vaccine • Ivermectin • Aspirin as prophylaxis against COVID-19 induced coagulopathy	• Ibuprofen and worse COVID-19 symptoms • Melatonin • N-Acetylcysteine • Virgin Coconut Oil • Vitamin C • Vitamin D • Zinc • Oral fatty acid supplements • Vitamin B • Aspirin as maintenance therapy • RAAS antagonists as maintenance therapy

Evidence Synthesis

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

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

SEARCH METHODS

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

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

(https://www.who.int/publications/i/item/therapeutics-and-covid-19-living-guideline)

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

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

INCLUSION AND EXCLUSION CRITERIA

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

The target population depended on the clinical question, whether it was on patients with COVID-19, individuals at high risk of COVID-19, or the general population. Due to the limited resources available, only those articles in the English language were included. Specific details on inclusion and exclusion criteria were presented in the respective full-text evidence summaries.

STUDY QUALITY ASSESSMENT

Quality appraisal of primary studies and systematic reviews was done by at least two independent reviewers. The Painless EBM questions on validity [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.

DATA SYNTHESIS

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

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

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

Evidence to Decision: Formulating Recommendations

The Consensus Panel evaluated the direction and strength of recommendation using the GRADE approach, 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 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	Further research is **likely to have an important impact on confidence** in the estimate of

GRADE Certainty of Evidence	Definition	Implication
	estimate of the effect, but there is a possibility that it is substantially different	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 conditional. However, there were three reasons where the consensus panels were unable to make a recommendation [6]:

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

A strong recommendation was stated as "We recommend/ We recommend against…", while a conditional recommendation was worded "We suggest/ We suggest against…". Finally, when no recommendation can be made, the sentence starts with "There is no/ insufficient evidence to recommend…"

The implications of strong and conditional recommendations are enumerated in Table 4 [6].

PATIENT VIEWS AND PREFERENCES

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

19. This strategy ensured that patient views and preferences are still considered in the formulation of recommendations.

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

	Strong Recommendation	Conditional 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 adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and the involvement of many stakeholders. Policies are also more likely to vary between regions.

RESOURCE IMPLICATIONS

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

RATING OF OUTCOMES

The Consensus Panel rated outcomes for each set of clinical questions according to whether they were critical, important but not critical, or of low importance for decision making. Critical outcomes were primary factors that should influence a recommendation, while those with lower importance did not bear on these recommendations. On a scale of 1-9, those rated 7-9 were critical outcomes, 4-6 were

important but not critical outcomes, and 1-3 were outcomes of limited importance. Table 5 below shows the result of the ranking of outcomes per CPG panel:

Table 5. Outcome ratings for each CPG panel.

CPG Panel	Critical and Important Outcomes	Not Important Outcomes
Screening and Diagnosis	• Sensitivity and specificity • Positive and negative predictive values • Development of COVID-19 • Mortality • Positive and negative likelihood ratios • False positive and false negative rates	• Number of RT-PCR positive samples
Treatment – Outpatients and Mild to Moderate COVID Patients	• All-cause mortality • Clinical improvement/ Time to clinical cure • Respiratory distress/ Need for mechanical ventilation (and duration) • WHO progression level/ Progression to severe COVID-19 • Hospitalization (and duration) • ICU admission • Need for supportive oxygen therapy • Adverse events • Serious adverse events	• Viral negative conversion/ Viral clearance • Improvement in Chest X-ray/ CT Scan
Treatment – Severe to Critical COVID Patients	• All-cause mortality • Clinical improvement/ Time to clinical cure • Respiratory distress/ Need for mechanical ventilation (and duration) • WHO progression level • Hospitalization (and duration) • ICU admission • Need for supportive oxygen therapy • Adverse events	• Viral negative conversion/ Viral clearance • Improvement in Chest X-ray/ CT Scan

CPG Panel	Critical and Important Outcomes	Not Important Outcomes
	• Serious adverse events	
Critical Care and Respiratory Management	• All-cause mortality • Need for mechanical ventilation/ Ventilator-free days/ Successful weaning from mechanical ventilation • Clinical improvement • Pulmonary function (PaO2/FiO2 ratio, PaO2, SpO2, etc.) • Length of hospital and ICU stay • Thromboembolic events • Bleeding • Other adverse events • Serious adverse events	• Serum interleukin-6 level • Viral clearance/ Viral negative conversion
Non-Pharmacologic Interventions	• Development of COVID-19 infection • Filtration efficacy • Prevention of influenza-like illness • Reduction of colonization • Adverse events	
Vaccines and Prophylactic Interventions	• COVID-19-related deaths • Incidence of COVID-19 • Hospitalization or ER visit • Mechanical ventilation • Adverse events • Serious adverse events	• Prevention of common cold symptoms • Number of days with URTI
Adjunct Interventions	• Clinical recovery • Reduction of symptoms • All-cause mortality • Need for/ Duration of mechanical ventilation • Duration of hospital stay/ ICU admission • Adverse events	

CONSENSUS PROCESS

A skilled facilitator moderated the discussions during the consensus meetings. Each member voted on the draft recommendation as follows: yes, no, or abstain. The consensus was defined as at least 75% agreement among the members for both the direction and strength of recommendation. If consensus was not reached, members

discussed the reasons in support of their votes for or against the recommendation. The voting was repeated, up to three rounds, until a consensus was reached. Any issues left unsettled after the *en banc* meeting were finalized through a modified Delphi activity.

There were no recommendations that did not reach a consensus after voting or a repeat meeting without the modified Delphi activity.

Guideline Dissemination

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

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

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

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

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

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

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

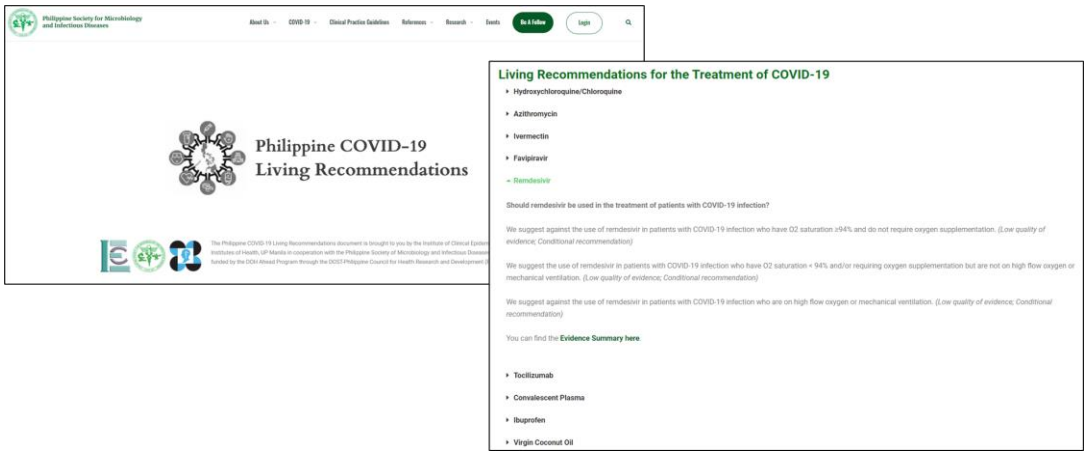


Figure 3. Latest PSMID Webpage for the Philippine COVID-19 LCPG.

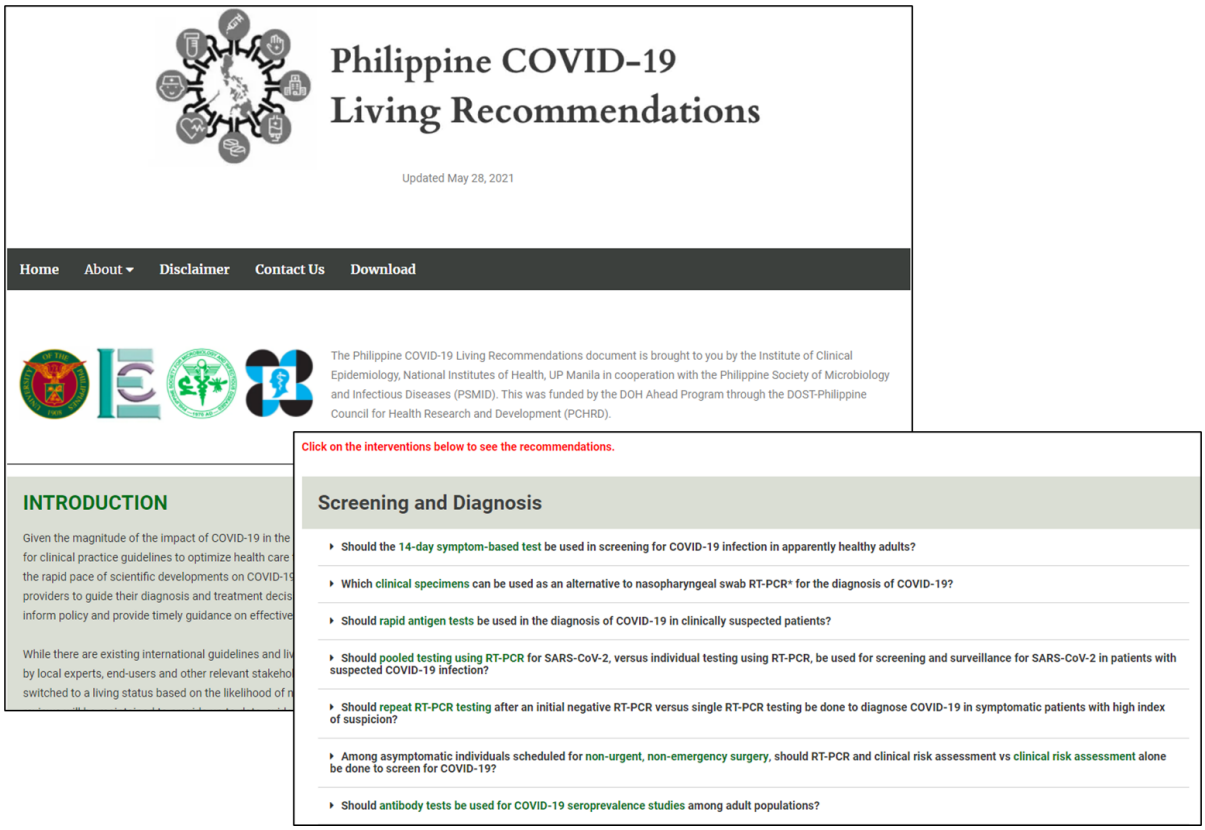
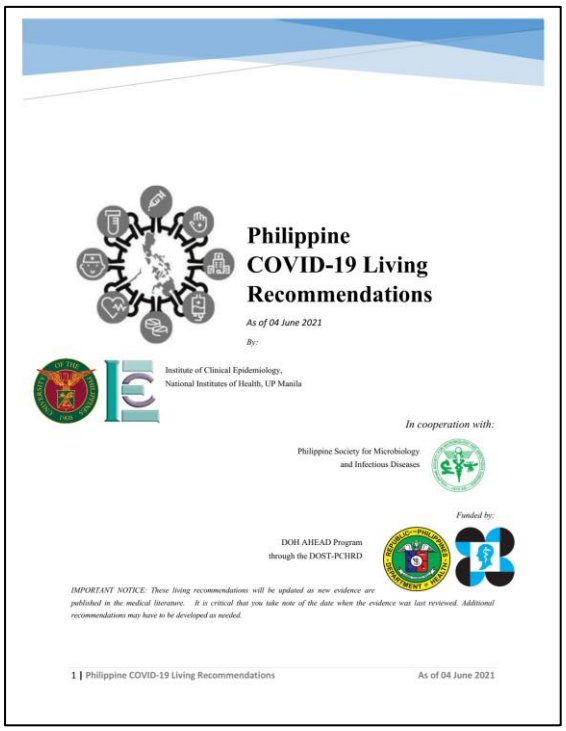


Figure 4. Living Recommendations Document for the Philippine COVID-19 Living CPG.



Philippine
COVID-19 Living
Recommendations

As of 04 June 2021

By:

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

In cooperation with:

Philippine Society for Microbiology
and Infectious Diseases

Funded by:

DOH AHEAD Program
through the DOST-PCHRD

IMPORTANT NOTICE: These living recommendations will be updated as new evidence are published in the medical literature. It is critical that you take note of the date when the evidence was last reviewed. Additional recommendations may have to be developed as needed.

1 | Philippine COVID-19 Living Recommendations As of 04 June 2021

Guideline Monitoring and Evaluation

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

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

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

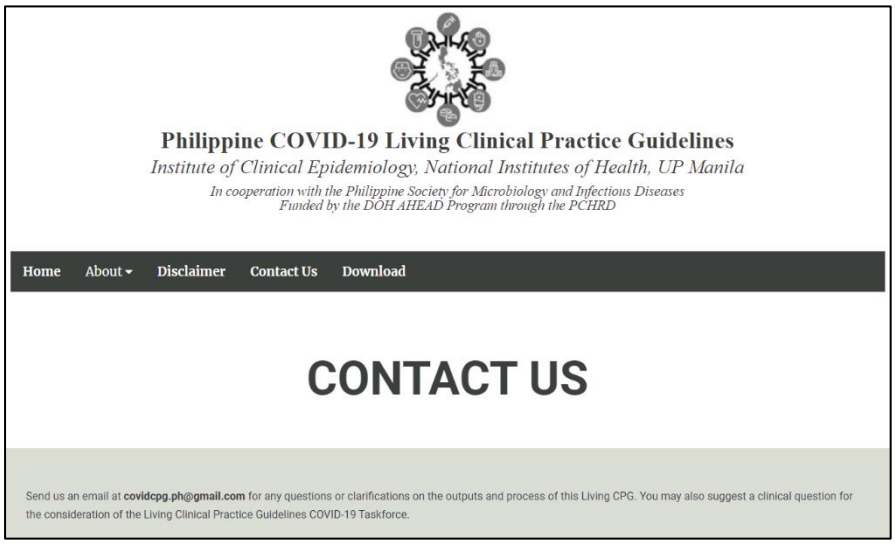
Finally, a scheduled bi-annual review would be conducted to evaluate the process efficiency and scientific quality of the Philippine COVID-19 Living CPG.

External Review

The CPG webpage served the dual purpose of a dissemination method and a way to collect the external reviews of the CPG processes, evidence summaries, and

recommendations. This website (Figure 5) also allowed health professionals and key stakeholders to suggest additional clinical questions that could be included in the scope of this CPG.

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



Over the weeks and months, we have gathered feedback from users and members of the Living CPG Taskforce to improve the readability of the webpage, such as toggling of topics, recommendations, and evidence summaries, changing from topics to questions in the listing, rearranging various sections into headers (such as CPG methodology, task force members, contact details, etc.), and other formatting changes. As an illustration, one feedback received on Lianhua led to the update of that evidence summary, and the inclusion of the health professional who gave the feedback in the evidence review team on Lianhua.

Updating of Guidelines

Due to the rapidly evolving science of COVID-19 treatment and diagnosis, the Philippine COVID-19 Living CPG was updated continuously. See the *Living CPG Process* under the *Overview of Philippine COVID-19 Living CPG Development Process* section for specific details on the process of updating this Living CPG.

After the initial DOH-PCHRD funding for six months, the DOH Disease Prevention and Control Bureau will provide 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.

Editorial Independence

FUNDING SOURCE

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

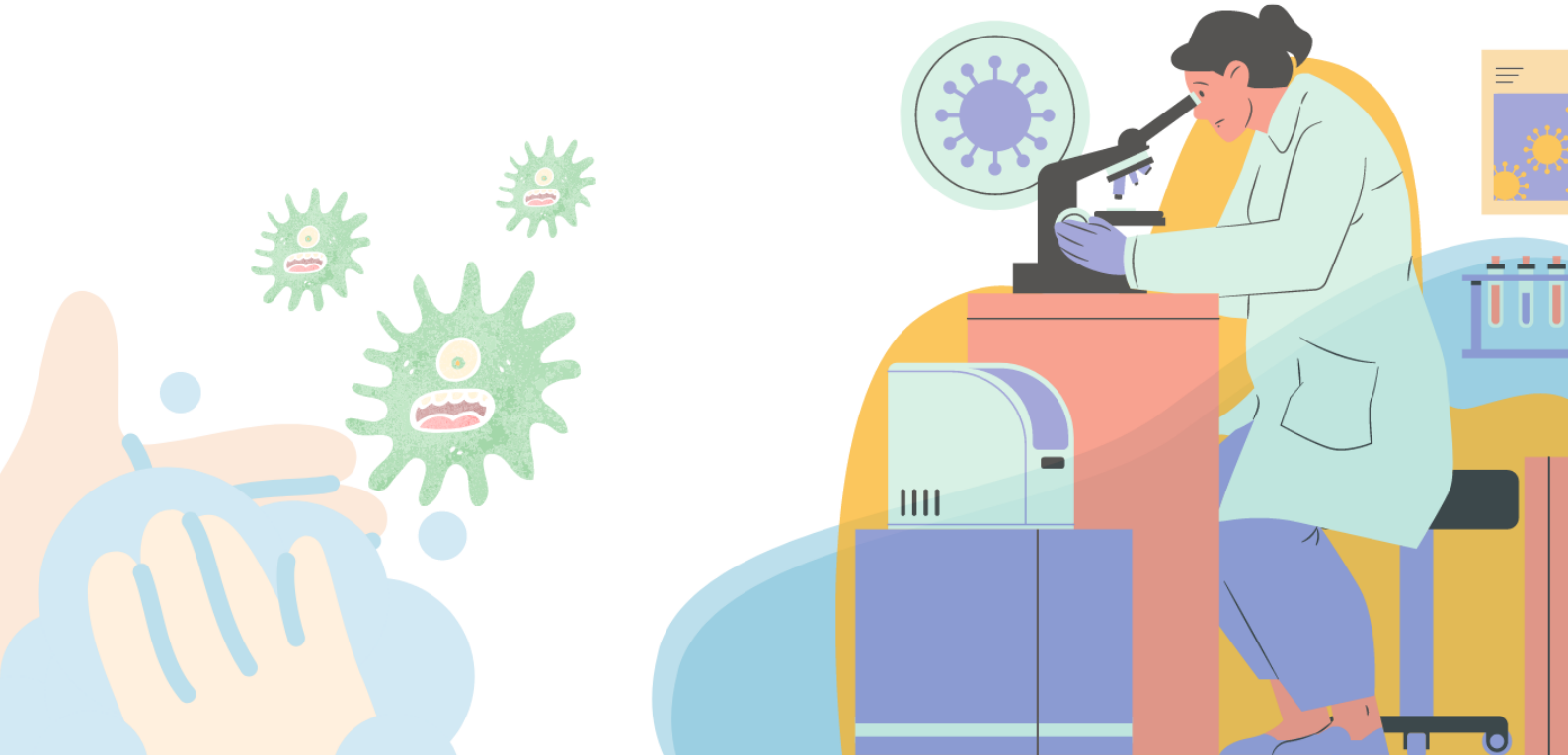
MANAGEMENT OF CONFLICTS OF INTEREST

All members involved in the creation of this Clinical Practice Guideline, including the Steering Committee, Technical Working Group, and Consensus Panel, declared any potential conflicts of interest within the last 4 years, using a uniform Declaration of Conflict of Interest (DCOI) form as recommended in the DOH Manual [5]. These were reviewed by the central project team and the Steering Committee, to screen and manage the COIs declared. Those without COIs were selected to be members of the CPG task force. Those with non-significant COIs participated if their COIs were declared in the meetings and documented in the reports. Finally, those with significant personal and financial COIs related to COVID-19 were not selected to be involved in any part of the CPG project.

None of the Steering Committee and Project Staff had any conflicts of interest. The declared COIs of several members of the Consensus Panel and Evidence Reviewers are listed in Appendix B. These were assessed to be non-significant related to the nature of the COI as well as the topics handled by the panelist/ reviewer. The other members of the Consensus Panel and Evidence Review Experts did not have any conflicts of interest.

PHILIPPINE COVID-19 LIVING RECOMMENDATIONS

Screening and Diagnosis



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

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

RECOMMENDATION
We suggest an initial screening for COVID-19 by checking for any influenza-like illness symptoms and typical COVID-19 symptoms* within the past 14 days in apparently healthy adults. (Low quality of evidence; Conditional recommendation) Symptoms include fever, cough, sore throat, runny nose, myalgia, headache, fatigue/malaise, diarrhea, nausea/vomiting, anosmia, ageusia, shortness of breath/dyspnea

KEY FINDINGS

Limited evidence was found from two observational studies (n= 8,290) [1,2] to support the use of the 14-day symptom-based test in screening for COVID-19 in apparently healthy adults. This symptom-based test had moderate sensitivity and specificity in detecting COVID-19 among adults. We found no randomized trials showing the benefits and harms of a symptom-based screening strategy. The studies were of moderate risk of bias due to inability to assure independent test performance and to eliminate potential bias in patient selection.

CONSENSUS ISSUES

The 14-day symptom-based test is a screening strategy wherein the presence of any influenza-like illness symptoms within the past 14 days is designated as presumptive for COVID-19. It should be noted that since the recommendation is for initial screening, a follow-up confirmatory diagnostic test should be done.

See updated WHO Surveillance Case Definition December 2020.

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

RECOMMENDATION
We recommend the use of the following specimens as alternative specimens to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 among symptomatic and asymptomatic patients suspected of COVID-19 in hospital and outpatient settings: • oropharyngeal swab (Moderate quality of evidence; Strong recommendation) • saliva drool/spit and oral saliva (Moderate quality of evidence; Strong recommendation) • nasal swab/wash (Moderate quality of evidence; Strong recommendation)

- throat swab (Low quality of evidence; Strong recommendation)

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

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

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

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

KEY FINDINGS

One cross sectional study [3] on the use of oropharyngeal swab RT-PCR as an alternative clinical specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 showed that oropharyngeal swab had comparable sensitivity and specificity to nasopharyngeal swab RT-PCR.

A meta-analysis [4] of 19 observational studies on the use of saliva as an alternative clinical specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 concluded that saliva had comparable sensitivity and specificity to nasopharyngeal swab RT-PCR.

Two cross sectional studies [3,5] on the use of nasal swab/wash RT-PCR as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 showed that nasal swab/wash had comparable sensitivity and specificity to nasopharyngeal swab RT-PCR.

A cross sectional study [5] on the use of throat swab RT-PCR as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 also showed that throat swab had comparable sensitivity and specificity to nasopharyngeal swab RT-PCR.

A cross-sectional study from a meta-analysis [4] on the use of sputum RT-PCR as an alternative specimen to nasopharyngeal swab RT-PCR for the diagnosis of COVID-19 showed that sputum had lower sensitivity and specificity compared to nasopharyngeal swab RT-PCR.

All the above studies were assessed to have low risk of bias.

No studies were found that compared the sensitivity and specificity of bronchoalveolar lavage RT-PCR to nasopharyngeal swab RT-PCR. Hence, no conclusion and recommendation can be made for this clinical specimen.

CONSENSUS ISSUES

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

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

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

Should rapid antigen tests be used in the diagnosis of COVID-19 in clinically suspected patients?

RECOMMENDATION
We recommend the use of rapid antigen test in patients suspected of COVID-19 infection meeting all the following conditions: (Moderate quality of evidence; Strong recommendation) • Symptomatic AND • Early phase of infection </=7 days from onset of symptoms AND • Specific brands that have demonstrated sensitivity ≥80% and very high specificity (≥97-100%)

RECOMMENDATION
We recommend against the use of saliva as a specimen for rapid antigen test in patients suspected of COVID-19 infection. (Moderate quality of evidence; Strong recommendation) We recommend against the use of rapid antigen test alone in diagnosing COVID-19 in asymptomatic patients suspected of COVID-19 infection. (Moderate to high quality of evidence; Strong recommendation)

KEY FINDINGS

Moderate quality evidence from 30 [6-32] studies and 10 [33-44] evaluation reports showed that the pooled sensitivity of RAgTs is 72% (95% CI 64-78%; I2 = 95.77). The specificity of RAgTs remained consistently very high in all studies, with a pooled specificity of 99%. The sensitivity of the RAgTs varied widely across studies, with higher sensitivity estimates noted for specific test brands, symptomatic patients, and nasopharyngeal/nasal swab specimens.

CONSENSUS ISSUES

There were only two studies that used saliva as a specimen for rapid antigen test, which produced a pooled sensitivity of 17% (95% CI 13-23%) and a pooled specificity of 99% (95% CI 99-100%). Given that the current evidence shows very low sensitivity for saliva, it is necessary to qualify which specimen is used for a rapid antigen test.

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

RECOMMENDATION
We suggest the use of pooled RT-PCR testing in targeted* low-risk and low-prevalence populations using a pool size of 5 in individuals suspected of COVID-19 infection. (Moderate quality of evidence; Conditional recommendation) *For targeted populations refer to the list of Philippine Society of Pathologists and Department of Health

KEY FINDINGS

Twenty-one cross-sectional studies [43-63] (N = 220,253) were found that used pooled RT-PCR testing for SARS-CoV2. Six were diagnostic accuracy studies that compared pooled testing with individual testing, while 15 were pragmatic clinical validation studies of pooled testing that did individual testing of positive pools. Studies had

varying study population, use case, index test kit and pool size (5 to 16). Among the 6 diagnostic accuracy studies with a total of 5,987 participants, there was moderately high pooled sensitivity, 81% (95% CI 72-88%; I2=73.6%) (moderate certainty of evidence) and high pooled specificity, 99% (95% CI, 98-100%; I2=1.84%) (high certainty of evidence), given the positivity rate of 2.7 to 15% within the study populations. The positive predictive value based on 21 studies ranged from 67 to 100%. Resource savings in the number of test kits used ranged from 49 to 89%. Identified harms of pooled testing were delayed turnaround time for positive samples and laboratory errors. The overall risk of bias was low in 7 studies, 6 of which were diagnostic accuracy studies that contributed to pooled sensitivity and specificity, and low in 14 studies, mainly due to the lack of independent assessment between index and reference tests.

CONSENSUS ISSUES

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

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

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

KEY FINDINGS

Two cohort studies [64,65] involving 368 patients were found on the accuracy of repeat RT-PCR testing after an initial negative test to diagnose COVID-19 in symptomatic patients with high index of suspicion. The evidence was assigned a low quality rating due to serious risk of bias and serious imprecision. The sensitivity of repeat RT-PCR testing ranged from 0.83 (95% CI 0.75-0.90) to 0.85 (95% CI 0.62-0.97), which was approximately 15% higher compared to the sensitivity of a single RT-PCR test, which ranged from 0.68 (95% CI 0.58-0.76) to 0.70 (95% CI 0.46-0.88). Specificity of repeat testing was consistently very high (1.00, 95% CI 0.89-1.00).

CONSENSUS ISSUES

The recommendation applies only to symptomatic patients with high index of suspicion for COVID-19. Since the disease severity and the level of suspicion were not clearly defined in the studies, the level of suspicion may vary. Moreover, no specific

recommendation was made regarding the specific time interval between the initial and the repeat test as well as the frequency of repeat PCR tests.

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

RECOMMENDATION
We recommend using both clinical risk assessment and RT-PCR* to screen for COVID-19 among asymptomatic individuals scheduled for non-emergency surgery. (Very low quality of evidence; Strong recommendation) We recommend using both clinical risk assessment and Antigen-Rapid Diagnostic Test (Ag-RDT)** to screen for COVID-19 among asymptomatic individuals scheduled for non-emergency surgery when RT-PCR testing is not available or when prolonged turnaround time is a concern. (Very low quality of evidence; Strong recommendation) *Always use high-risk PPE regardless of RT-PCR or Ag-RDT test results in areas with prevalence of 1% or higher **Ag-RDT should have a Sn of 80% and Sp of 97%

KEY FINDINGS

Based on 1 cohort study [66] with very low quality, the diagnostic accuracy of clinical risk assessment alone in detecting COVID-19 compared to RT-PCR was found to be poor, with a sensitivity of 0.42 (95% CI 0.15-0.72) and a specificity of 0.85 (95% CI 0.76-0.92). Clinical risk assessment also resulted in more false negative and false positive results.

Very low certainty evidence from one economic modeling study [67] suggested that universal pre-endoscopy virus testing using Ag-RDT, standard RT-PCR, or rapid PCR combined with high-risk PPE use in all patients irrespective of test results was more cost-effective compared to no pre-endoscopy testing and no high risk PPE use, at an assumed prevalence rate of 1% or higher among asymptomatic individuals.

Patients for elective surgery who tested positive on any pre-operative COVID-19 tests or clinical assessment were at least 3 times more at risk of experiencing pulmonary complications or death compared to those who tested negative based on 1 cohort study [71] with very low quality. Delaying surgery to at least 7 weeks from a COVID-19 diagnosis also showed benefit. Given this data on the risks and benefits associated with a COVID-19 diagnosis as well as the high false negative rates of clinical risk assessment alone, clinical risk assessment would appear to cause more harm compared to more objective tests.

CONSENSUS ISSUES

Despite the very low quality of evidence, the majority voted to strongly recommend the use of both RT-PCR testing and clinical risk assessment to screen for COVID-19 among asymptomatic individuals scheduled for non-emergency surgery primarily due to the potential impact of a false negative result on the safety of the patient and health care staff involved as well as on the infection control processes of hospitals. RT-PCR was also recommended as it is now readily available in most hospitals. However, a panelist suggested that RT-PCR and PPE should only be conditionally recommended in areas with prevalence rates of 1% or higher.

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

Should antibody tests be used for COVID-19 seroprevalence studies among adult populations?

RECOMMENDATION
We suggest using antibody tests with high sensitivity and specificity (e.g., total antibody or IgG assays, ELISA, ECLIA) to determine COVID-19 seroprevalence among adults. (Very low quality of evidence; Conditional recommendation)

RECOMMENDATION
We recommend against using antibody tests detecting IgM to determine COVID-19 seroprevalence among adults (Very low quality of evidence; Strong recommendation) We recommend against using rapid antibody tests (e.g., LFIA) to determine COVID-19 seroprevalence among adults (Very low quality of evidence; Strong recommendation)

KEY FINDINGS

There is very low-quality evidence from 13 observational studies [68-82] (n = 24,082) on the use of antibody tests for COVID-19 seroprevalence studies. Four studies were at moderate risk of bias due to issues with defining the reference standard and susceptibility to recall bias; the rest were at low risk of bias. Heterogeneity across all studies was substantial. Sensitivity ranged from 14.4 to 100% while specificity ranged from 59.4 to 99.6%.

CONSENSUS ISSUES

Different recommendations were made in consideration of the different laboratory techniques and the antibodies detected when using antibody testing to detect COVID-19.

Majority voted for a strong recommendation against the use of antibody tests detecting IgM to determine COVID-19 seroprevalence among adults. This was due to the very low quality of evidence; IgM only suggests relatively recent infection. Others voted for a conditional recommendation because of the very low certainty of evidence resulting from the low sensitivity found for IgM antibody tests detecting IgM. One panelist opined that there may still be settings in which IgM antibody tests can be useful because of its good correlation with IgG tests based on local experience in a hospital setting. Lastly, the use of rapid antibody tests was not recommended due to the very low quality of evidence resulting from the significant heterogeneity detected across studies.

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

RECOMMENDATION
We recommend against the use of SARS-CoV-2 Ab testing to diagnose presumptive COVID-19 reinfection among symptomatic patients previously diagnosed with COVID-19* (Very low quality of evidence; Strong recommendation). *NAAT (RT-PCR) and Genomic sequencing are the recommended diagnostic tests to confirm COVID-19 reinfection.

KEY FINDINGS

There were no studies that directly assessed the accuracy of SARS-CoV-2 Ab in diagnosing presumptive COVID-19 reinfection, compared to RT-PCR as the reference standard. Only three retrospective observational studies [83-85] reported on the accuracy of SARS-CoV-2 IgG/IgM Ab in diagnosing COVID-19. There is very low certainty regarding these estimates due to very serious risk of bias concerns, imprecision, indirectness, and inconsistency.

The sensitivity of SARS-CoV-2 IgG/IgM ranged from 0.19 (95% CI 0.4- 0.46) to 0.89 (95% CI 0.71- 0.98) and specificity of 0.50 (95% CI 0.01-0.99) to 1.00 (95% CI 0.89-1.00). Subgroup analysis suggested that the sensitivity of Ab testing was low under the following conditions: (a) when used within 0-15 days from symptom onset, (b) Ab tests that assess IgM, (c) using LFIA technique. Specificity was consistently high (>89%) regardless of the type of antibody detected or if either LFIA or CLIA techniques were done. However, specificity was high only if the test was performed more than 16 days from symptom onset.

CONSENSUS ISSUES

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

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

RECOMMENDATION
We recommend the use of symptom-based strategy for the discontinuation of isolation and return to work clearance of the following: 1. Asymptomatic adults who are not severely immunocompromised if they fulfill the following (Very low quality of evidence; Strong recommendation): ● remained asymptomatic throughout their infection ● 10 days have passed from the first positive viral diagnostic test (RT-PCR or rapid antigen) 2. Adults who had mild to moderate COVID-19 who are not severely immunocompromised if they fulfill the following (Very low quality of evidence; Strong recommendation): ● Afebrile for at least 24 hours without use of antipyretic medications ● Respiratory symptoms have improved (cough, shortness of breath) ● 10 days have passed from symptom onset 3. Adults who had severe to critical COVID-19 who are not severely immunocompromised if they fulfill the following (Very low quality of evidence; Strong recommendation): ● Afebrile for at least 24 hours without use of antipyretic medications ● Respiratory symptoms have improved (cough, shortness of breath) ● 21 days have passed from symptom onset *A repeat negative RT-PCR test is no longer needed for discharge of immunocompetent patients with probable or confirmed COVID-19 regardless of severity, because, in most cases, it results in prolonged isolation of patients who continue to shed detectable SARS-CoV-2 RNA but are no longer infectious.*

RECOMMENDATION
We suggest the use of test-based strategy using RT-PCR for the discontinuation of isolation and return to work clearance of the following: (Very low quality of evidence; Conditional recommendation) 1. Severely immunocompromised adults 2. Health care workers if they fulfill the following:

- Afebrile for at least 24 hours without use of antipyretic medications
- Respiratory symptoms have improved (cough, shortness of breath)
- With at least 1 negative RT-PCR test of a respiratory specimen

Severely immunocompromised: Ongoing chemotherapy for cancer, or within one year from receiving a hematopoietic stem cell or solid organ transplant; untreated HIV infection with CD4 count < 200, combined primary immunodeficiency disorder, and receipt of prednisone >20mg/day for more than 14 days, may cause a higher degree of immunocompromised and require actions such as lengthening the duration of work restrictions. Other less immunocompromising conditions include advanced old age, DM, CKD. The degree of immunocompromise is determined by the health care provider, and preventive actions are adapted to each individual and situation.

KEY FINDINGS

Evidence for this review question came from 5 observational studies [86-90] and 2 case series. Very low certainty of evidence suggests that a test-based strategy is associated with higher false negative rates after 9 days from symptom onset, higher excess costs and length of stay for hospitalized patients, and greater lost work days. For workers who have recovered from mild-to-moderate COVID-19, a symptom-based strategy may be indicated as replication competent virus has not been recovered among these groups after 10 days following symptom onset. Test-based strategies may be appropriate for workers who have recovered from severe COVID-19 and/or with immunocompromised states, as data on infectivity show prolonged viral shedding that can last for several months from symptom onset.

CONSENSUS ISSUES

Considerations related to resource implications, cost-effectiveness, and the perceived balance of benefits and harms of test-based strategies were the main reasons for recommending the use of symptom-based strategy as a method to guide decisions on return to work. These recommendations were made despite the very low quality of evidence presented.

Should Chest X-Ray be used to diagnose COVID-19 among suspected patients?

RECOMMENDATION
We suggest against the use of chest x-ray to diagnose COVID-19 infection among asymptomatic individuals (Very low quality of evidence; Conditional recommendation)

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

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

KEY FINDINGS

CXR typically shows bilateral and diffuse involvement with ground-glass opacities and consolidation in the lung periphery and is only moderately sensitive and moderately specific in the diagnosis of COVID-19 in suspected cases. Very low certainty evidence from 9 observational studies showed that the sensitivity of CXR ranged from 56% to 94%, while its specificity ranged from 60% to 89%. The pooled sensitivity for CXR was 74% (95%CI 59 to 85%) while pooled specificity was 76% (95%CI 67 to 83%). Significant heterogeneity was observed across studies, possibly because of a number of factors including patients' characteristics, timing of CXR in relation to symptom onset, definition of index test positivity and experience of CXR readers.

CONSENSUS ISSUES

The use of chest X-ray to diagnose COVID-19 infection among asymptomatic individuals was not suggested due to the very low quality of evidence related to its diagnostic accuracy. High heterogeneity across studies was also observed and the studies reviewed did not perform subgroup analysis according to severity of COVID-19. However, chest x-ray is still suggested for specific instances as there would be a high yield in detecting significant pulmonary abnormalities in these settings.

Should Chest CT Scan be used to diagnose COVID-19 among suspected patients?

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

RECOMMENDATION
If RT-PCR test is not available, we suggest using non-contrast chest CT scan for symptomatic patients suspected of having COVID-19 to guide early triage and management under the following conditions: (Very low quality of evidence; Conditional recommendation) • Mild COVID-19 patients who are at risk for progression • Moderate to severe COVID-19 patients

KEY FINDINGS

There is very low-quality evidence from 42 observational studies on the use of CT scans in diagnosing COVID-19 infection. Uncertainty arises mainly from the unclear reporting of the threshold and variations in the reporting of CT scan findings. Heterogeneity across studies was also substantial. The sensitivity ranged from 84.3 to 90.3%, and the specificity ranged from 74.2 to 83.9%.

CONSENSUS ISSUES

There were no issues raised by the panel.

Should Lung Ultrasound be used to diagnose COVID-19 among suspected patients?

RECOMMENDATION
We suggest against the use of lung ultrasound alone in diagnosing patients with suspected COVID-19 infection. (Low quality of evidence, Conditional recommendation)

KEY FINDINGS

Moderate quality evidence from 8 studies [90-98] showed that the pooled sensitivity of lung ultrasound (LUS) is 88% (95% CI 79-93%; I2 = 70.18) and the pooled specificity of LUS is 63% (95% CI 47-77%; I2 = 89.64). In these studies, the sensitivity of lung ultrasound ranged from 68 to 97% while the specificity ranged from 21 to 89%. Overall, lung ultrasound was found to be sensitive but not specific for the diagnosis of COVID-19.

CONSENSUS ISSUES

Majority of the panelists voted for a conditional recommendation against lung ultrasound alone due to the low quality of evidence related to its diagnostic accuracy. However, other panelists argued that a strong recommendation should be made against the use of lung ultrasound alone in diagnosing suspected COVID-19 patients since it has not been found to be as accurate as the current gold standard, which is RT-PCR. Lung ultrasound is still considered a valuable prognostic tool to assess clinical deterioration as it can predict the presence of abnormalities in the lung findings of COVID-19 patients.

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

RECOMMENDATION
<u>To guide the decision to admit patients with COVID-19 to the hospital:</u>

We suggest the use of the following scoring systems:

- Age, BUN, number of Comorbidities, CRP, SpO2/FiO2 ratio, Platelet count, Heart rate (ABC2-SPH) risk score,
- Confusion Urea Respiration Blood Pressure (CURB-65) severity score,
- Risk Stratification in the Emergency Department in Acutely Ill Older Patients (RISE-UP) score, and
- Rapid Emergency Medicine Score (REMS).

(Low quality of evidence; Conditional recommendation)

RECOMMENDATION
There is insufficient evidence to recommend the use of 4C Mortality Score, COVID Outcome Prediction in the Emergency Department (COPE) model, and Quick Sepsis-related Organ Failure Assessment (qSOFA) score. (Very low quality of evidence)

RECOMMENDATION
To guide in the expectant monitoring of hospitalized patients: We suggest the use of the 4C Deterioration model. (Low quality of evidence; Conditional recommendation)

RECOMMENDATION
There is insufficient evidence to recommend the use of Modified Early Warning Score (MEWS) and National Early Warning Score 2 (NEWS2). (Very low quality of evidence)

KEY FINDINGS

Thirty-three cohort studies [99-131] on prognostic models for clinical deterioration and mortality of individuals with COVID-19 were found. Most of the studies (n = 28) were assessed to have high risk of bias due to issues in participant selection and analysis. There were four (4) studies with unclear, and three (3) with low, risk of bias.

There are a few models that have been validated in more than one population. The 4C mortality score, ABC2-SPH, CURB-65, REMS, and RISE UP models have fair to good prediction of mortality for inpatients, while qSOFA has poor to fair prediction. The MEWS model has poor prediction of clinical deterioration while NEWS2 has inconsistent prediction (poor to good). The 4C deterioration score, which has been investigated in only one study but was found to have low risk of bias, has fair predictive ability for clinical deterioration. None of these models has been validated in the Philippine population. The QCOVID model for mortality, while with high certainty of evidence, is specific for use in England and needs to modified to and validated in the local setting before any recommendations can be made.

CONSENSUS ISSUES

There was a high certainty of evidence that the QCOVID model can predict mortality from COVID-19. However, there was an issue on applicability as some of the components of this model (i.e., geographic region and Townsend deprivation quintile) is specific for the general population of England. Hence, its use warrants reconsideration of the component prognostic factors and validation in the Philippine setting before any recommendations can be made.

It was noted that the qSOFA model was already being used by some hospitals and centers in the Philippines. Clinicians should be guided on its use as it was found to have a very low quality of evidence for prediction of mortality of inpatients. There are other prognostic models such as the CURB-65, RISE-UP and REMS which are pre-existing models designed for specific patient populations and the ABC2-SPH model which has a good discrimination performance. All of these were found to have better quality of evidence compared with qSOFA. The 4C Mortality score and COPE model were also found to have a very low quality of evidence to predict mortality. Further, it was observed that there was a decrease in the discriminatory ability of the COPE model when externally validated. In terms of clinical deterioration, the 4C deterioration score was found to have a better predictive ability and quality of evidence compared to MEWS and NEWS2 model. Like the QCOVID model, these prognostic models also need to be locally validated but the components of these models can be easily obtained especially in the hospital setting, making the validation process easier.

Should breath test be used to detect COVID-19 infection?

RECOMMENDATION
There is insufficient evidence to recommend the use of breath test in detecting COVID-19 infection (Moderate quality of evidence)

KEY FINDINGS

Based on one prospective population-based [132] diagnostic accuracy study with high methodological quality, breath test analysis showed high sensitivity and specificity in detecting COVID-19 infection among symptomatic and asymptomatic individuals in the Netherlands. Further studies are needed to validate the findings and to recommend the use of breath test analysis as a real-time diagnostic modality to detect COVID-19 infection in the general population.

CONSENSUS ISSUES

Despite the high quality of evidence, no recommendation was made as there was only one study found that also used a technology that is not currently accessible.

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

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

KEY FINDINGS

Very low quality evidence from 25 retrospective [133-154] and prospective observational studies [155-157] revealed varying cut-off values of lactate dehydrogenase (LDH), C-reactive protein (CRP), and ferritin producing heterogenous effect estimates for predicting mortality, severity on admission, and disease progression in hospitalized COVID-19 patients.

CONSENSUS ISSUES

It was noted that varying cut-off values of LDH, CRP and Ferritin to predict mortality and severity of disease were used in the studies included in this review, hence, no specific levels can be recommended to guide initiation of immunotherapy for COVID-19 patients.

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

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

KEY FINDINGS

We found a total of 25 observational studies [158-179] on the association between D-dimer and the outcomes of mortality, worsening severity, or thromboembolism. In general, the included studies showed increased odds of in-hospital mortality (OR 5.57 [95% CI 2.74, 11.31), worsening severity (critical illness (OR 1.91-2.58); disease progression (HR 2.84 [95% CI 2.10, 3.85]), or need for mechanical ventilation (HR 3.28 [95% CI 1.07, 10.10])), and thromboembolism (OR 5.61 [95% CI 3.97, 7.94]), with higher D-dimer levels across different COVID-19 severities. However, most studies yielded imprecise effect measures, due to the small number of event outcomes. Most of the studies were found to have serious risk of bias, with issues on data censoring, incomplete laboratory data, and unclear adequacy of follow-up rates. Differences in D-dimer cut-offs, definitions of critical illness and disease progression, and severities of COVID-19 in the study population contributed to the heterogeneity across studies. While the predictive ability of D-dimer for mortality appeared to be fair to good, prediction of worsening severity or progression of disease is inconsistent.

CONSENSUS ISSUES

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

References

1. Dixon BE, Wools-Kaloustian K, Fadel WF, et al. Symptoms and symptom clusters associated with SARS-CoV-2 infection in community-based populations: Results from a statewide epidemiological study. medRxiv [Internet]. 2020;e00146. Available from: https://doi.org/10.1016/j.sciaf.2019.e00146
2. Kimball A, Hatfield KM, Arons M, et al. Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility —. Morb Mortal Wkly Rep Summ CDC. 2020;69(13):377–81.
3. Agulló V, Fernández-González M, Ortiz de la Tabla V, et al. Evaluation of the rapid antigen test Panbio COVID-19 in saliva and nasal swabs in a population-based point-of-care study. J Infect. 2020 Jan 1. Available from: https://doi.org/10.1016/j.jinf.2020.12.007
4. Albert E, Torres I, Bueno F, et al. Field evaluation of a rapid antigen test (Panbio™ COVID-19 Ag Rapid Test Device) for COVID-19 diagnosis in primary healthcare centres. Clin Microbiol Infect. 2020.
5. Cerutti F, Burdino E, Milia M, et al. Urgent need of rapid tests for SARS CoV-2 antigen detection: Evaluation of the SD-Biosensor antigen test for SARS-CoV-2. J Clin Virol. 2020;132:104654.
6. Chaimayo C, Kaewnaphan B, Tanlieng N, et al. Rapid SARS-CoV-2 antigen detection assay in comparison with real-time RT-PCR assay for laboratory diagnosis of COVID-19 in Thailand. Virol J 17, 177. 2020. Available from: https://doi.org/10.1186/s12985-020-01452-5
7. Ciotti M, Maurici M, Pieri M, Andreoni M, Bernardini S. Performance of a rapid antigen test in the diagnosis of SARS-CoV-2 infection. Journal of Medical Virology. 2021;.
8. Diao B, Wen K, Zhang J, et al. Accuracy of a nucleocapsid protein antigen rapid test in the diagnosis of SARS-CoV-2 infection. Clin Microbiol Infect. 2021;27(2):289.e1-289.e4.
9. Favresse J, Gillot C, Oliveira M, et al. Head-to-Head Comparison of Rapid and Automated Antigen Detection Tests for the Diagnosis of SARS-CoV-2 Infection. J Clin Med. 2021;10(2):265.
10. Gremmels H, Winkel B, Schuurman R, et al. Real-life validation of the Panbio™ COVID-19 antigen rapid test (Abbott) in community-dwelling subjects with symptoms of potential SARS-CoV-2 infection. EClinicalMedicine. 2021;31:100677.
11. Herrera V, Hsu V, Adewale A, et al. Testing Healthcare Workers Exposed to COVID19 using Rapid Antigen Detection. 2020.
12. Hirotsu Y, Maejima M, Shibusawa M, et al. Comparison of automated SARS-CoV-2 antigen test for COVID-19 infection with quantitative RT-PCR using 313 nasopharyngeal swabs, including from seven serially followed patients. Int J Infect Dis. 2020;99:397-402.
13. James A, Gulley T, Kothari A, Holder K, Garner K, Patil N. Performance of the BinaxNOW coronavirus disease 2019 (COVID-19) Antigen Card test relative to the severe acute respiratory coronavirus virus 2 (SARS-CoV-2) real-time reverse transcriptase polymerase chain reaction (rRT-PCR) assay among symptomatic and asymptomatic healthcare employees. Infection Control & Hospital Epidemiology. 2021:1-3.
14. Nagura-Ikeda M, Imai K, Tabata S, et al. Clinical Evaluation of Self-Collected Saliva by Quantitative Reverse Transcription-PCR (RT-qPCR), Direct RT-qPCR, Reverse Transcription–Loop-Mediated Isothermal Amplification, and a Rapid Antigen Test To Diagnose COVID-19. J Clin Microbiol. 2020;58(9).
15. Krüttgen A, Cornelissen C, Dreher M, Hornef M, Imöhl M, Kleines M. Comparison of the SARS-CoV-2 Rapid antigen test to the real star Sars-CoV-2 RT PCR kit. J Virol Methods. 2021;288:114024.
16. Lambert-Niclot S, Cuffel A, Le Pape S, et al. Evaluation of a Rapid Diagnostic Assay for Detection of SARS-CoV-2 Antigen in Nasopharyngeal Swabs. J Clin Microbiol. 2020;58(8).
17. Linares M, Pérez-Tanoira R, Carrero A, et al. Panbio antigen rapid test is reliable to diagnose SARS-CoV-2 infection in the first 7 days after the onset of symptoms. J Clin Virol. 2020;133:104659.
18. Mak G, Cheng P, Lau S, et al. Evaluation of rapid antigen test for detection of SARS-CoV-2 virus. J Clin Virol. 2020;129:104500.

19. Mertens P, De Vos N, Martiny D, et al. Development and Potential Usefulness of the COVID-19 Ag Respi-Strip Diagnostic Assay in a Pandemic Context. Frontiers in Medicine. 2020;7.
20. Möckel M, Corman V, Stegemann M, et al. SARS-CoV-2 antigen rapid immunoassay for diagnosis of COVID-19 in the emergency department. Biomarkers. 2021:1-10.
21. Nalumansi A, Lutalo T, Kayiwa J, et al. Field evaluation of the performance of a SARS-CoV-2 antigen rapid diagnostic test in Uganda using nasopharyngeal samples. Int J Infect Dis. 2021;104:282-286.
22. Osterman A, Baldauf H, Eletreby M, et al. Evaluation of two rapid antigen tests to detect SARS-CoV-2 in a hospital setting. Medical Microbiology and Immunology. 2021.
23. Pilarowski G, Marquez C, Rubio L, et al. Field performance and public health response using the BinaxNOW TM Rapid SARS-CoV-2 antigen detection assay during community-based testing. Clinical Infectious Diseases. 2020.
24. Porte L, Legarraga P, Vollrath V, Aguilera X, Munita J, Araos R et al. Evaluation of a novel antigen-based rapid detection test for the diagnosis of SARS-CoV-2 in respiratory samples. Int J Infect Dis. 2020;99:328-333.
25. Pray IW, Ford L, Cole D, et al. Performance of an Antigen-Based Test for Asymptomatic and Symptomatic SARS-CoV-2 Testing at Two University Campuses — Wisconsin, September–October 2020. MMWR Morb Mortal Wkly Rep 2021;69:1642–1647. doi: http://dx.doi.org/10.15585/mmwr.mm695152a3external icon.
26. Prince-Guerra J, Almendares O, Nolen L, et al. Evaluation of Abbott BinaxNOW Rapid Antigen Test for SARS-CoV-2 Infection at Two Community-Based Testing Sites — Pima County, Arizona, November 3–17, 2020. MMWR Morbidity and Mortality Weekly Report. 2021;70(3):100-105.
27. Rottenstreich A, Zarbiv G, Kabiri D, et al. Rapid antigen detection testing for universal screening for severe acute respiratory syndrome coronavirus 2 in women admitted for delivery. Am J Obstet Gynecol. 2021.
28. Scohy A, Anantharajah A, Bodéus M, Kabamba-Mukadi B, Verroken A, Rodriguez-Villalobos H. Low performance of rapid antigen detection test as frontline testing for COVID-19 diagnosis. J Clin Virol. 2020;129:104455.
29. Torres I, Poujois S, Albert E, Colomina J, Navarro D. Evaluation of a rapid antigen test (Panbio™ COVID-19 Ag rapid test device) for SARS-CoV-2 detection in asymptomatic close contacts of COVID-19 patients. Clinical Microbiology and Infection. 2021.
30. Turcato G, Zaboli A, Pfeifer N, et al. Clinical application of a rapid antigen test for the detection of SARS-CoV-2 infection in symptomatic and asymptomatic patients evaluated in the emergency department: A preliminary report. J Infect. 2020.
31. Weitzel T, Legarraga P, Iruretagoyena M, et al. Comparative evaluation of four rapid SARS-CoV-2 antigen detection tests using universal transport medium. Travel Medicine and Infectious Disease. 2021;39:101942.
32. Young S, Taylor S, Cammarata C, et al. Clinical Evaluation of BD Veritor SARS-CoV-2 Point-of-Care Test Performance Compared to PCR-Based Testing and versus the Sofia 2 SARS Antigen Point-of-Care Test. J Clin Microbiol. 2020;59(1).
33. FIND Evaluation of Abbott Panbio COVID-19 Ag Rapid Test Device External Report [Internet]. Finddx.org. 2021 [cited 19 February 2021]. Available from: https://www.finddx.org/wp-content/upoads/220/12/Panbio_Ag-Public-Report_v2.1.pdf CD
34. FIND Evaluation of Abbott Panbio COVID-19 Ag Rapid Test Device (NASAL) External Report [Internet]. Finddx.org. 2021 [cited 19 February 2021]. Available from: https://www.finddx.org/wp-content/uploads/2021/02/Panbio_Nasal_Ag-Public-Report_20210211v1.pdf E
35. FIND Evaluation of Bionote, Inc. NowCheck COVID-19 Ag Test External Report [Internet]. Finddx.org. 2021 [cited 19 February 2021]. Available from: https://www.finddx.org/wp-content/uploads/2020/12/Bionote_Ag-INTERIM-Public-Report_20201210-v1-4.pdf G
36. FIND Evaluation of Coris BioConcept COVID-19 Ag Respi-Strip External Report [Internet]. Finddx.org. 2021 [cited 19 February 2021]. Available from: https://www.finddx.org/wp-content/uploads/2020/12/Coris-RespiStrip-Ag_Public-Report_20201210-v1-2.pdf H

37. FIND Evaluation of Joysbio (Tianjin) Biotechnology Co., Ltd. SARS-CoV-2 Antigen Rapid Test Kit (Colloidal Gold) External Report [Internet]. Finddx.org. 2021 [cited 19 February 2021]. Available from: https://www.finddx.org/wp-content/uploads/2021/02/Joysbio_Ag-Public-Report_v1_20210211.pdf I
38. FIND Evaluation of RapiGEN Inc. BIOCREDIT COVID-19 Ag External Report [Internet]. Finddx.org. 2021 [cited 19 February 2021]. Available from: https://www.finddx.org/wp-content/uploads/2020/12/Rapigen_Ag-Public-Report_20201210-v2-1.pdf JK
39. FIND Evaluation of SD Biosensor, Inc. STANDARD™ F COVID-19 Ag FIA External Report [Internet]. Finddx.org. 2021 [cited 19 February 2021]. Available from: https://www.finddx.org/wp-content/uploads/2020/12/STANDARD_F_Ag-Public-Report_20201210-v2-1.pdf AB
40. FIND Evaluation of SD Biosensor, Inc. STANDARD Q COVID-19 Ag Test External Report [Internet]. Finddx.org. 2021 [cited 19 February 2021]. Available from: https://www.finddx.org/wp-content/uploads/2020/12/SDQ-Ag-Public-Report_20201210-v2-1.pdf LMN
41. FIND Evaluation of SD Biosensor, Inc. STANDARD Q COVID-19 Ag Test, nasal swab External Report [Internet]. Finddx.org. 2021 [cited 19 February 2021]. Available from: https://www.finddx.org/wp-content/uploads/2021/01/SDQ_Nasal_Ag-Public-Report_20210119v1.pdf O
42. FIND Evaluation of Shenzhen Bioeasy Biotechnology Co. Ltd. 2019-nCoV Ag Rapid Test Kit (Fluorescence) External Report [Internet]. Finddx.org. 2021 [cited 19 February 2021]. Available from: https://www.finddx.org/wp-content/uploads/2021/01/Bioeasy-Ag_Public-Report_20210119-V1.0.pdf Q
43. Centers for Disease Control and Prevention. Interim Guidance for Use of Pooling Procedures in SARS-CoV-2 Diagnostic, Screening, and Surveillance Testing. 2020 Oct 23. Available from: https://www.cdc.gov/coronavirus/2019-ncov/lab/pooling-procedures.html.
44. Christoff AP, Cruz GNF, Sereia AFR, et al. Swab Pooling for Large-Scale RT-qPCR Screening of SARS-CoV-2. SSRN Electron J. 2020.
45. de Salazar A, Aguilera A, Trastoy R, et al. Sample pooling for SARS-CoV-2 RT-PCR screening. Clin Microbiol Infect. 2020;26.
46. Lüsebrink J, Schildgen V, Schildgen O. Pooling is an insufficient strategy to avoid health care staff to patient transmission of SARS-CoV-2. Infect Control Hosp Epidemiol. 2020;1–3.
47. Singh AK, Nema RK, Joshi A, et al. Evaluation of pooled sample analysis strategy in expediting case detection in areas with emerging outbreaks of COVID-19: A pilot study. PLoS One [Internet]. 2020;15(9 September 2020):1–8. Available from: http://dx.doi.org/10.1371/journal.pone.0239492
48. Wang H, Hogan CA, Miller JA, et al. Performance of Nucleic Acid Amplification Tests for Detection of Severe Acute Respiratory Syndrome Coronavirus 2 in Prospectively Pooled Specimens. Emerg Infect Dis [Internet]. 2020;27(1). Available from: http://www.ncbi.nlm.nih.gov/pubmed/33183494
49. Abdalhamid B, Bilder CR, McCutchen EL, Hinrichs SH, Koepsell SA, Iwen PC. Assessment of Specimen Pooling to Conserve SARS CoV-2 Testing Resources. Am J Clin Pathol. 2020;153(6):715–8.
50. Hogan CA, Sahoo MK, Pinsky BA. Sample Pooling as a Strategy to Detect Community Transmission of SARS-CoV-2: Letter. JAMA. 323(1967–9).
51. Lo R, Barrientos A, Espiritu B, et al. An Evaluation of Pooling Strategies for qRT-PCR Testing for SARS-CoV-2 Infection : A pragmatic multi-site parallel operational study by The Philippine Society of Pathologists, Inc. Philipp J Pathol. 2020;5(2):1–22.
52. Mastrianni D, Falivena R, Brooks T, et al. Pooled Testing for SARS-CoV-2 in Hospitalized Patients. J Hosp Med. 2020;15(9):538–9.
53. Pasomsub E, Watcharananan SP, Watthanachockchai T, et al. Saliva sample pooling for the detection of SARS-CoV-2. J Med Virol [Internet]. 2020;0–3. Available from: http://dx.doi.org/10.1002/jmv.26460

54. Health Technology Assessment Department of Health. Pooled Testing for COVID-19 [Internet]. [cited 2020 Jan 1]. Available from: https://hta.doh.gov.ph/2020/12/11/pooled-testing-for-screening-and-monitoring-covid-19/
55. Philippine DOH. Use of Pooled Testing for the Diagnosis, Screening and Surveillance of COVID-19: Rapid Review V 4.0.
56. Alizad-Rahvar AR, Vafadar S, Totonchi M, Sadeghi M. False-negative mitigation in group testing for COVID-19 screening. medRxiv. 2020;1–18.
57. Cesselli D, Bulfoni M, Marzinotto S, et al. Implementation and validation of a pooling strategy for a sustainable screening campaign for the presence of SARS-CoV-2. medRxiv [Internet]. 2020;2020.08.28.20174946. Available from: https://doi.org/10.1101/2020.08.28.20174946
58. Mohanty S, Ravindra A, Gupta K, et al. Intricacies in characterizing positivity in pooled sample testing for SARS-CoV-2. J Med Virol. 2020;0–2.
59. Gavars D, Perminovs D, Stasulans J, et al. Saliva as testing sample for SARS-CoV-2 detection by RT-PCR in low prevalence community setting [Preprint]. Medrxiv [Internet]. 2020;2020.10.20.20216127. Available from: http://medrxiv.org/content/early/2020/10/21/2020.10.20.20216127.abstract
60. Chhikara K, Kanta P, Ghosh A, Prakash RC, Goyal K, Singh MP. Validation of SARS CoV-2 detection by real-time PCR in matched pooled and deconvoluted clinical samples before and after nucleic acid extraction: a study in tertiary care hospital of North India. Diagn Microbiol Infect Dis. 2020;99(January):115206.
61. Li H, Sun K, Persing DH, Tang Y-W, Shen D. Real-time Screening of Specimen Pools for Coronavirus Disease 2019 (COVID-19) Infection at Sanya Airport, Hainan Island, China. Clin Infect Dis. 2020;2019(Figure 1):2019–21.
62. Chong BSW, Tran T, Druce J, Ballard SA, Simpson JA, Catton M. Sample pooling is a viable strategy for SARS-CoV-2 detection in low-prevalence settings. Pathology. 2020;52(7):796–800.
63. Kim SY, Lee J, Sung H, et al. Pooling upper respiratory specimens for rapid mass screening of COVID-19 by real-time RT-PCR. Emerg Infect Dis. 2020;26(10):2469–72.
64. Ai J, Gong J, Xing L, et al. 2020. "Analysis of Factors Associated Early Diagnosis in Coronavirus Disease 2019 (COVID-19)." MedRxiv. medRxiv. doi:10.1101/2020.04.09.20059352.
65. Ai J, Zhang H, Xu T, et al. 2020. "Optimizing Diagnostic Strategy for Novel Coronavirus Pneumonia, a Multi-Center Study in Eastern China." MedRxiv. medRxiv. doi:10.1101/2020.02.13.20022673.
66. Gruskay JA, Dvorzhinskiy A, Konnaris MA, et al. Universal Testing for COVID-19 in Essential Orthopaedic Surgery Reveals a High Percentage of Asymptomatic Infections. J Bone Joint Surg Am. 2020 Aug 19;102(16):1379-1388. doi: 10.2106/JBJS.20.01053. PMID: 32516279.
67. Ebigbo A, Römmele C, Bartenschlager C, et al. Cost-effectiveness analysis of SARS-CoV-2 infection prevention strategies including pre-endoscopic virus testing and use of high risk personal protective equipment. Endoscopy. 2021 Feb;53(2):156-161. doi: 10.1055/a-1294-0427. Epub 2020 Oct 20. PMID: 33080647; PMCID: PMC7869042.
68. Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. COVIDSurg Collaborative. Anaesthesia. Published 09 Mar 2021. Available from: https://associationofanaesthetists-publications.onlinelibrary.wiley.com/action/doSearch?ContribAuthorStored=COVIDSurg+Collaborative). https://doi.org/10.1111/anae.15458
69. Mortgat L, Barbezange C, Fischer N, et al. SARS-CoV-2 Prevalence and Seroprevalence among Healthcare Workers in Belgian Hospitals: Baseline Results of a Prospective Cohort Study. medRxiv. 2020.
70. Jespersen S, Mikkelsen S, Greve T, et al. Severe Acute Respiratory Syndrome Coronavirus 2 Seroprevalence Survey Among 17 971 Healthcare and Administrative Personnel at Hospitals, Prehospital Services, and Specialist Practitioners in the Central Denmark Region. Clin Infect Dis. 2020;(Xx Xxxx):1–8.
71. Ko JH, Lee JY, Kim HA, et al. Serologic Evaluation of Healthcare Workers Caring for COVID-19 Patients in the Republic of Korea. Front Microbiol. 2020;11(November):1–6.

72. Mulchandani R, Taylor-Philips S, Jones HE, et al. Self assessment overestimates historical COVID-19 disease relative to sensitive serological assays: Cross sectional study in UK key workers. medRxiv. 2020.
73. Robinson AV, Weaving G, Philips BJ, Eziefula AC, Shipman KE, Chevassut T. Real-world experience of SARS-CoV-2 antibody assays in UK healthcare workers. 2021;21(3):1–6.
74. Shields AM, Faustini SE, Perez-Toledo M, et al. Serological responses to SARS-CoV-2 following non-hospitalised infection: Clinical and ethnodemographic features associated with the magnitude of the antibody response. medRxiv. 2020.
75. Afzal N, Tariq N, Raza S, Shakeel D. Diagnostic Accuracy of Electro-Chemiluminescence Immunoassay Anti-SARS-CoV-2 Serological Test. Cureus. 2021;13(1):1–6.
76. Flannery DD, Gouma S, Dhudasia MB, et al. SARS-CoV-2 seroprevalence among parturient women. medRxiv. 2020;5709(July):1–9.
77. Fong D, San Nicolò KO, Alber M, Mitterer M. Evaluating the longitudinal effectiveness of preventive measures against COVID-19 and seroprevalence of IgG antibodies to SARS-CoV-2 in cancer outpatients and healthcare workers. Wien Klin Wochenschr. 2021.
78. Ige O, Buru AS, Lamido TZ, et al. Evaluation of SARS-CoV2 antibody Rapid Diagnostic Test kits (RDTs) and Real Time-Polymerase Chain Reaction (Rt-PCR) for COVID-19 Diagnosis in Kaduna, Nigeria. 1995;2196482:1–24.
79. Gonzalez JM, Santos-Barbosa JC, Jaller C, et al. Seroreactivity to SARS-CoV-2 in individuals attending a university campus in Bogotá Colombia. medRxiv. 2020;1–13.
80. Percivalle E, Cambiè G, Cassaniti I, et al. Prevalence of SARS-CoV-2 specific neutralising antibodies in blood donors from the Lodi Red Zone in Lombardy, Italy, as at 06 April 2020. Eurosurveillance [Internet]. 2020;25(24):1–5. Available from: http://dx.doi.org/10.2807/1560-7917.ES.2020.25.24.2001031
81. Santarelli A, Lalitsasivimol D, Bartholomew N, et al. The seroprevalence of SARS-CoV-2 in a rural southwest community. J Am Osteopath Assoc [Internet]. 2021;121(2):199–210. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33567087
82. Silva VO, de Oliveira EL, Castejon MJ, et al. Prevalence of antibodies against SARS-CoV-2 in professionals of a public health laboratory at São Paulo, SP, Brazil. medRxiv. 2020.
83. Jin Y, Wang M, Zuo Z, Fan C, Ye F, Cai Z, et al. Diagnostic value and dynamic variance of serum antibody in coronavirus disease 2019. Int J Infect Dis. 2020 May; 94:49-52. doi: 10.1016/j.ijid.2020.03.065. Epub 2020 Apr 3. PMID: 32251798; PMCID: PMC7194885.
84. Liu Ying, Liu Yue-ping, Diao Bo, Ren Feifei, Wang Yue, Ding Jinya, et al. Diagnostic Indexes of a Rapid IgG/IgM Combined Antibody Test for SARS-CoV-2 medRxiv 2020.03.26.20044883; doi: https://doi.org/10.1101/2020.03.26.20044883
85. Paradiso A, De Summa S, Loconsole D, Procacci V, Sallustio A, Centrone F, et al. Clinical meanings of rapid serological assay in patients tested for SARS-Co2 RT-PCR medRxiv 2020.04.03.20052183; doi: https://doi.org/10.1101/2020.04.03.20052183
86. Young B, Ong S, Ng L, Anderson D, Chia W, Chia P et al. Viral Dynamics and Immune Correlates of Coronavirus Disease 2019 (COVID-19) Severity. Clinical Infectious Diseases [Internet]. 2020 [cited 27 March 2021];. Available from: https://pubmed.ncbi.nlm.nih.gov/32856707/
87. Wu C, Glass S, Demars S, Tulloch-Palomino L, Wander P. Estimated excess acute-care length of stay and extra cost of testing-based versus symptom-based isolation strategies among veterans hospitalized with coronavirus disease 2019 (COVID-19) discharging to a congregate setting. Infection Control & Hospital Epidemiology [Internet]. 2020 [cited 27 March 2021];42(3):356-358. Available from: https://www.cambridge.org/core/journals/infection-control-and-hospital-epidemiology/article/estimated-excess-acutecare-length-of-stay-and-extra-cost-of-testingbased-versus-symptombased-isolation-strategies-among-veterans-hospitalized-with-coronavirus-disease-2019-covid19-discharging-to-a-congregate-setting/87C02B0D24CAA9E73F7197A327225E9D
88. Shenoy E, West L, Hooper D, Sheehan R, Hashimoto D, Boukus E et al. Healthcare worker infection with SARS-CoV-2 and test-based return to work. Infection Control & Hospital Epidemiology [Internet]. 2020 [cited 27 March 2021];41(12):1464-1466. Available from:

https://www.cambridge.org/core/journals/infection-control-and-hospital-epidemiology/article/healthcare-worker-infection-with-sarscov2-and-testbased-return-to-work/434FE26D6FAF17B2E831E4618D86A272
89. Bullard J, Dust K, Funk D, Strong J, Alexander D, Garnett L et al. Predicting Infectious Severe Acute Respiratory Syndrome Coronavirus 2 From Diagnostic Samples. Clinical Infectious Diseases [Internet]. 2020 [cited 27 March 2021];71(10):2663-2666. Available from: https://pubmed.ncbi.nlm.nih.gov/32442256/
90. van Kampen J, van de Vijver D, Fraaij P, Haagmans B, Lamers M, Okba N et al. Duration and key determinants of infectious virus shedding in hospitalized patients with coronavirus disease-2019 (COVID-19). Nature Communications. 2021;12(1).
91. Narinx N, Smismans A, Symons R, Frans J, Demeyere A, Gillis. Feasibility of using point-of-care lung ultrasound for early triage of COVID-19 patients in the emergency room. Emerg Radiol. 2020;27(6):663-70.
92. Dini FL, Bergamini C, Allegrini A, et al. Bedside wireless lung ultrasound for the evaluation of COVID-19 lung injury in senior nursing home residents.Monaldi Archives for Chest Disease 2020;90(3). doi: 10.4081/monaldi.2020.1446
93. Fonsi GB, Sapienza P, Brachini G, et al. Is lung ultrasound imaging a worthwhile procedure for severe acute respiratory syndrome coronavirus 2 pneumonia detection? J Ultrasound Med. 2020. doi: 10.1002/jum.15487
94. Bar S, Lecourtois A, Diouf M, et al. The association of lung ultrasound images with COVID-19 infection in an emergency room cohort. Anaesthesia. 2020;75(12):1620-25.
95. Peyrony O, Marbeuf-Gueye C, Truong V, et al. Accuracy of Emergency Department Clinical Findings for Diagnosis of Coronavirus Disease 2019. Ann Emerg Med. 2020;76(4):405-412. doi:10.1016/j.annemergmed.2020.05.022
96. Haak SL, Renken IJ, Jager LC, Lameijer H, van der Kolk BBY. Diagnostic accuracy of point-of-care lung ultrasound in COVID-19. Emerg Med J. 2020, 38:94–99.
97. Lieveld AWE, Kok B, Schuit FH, et al. Diagnosing COVID-19 pneumonia in a pandemic setting: Lung Ultrasound versus CT (LUVCT) – a multicentre, prospective, observational study. ERJ Open Res 2020; 6: 00539-2020. https://doi.org/10.1183/23120541.00539-2020.
98. Pare J, Camelo I, Mayo K, et al. Point-of-care lung ultrasound is more sensitive than chest radiograph for evaluation of COVID-19. West J Emerg Med. 2020;21(4):771-8. doi: 10.5811/westjem.2020.5.47743
99. Clift AK, Coupland CAC, Keogh RH, Diaz-Ordaz K, Williamson E, Harrison EM et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. BMJ 2020;371:m3731 http://dx.doi.org/10.1136/bmj.m3731
100. Nafilyan V, Humberstone B, Mehta N, Diamond I, Coupland C, Lorenzi L et al. An external validation of the QCovid risk prediction algorithm for risk of mortality from COVID-19 in adults: national validation cohort study in England. medRxiv preprint https://doi.org/10.1101/2021.01.22.21249968 this version posted January 25, 2021
101. Jimenez-Solem E et al. Developing And Validating Covid-19 Adverse Outcome Risk Prediction Models From A Bi-National European Cohort Of 5594 Patients. doi: https://doi.org/10.1101/2020.10.06.20207209
102. Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. BMJ. 2020;370:m3339.
103. Marcolino M, Pires M, Ramos L, Silva R, Oliveira L, Carvalho R, et al. ABC2-SPH risk score for in-hospital mortality in COVID-19 patients: development, external validation and comparison with other available scores. medRxiv preprint doi: https://doi.org/10.1101/2021.02.01.21250306; this version posted February 3, 2021
104. Gupta R, Harrison E, Ho A, Docherty A, Knight S, Smeden M et al. Development and validation of the ISARIC 4C Deterioration model for adults hospitalised with COVID-19: a prospective cohort study. Lancet Respir Med 2021.https://doi.org/10.1016/S2213-2600(20)30559-2

105. Adderley N, Taverner T, Price M, Sainsbury C, Greenwood D, Chandan J et al. Development and external validation of prognostic models for COVID-19 to support risk stratification in secondary care. medRxiv preprint doi: https://doi.org/10.1101/2021.01.25.21249942; this version posted January 30, 2021.
106. Ageno W, Cogliati C, Perego M, Girelli D, Crisaffuli E, Pizzolo F et al. Clinical risk scores for the early prediction of severe outcomes in patients hospitalized for COVID-19. Internal and Emergency Medicine 2020. https://doi.org/10.1007/s11739-020-02617-4
107. Artero A, Madrazo M, Fernandez-Garces M, Miguez A, Garcia A, Vieitez ASeverity Scores in COVID-19 Pneumonia: a Multicenter, Retrospective, Cohort Study. J Gen Intern Med DOI: 10.1007/s11606-021-06626-7.
108. Baker KF, Hanrath A, van der Loeff I, Kay L, Back J, Duncan C. National Early Warning Score 2 (NEWS2) to identify inpatient COVID-19 deterioration: a retrospective analysis. Clinical Medicine 2021, Vol 21 No 2 March 2021.
109. Bartoletti M, Giannella M, Scudeller L, Tedeschi S, Rinaldi M, Bussini L et al. Development and validation of a prediction model for severe respiratory failure in hospitalized patients with SARS-CoV-2 infection: a multicentre cohort study (PREDI-CO study). Clinical Microbiology and Infection. 2020 https://doi.org/10.1016/j.cmi.2020.08.003.
110. Berenguer J, Borobia A, Ryan P, Rodriguez-Bano J, Bellon J, Harrin I et al. Development and validation of a prediction model for 30-day mortality in hospitalised patients with COVID-19: the COVID-19 SEIMC score. Thorax 2020. http://dx.doi.org/10.1136/ thoraxjnl-2020-216001).
111. Bradley P, Frost F,Tharmaratnam K, et al. Utility of established prognostic scores in COVID-19 hospital admissions: multicenter prospective evaluation of CURB-65, NEWS2 and qSOFA. BMJ Open Resp Res 2020;7:e000729. doi:10.1136. Bmjresp-2020-000729.
112. Carr E, Bendayan R, Bean D, Stammers M. Wang W, Zhang H, Searle T et al. Evaluation and improvement of the NEWS2 for COVID-19: a multi-hospital study. BMC Medicine 19:23. https://doi.org/10.1186/s12916-020-01893-3.
113. Castro V, McCoy T, Perlis R. Consistency of performance of adverse outcome prediction models for hospitalized COVID-19 patients. medRxiv preprint doi: https://doi.org/10.1101/2021.02.25.21252410; this version posted March 1, 2021.
114. Chua F, Vancheeswaran R, Draper A, Vaghela T, Knight M, Mogal R et al. Early prognostication of COVID-19 to guide hospitalisation versus outpatient monitoring using a point-of-test risk prediction scoreThorax Published Online First: 10 March 2021. doi: 10.1136/thoraxjnl-2020-216425
115. Codon J, Lip G, Rey H, Iniesta A, Rosillo S, Castrejon S et al. Prediction of thromboembolic events and mortality by the CHADS2 and the CHA2DS2-VASc in COVID-19. Europace (2021) 00, 1–11 doi:10.1093/europace/euab015.
116. El-Solh AA, Lawson Y, Carter M, El-Solh DA, Mergenhagen KA (2020) Comparison of in-hospital mortality risk prediction models from COVID-19. PLoS ONE 15(12): e0244629. https://doi.org/10.1371/journal.pone.0244629
117. Gupta RK, Marks M, Samuels THA, et al. Systematic evaluation and external validation of 22 prognostic models among hospitalised adults with COVID-19: An observational cohort study. Eur Respir J 2020; in press (https://doi.org/10.1183/13993003.03498-2020).
118. King JT, Jr., Yoon JS, Rentsch CT, Tate JP, Park LS, Kidwai-Khan F, et al. (2020) Development and validation of a 30-day mortality index based on pre-existing medical administrative data from 13,323 COVID-19 patients: The Veterans Health Administration COVID-19 (VACO) Index.PLoS ONE 15(11): e0241825. https://doi.org/10.1371/journal.pone.0241825
119. Li, J., Chen, Y., Chen, S. et al. Derivation and validation of a prognostic model for predicting in-hospital mortality in patients admitted with COVID-19 in Wuhan, China: the PLANS (platelet lymphocyte age neutrophil sex) model. BMC Infect Dis 20, 959 (2020). https://doi.org/10.1186/s12879-020-05688-y
120. Fang-Yan Liu, Xue-Lian Sun, Yong Zhang, Lin Ge, Jing Wang, Xiao Liang, Jun-Fen Li, Chang-Liang Wang, Zheng-Tao Xing, Jagadish K. Chhetri, Peng Sun, Piu Chan. Evaluation of the Risk Prediction Tools for Patients With Coronavirus Disease 2019 in Wuhan, China: A Single-

Centered, Retrospective, Observational Study. Critical Care Medicine DOI: 10.1097/CCM.0000000000004549.
121. Liu H, Chen J, Yang Q, Wang Y, Cai J, Li H. Development and validation of a risk score using complete blood count to predict in-hospital mortality in COVID-19 patients, Med (2020), https://doi.org/10.1016/j.medj.2020.12.013
122. Mancilla-Galindo J, Vera- Zertuche JM, Navarro-Cruz AR, Segura-Badilla O, Reyes-Velázquez G, Tepepa-López FJ, Aguilar-Alonso P, Vidal-Mayo JdeJ, Kammar- García A (2020). Development and validation of the patient history COVID-19 (PH-Covid19) scoring system: a multivariable prediction model of death in Mexican patients with COVID-19. Epidemiology and Infection 148, e286, 1–8. https://doi.org/10.1017/ S0950268820002903
123. Guillermo Rodriguez-Nava, Maria Adriana Yanez-Belloa, Daniela Patricia Trelles-Garciaa, Chul Won Chunga, Harvey J. Friedmanb,c, David W. Hinesd. Performance of the quick COVID-19 severity index and the Brescia-COVID respiratory severity scale in hospitalized patients with COVID-19 in a community hospital setting. International Journal of Infectious Diseases 102 (2021) 571–576
124. Nicholson C, Wooster L, Sigurslide H, Li R, Jiang W, Tian W, Cardenas C, Malhotra R. Estimating risk of mechanical ventilation and in-hospital mortality among adult COVID-19 patients admitted to Mass General Brigham: The VICE and DICE scores. EClinicalMedicine 33 (2021) 100765
125. Paranjape N, Staples L, Stradwick C, Ray H, Saldanha I. Development and validation of a predictive model for critical illness in adult patients requiring hospitalization for COVID-19 medRxiv preprint doi: https://doi.org/10.1101/2021.01.22.21250289; this version posted January 22, 2021.
126. Richardson D, Faisal M, Fiori M, et al. Use of the first National Early Warning Score recorded within 24 hours of admission to estimate the risk of in-hospital mortality in unplanned COVID-19 patients: a retrospective cohort study. BMJ Open 2021;11:e043721. doi:10.1136/bmjopen-2020-043721
127. Schöning V, Liakoni E, Baumgartner C, Exadaktylos A, Hautz W, Atkinson A, Hammann F Development and validation of a prognostic COVID-19 severity assessment (COSA) score and machine learning models for patient triage at a tertiary hospital. J Transl Med (2021) 19:56 https://doi.org/10.1186/s12967-021-02720-w
128. Tanboga IH, Canpolat U, Çetin E, Kundi H, Çelik O, Çağlayan M, Ata N, Özeke O, Çay S, Kaymaz C, Topaloğlu S. Development and validation of clinical prediction model to estimate the probability of death in hospitalized patients with COVID-19: Insights from a nationwide database. J Medical Virology 2021;1–8 DOI: 10.1002/jmv.26844
129. van Dam P, Zelis N, van Kuijk S, Linkens A, Bruggemann R, Spaetgens B et al. Performance of prediction models for short term outcome in COVID-19 patients in the emergency department: a retrospective study. Ann Med 2021 Dec;53(1):402-409. doi: 10.1080/07853890.2021.1891453
130. van Dam PMEL, Zelis N, Stassen P, et al. Validating the RISE UP score for predicting prognosis in patients with COVID-19 in the emergency department: a retrospective study. BMJ Open 2021;11:e045141. doi:10.1136/bmjopen-2020-045141
131. van Klaveren D, Rekkas A, Alsma J, Verdonschot R, Koning D, Kamps M et al. COVID Outcome Prediction in the Emergency Department (COPE): Development and validation of a model for predicting death and need for intensive care in COVID-19 patients. medRxiv preprint doi: https://doi.org/10.1101/2020.12.30.20249023; this version posted February 8, 2021
132. de Vries R, Vigeveno RM, Mulder S, Farzan N, Vintges DR, Goeman JJ, Bruisten S, van den Corput B, Geelhoed JJM, Visser LG, van der Lubben M, Sterk PJ, Veen JCCM, Groeneveld GH. Ruling out SARS-CoV-2 infection using exhaled breath analysis by electronic nose in a public health setting [cited 15 May 2021] from https://www.medrxiv.org/content/10.1101/2021.02.14.21251712v1#:~:text=In%20three%20independent%20validation%20cohorts,specificity%20between%2078%2D84%25.

133. Huang H, Cai S, Li Y, et al. Prognostic Factors for COVID-19 Pneumonia Progression to Severe Symptoms Based on Earlier Clinical Features: A Retrospective Analysis. Frontiers in Medicine; 7. Epub ahead of print October 5, 2020. DOI: 10.3389/fmed.2020.557453.
134. de Vera ME, Ombao G, Delos Reyes V. Risk Factors for Mortality of COVID-19 Confirmed Cases Admitted at Lung Center of the Philippines.
135. Luz M, Soria JB, Quiwa LQ, et al. Study: Clinical Profile and Factors Associated with Mortality of Hospitalized Patients.
136. Shang M, Wei J, Zou H dong, et al. Early Warning Factors of Death in COVID-19 Patients. Current Medical Science 2021; 41: 69–76.
137. Chen Z, Zhang F, Hu W, et al. Laboratory markers associated with COVID-19 progression in patients with or without comorbidity: A retrospective study. Journal of Clinical Laboratory Analysis; 35. Epub ahead of print January 1, 2021. DOI: 10.1002/jcla.23644.
138. Liu J, Tu C, Zhu M, et al. The clinical course and prognostic factors of severe COVID-19 in Wuhan, China: A retrospective case-control study. Medicine 2021; 100: e23996.
139. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020; 395: 1054–1062.
140. Yitao Z, Mu C, Ling Z, et al. Predictors of clinical deterioration in non-severe patients with COVID-19: a retrospective cohort study. Current Medical Research and Opinion 2021; 37: 385–391.
141. Almazeedi S, Al-Youha S, Jamal MH, et al. Characteristics, risk factors and outcomes among the first consecutive 1096 patients diagnosed with COVID-19 in Kuwait. EClinicalMedicine; 24. Epub ahead of print July 1, 2020. DOI: 10.1016/j.eclinm.2020.100448.
142. Tabata S, Imai K, Kawano S, et al. The clinical characteristics of COVID-19: A retrospective analysis of 104 patients from the outbreak on board the Diamond Princess cruise ship in Japan. medRxiv. Epub ahead of print April 7, 2020. DOI: 10.1101/2020.03.18.20038125.
143. Feng Y, Ling Y, Bai T, et al. COVID-19 with different severities: A multicenter study of clinical features. American Journal of Respiratory and Critical Care Medicine 2020; 201: 1380–1388.
144. Huang R, Zhuid L, Xue L, et al. Clinical findings of patients with coronavirus disease 2019 in Jiangsu Province, China: A retrospective, multi-center study. PLoS Neglected Tropical Diseases 2020; 14: 1–14.
145. Li K, Chen D, Chen S, et al. Radiographic findings and other predictors in adults with Covid-19. medRxiv. Epub ahead of print March 27, 2020. DOI: 10.1101/2020.03.23.20041673.
146. Shang W, Dong J, Ren Y, et al. The value of clinical parameters in predicting the severity of COVID-19. Journal of Medical Virology 2020; 92: 2188–2192.
147. Zhang X bin, Hu L, Ming Q, et al. Risk factors for mortality of coronavirus disease-2019 (COVID-19) patients in two centers of Hubei province, China: A retrospective analysis. PLoS ONE; 16. Epub ahead of print January 1, 2021. DOI: 10.1371/journal.pone.0246030.
148. Cheng B, Hu J, Zuo X, et al. Predictors of progression from moderate to severe coronavirus disease 2019: a retrospective cohort. Clinical Microbiology and Infection 2020; 26: 1400–1405.
149. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. Journal of Allergy and Clinical Immunology 2020; 146: 110–118.
150. Zhang J, Wang X, Jia X, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clinical Microbiology and Infection 2020; 26: 767–772.
151. Peiró ÓM, Carrasquer A, Sánchez-Gimenez R, et al. Biomarkers and short-term prognosis in COVID-19. Biomarkers 2021; 26: 119–126.
152. Mikami T, Miyashita H, Yamada T, et al. Risk Factors for Mortality in Patients with COVID-19 in New York City. Journal of General Internal Medicine 2021; 36: 17–26.
153. Núñez I, Priego-Ranero ÁA, García-González HB, et al. Common hematological values predict unfavorable outcomes in hospitalized COVID-19 patients. Clinical Immunology; 225. Epub ahead of print April 1, 2021. DOI: 10.1016/j.clim.2021.108682.
154. Vidal-Cevallos P, Higuera-De-La-Tijera F, Chávez-Tapia NC, et al. Lactate-dehydrogenase associated with mortality in hospitalized patients with COVID-19 in Mexico: a multi-centre

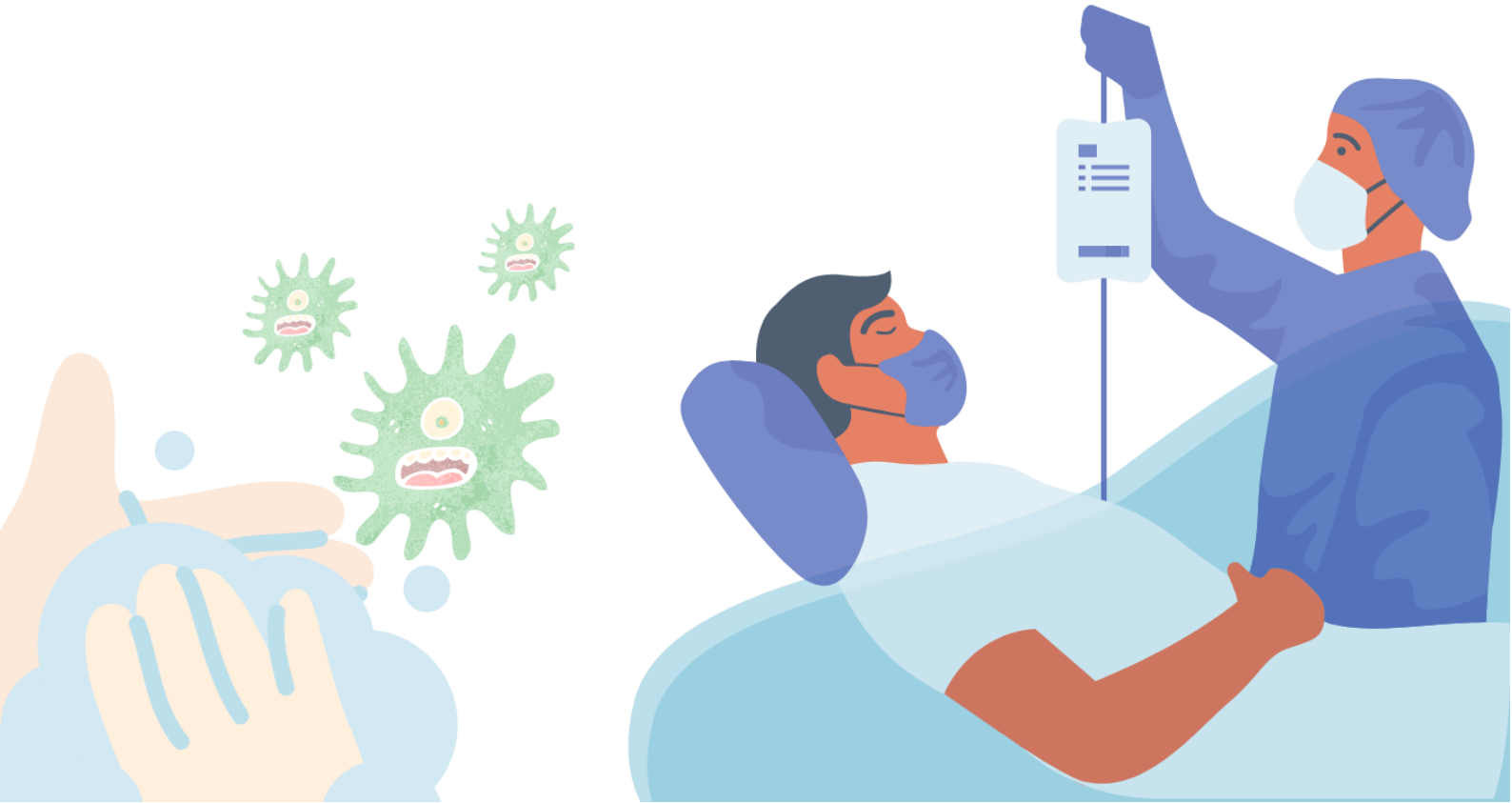
retrospective cohort study. Annals of Hepatology; 24. Epub ahead of print September 1, 2021. DOI: 10.1016/j.aohep.2021.100338.
155. Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARSCoV- 2: A prospective cohort study. European Respiratory Journal; 55. Epub ahead of print May 1, 2020. DOI: 10.1183/13993003.00524-2020.
156. Sayah W, Berkane I, Guermache I, et al. Interleukin-6, procalcitonin and neutrophil-to-lymphocyte ratio: Potential immune-inflammatory parameters to identify severe and fatal forms of COVID-19. Cytokine; 141. Epub ahead of print May 1, 2021. DOI: 10.1016/j.cyto.2021.155428.
157. Higuera-de la Tijera F, Servín-Caamaño A, Reyes-Herrera D, et al. Impact of liver enzymes on SARS-CoV-2 infection and the severity of clinical course of COVID-19. Liver Research 2021; 5: 21–27.
158. Benito N, Filella D, Mateo J, Fortuna AM, Gutierrez-Alliende JE, Hernandez N, Gimenez AM, Pomar V, Castellvi I, Corominas H, Casademont J and Domingo P (2020) Pulmonary Thrombosis or Embolism in a Large Cohort of Hospitalized Patients With Covid-19. Front. Med. 7:557. doi: 10.3389/fmed.2020.005574.
159. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, Zhang Z. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020 Jun;18(6):1324-1329. doi: 10.1111/jth.14859.
160. Duan J, Wang X, Chi J, Chen H, Bai L, Hu Q, Han X, Hu W, Zhu L, Wang X, Li Y, Zhou C, Mou H, Yan X, Guo S. Correlation between the variables collected at admission and progression to severe cases during hospitalization among patients with COVID-19 in Chongqing. J Med Virol. 2020 Nov;92(11):2616-2622. doi: 10.1002/jmv.26082. Epub 2020 Jun 9.
161. Zhang W, Sang L, Shi J, Zhong M, Jiang L, Song B, Kang L, Zhang Y, Zhang D, Yu Y, Zheng X. Association of D-dimer elevation with inflammation and organ dysfunction in ICU patients with COVID-19 in Wuhan, China: a retrospective observational study. Aging (Albany NY). 2021 Feb 11;13(4):4794-4810. doi: 10.18632/aging.202496. Epub 2021 Feb 11.
162. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054-1062. doi: 10.1016/S0140-6736(20)30566-3. Epub 2020 Mar 11. Erratum in: Lancet. 2020 Mar 28;395(10229):1038. Erratum in: Lancet. 2020 Mar 28;395(10229):1038.
163. Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, Goodarzi K, Bendapudi PK, Bornikova L, Gupta S, Leaf DE, Kuter DJ, Rosovsky RP. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood. 2020 Jul 23;136(4):489-500. doi: 10.1182/blood.2020006520.
164. Peiró ÓM, Carrasquer A, Sánchez-Gimenez R, Lal-Trehan N, Del-Moral-Ronda V, Bonet G, Fort-Gallifa I, Picó-Plana E, Bastón-Paz N, Gutiérrez C, Bardaji A. Biomarkers and short-term prognosis in COVID-19. Biomarkers. 2021 Mar;26(2):119-126. doi: 10.1080/1354750X.2021.1874052. Epub 2021 Jan 18.
165. Yang C, Liu F, Liu W, Cao G, Liu J, Huang S, Zhu M, Tu C, Wang J, Xiong B. Myocardial injury and risk factors for mortality in patients with COVID-19 pneumonia. Int J Cardiol. 2021 Mar 1;326:230-236. doi: 10.1016/j.ijcard.2020.09.048. Epub 2020 Sep 23.
166. Gil-Rodrigo A, Miró Ò, Piñera P, Burillo-Putze G, Jiménez S, Martín A, Martín-Sánchez FJ, Jacob J, Guardiola JM, García-Lamberechts EJ, Espinosa B, Martín Mojarro E, González Tejera M, Serrano L, Agüera C, Soy E, Llauger L, Juan MÁ, Palau A, Del Arco C, Rodríguez Miranda B, Maza Vera MT, Martín Quirós A, Tejada de Los Santos L, Ruiz de Lobera N, Iglesias Vela M, Torres Garate R, Alquézar-Arbé A, González Del Castillo J, Llorens P; en representación de la red de investigación SIESTA. Analysis of clinical characteristics and outcomes in patients with COVID-19 based on a series of 1000 patients treated in Spanish emergency departments. Emergencias. 2020 Ago;32(4):233-241.

167. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, Chen X, Chen S, Yu K, Huang Z, Hu B. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. J Intensive Care. 2020 Jul 10;8:49. doi: 10.1186/s40560-020-00466-z.
168. Cen Y, Chen X, Shen Y, Zhang XH, Lei Y, Xu C, Jiang WR, Xu HT, Chen Y, Zhu J, Zhang LL, Liu YH. Risk factors for disease progression in patients with mild to moderate coronavirus disease 2019-a multi-centre observational study. Clin Microbiol Infect. 2020 Sep;26(9):1242-1247. doi: 10.1016/j.cmi.2020.05.041. Epub 2020 Jun 9.
169. Yue T, Zhou W, He J, Wang H, Liu Y, Wang B, Zhu Q, Xia H, Hu H. Combined clinical and imaging features better predict the critical outcomes of patients with SARS-COV-2. Medicine (Baltimore). 2021 Mar 26;100(12):e25083. doi: 10.1097/MD.0000000000025083.
170. García-Ortega A, Oscullo G, Calvillo P, López-Reyes R, Méndez R, Gómez-Olivas JD, Bekki A, Fonfría C, Trilles-Olaso L, Zaldívar E, Ferrando A, Anguera G, Briones-Gómez A, Reig-Mezquida JP, Feced L, González-Jiménez P, Reyes S, Muñoz-Núñez CF, Carreres A, Gil R, Morata C, Toledo-Pons N, Martí-Bonmati L, Menéndez R, Martínez-García MÁ. Incidence, risk factors, and thrombotic load of pulmonary embolism in patients hospitalized for COVID-19 infection. J Infect. 2021 Feb;82(2):261-269. doi: 10.1016/j.jinf.2021.01.003. Epub 2021 Jan 10.
171. Mestre-Gómez B, Lorente-Ramos RM, Rogado J, Franco-Moreno A, Obispo B, Salazar-Chiriboga D, Saez-Vaquero T, Torres-Macho J, Abad-Motos A, Cortina-Camarero C, Such-Diaz A, Ruiz-Velasco E, Churruca-Sarasqueta J, Muñoz-Rivas N; Infanta Leonor Thrombosis Research Group. Incidence of pulmonary embolism in non-critically ill COVID-19 patients. Predicting factors for a challenging diagnosis. J Thromb Thrombolysis. 2021 Jan;51(1):40-46. doi: 10.1007/s11239-020-02190-9.
172. Demelo-Rodríguez P. Cervilla-Muñoz E, Ordieres-Ortega L, Parra-Virto A, Toledano-Macías M, Toledo-Samaniego N, García-García A et al. Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels. Thrombosis Research 2020: 192, 23-26. https://doi.org/10.1016/j.thromres.2020.05.018
173. Kampouri E, Filippidis P, Viala B, Méan M, Pantet O, Desgranges F, Tschopp J, Regina J, Karachalias E, Bianchi C, Zermatten MG, Jaton K, Qanadli SD, Bart PA, Pagani JL, Guery B, Alberio L, Papadimitriou-Olivgeris M, RegCOVID Research Group. Predicting Venous Thromboembolic Events in Patients with Coronavirus Disease 2019 Requiring Hospitalization: an Observational Retrospective Study by the COVIDIC Initiative in a Swiss University Hospital. Biomed Res Int. 2020 Nov 6;2020:9126148. doi: 10.1155/2020/9126148.
174. Creel-Bulos C, Liu M, Auld SC, Gaddh M, Kempton CL, Sharifpour M, Sniecinski RM, Maier CL, Nahab FB, Rangaraju S. Trends and diagnostic value of D-dimer levels in patients hospitalized with coronavirus disease 2019. Medicine 2020;99:46(e23186). http://dx.doi.org/10.1097/MD.0000000000023186
175. Nauka PC, Baronb SW, Assab A, Mohrmannb L, Jindala S, Oranb E et al. Utility of D-dimer in predicting venous thromboembolism in non-mechanically ventilated COVID-19 survivors Thrombosis Research 199 (2021) 82–84. https://doi.org/10.1016/j.thromres.2020.12.023
176. Zhang L, Feng X, Zhang D, Jiang C, Mei H, Wang J, Zhang C, Li H, Xia X, Kong S, Liao J, Jia H, Pang X, Song Y, Tian Y, Wang B, Wu C, Yuan H, Zhang Y, Li Y, Sun W, Zhang Y, Zhu S, Wang S, Xie Y, Ge S, Zhang L, Hu Y, Xie M. Deep Vein Thrombosis in Hospitalized Patients With COVID-19 in Wuhan, China: Prevalence, Risk Factors, and Outcome. Circulation. 2020 Jul 14;142(2):114-128. doi: 10.1161/CIRCULATIONAHA.120.046702. Epub 2020 May 18. Erratum in: Circulation. 2020 Jul 14;142(2):e33.
177. Alabyad D, Rangaraju S, Liu M, Imran R,Kempton CL, Sharifpour M, et al. (2021) Validation of an admission coagulation panel for risk stratification of COVID-19 patients. PLoS ONE 16(3): e0248230. https://doi.org/10.1371/journal.pone.0248230
178. Wang T, Tang C, Chen R, et al. Clinical Features of Coronavirus Disease 2019 Patients With Mechanical Ventilation: A Nationwide Study in China. Crit Care Med. 2020;48(9):e809-e812. doi:10.1097/CCM.0000000000004473
179. Hematology recommendations and dosing guidelines during COVID-19, version 9.0. In: Boston (MA): Massachusetts General Hospital; 2020:

https://www.massgeneral.org/assets/MGH/pdf/news/coronavirus/guidance-from-mass-general-hematology.pdf. Accessed 2021 May 23.

PHILIPPINE COVID-19 LIVING RECOMMENDATIONS

Treatment



Evidence and Recommendations for the Treatment of COVID-19

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

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

KEY FINDINGS

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

CONSENSUS ISSUES

None raised during panel meetings.

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

RECOMMENDATION
We recommend against the use of azithromycin among patients with COVID-19 infection. (Moderate quality of evidence; Strong recommendation)

KEY FINDINGS

Moderate certainty of evidence from 3 RCTs [23-25] comparing azithromycin with standard of care versus standard of care alone showed no significant benefit on all-cause mortality at day 28, 29 and 30. Results from 2 large trials (COALITION II, RECOVERY) showed no significant difference regarding the need for ECMO or mechanical ventilation at days 28 or 29 between the two groups. Subgroup analysis showed that azithromycin worsened the clinical status of patients aged < 60 years and on antiviral therapy. However, the results should be interpreted with caution as results varied significantly across age groups and concomitant use of antiviral therapy. The

proportion of adverse events were similar between azithromycin and standard of care. Most of the studies were found to be at moderate risk of bias with common issues on blinding and in two studies patients in the standard of care group had received azithromycin or other macrolides that could affect the results.

CONSENSUS ISSUES

No issues were raised during the consensus panel meeting.

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

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

KEY FINDINGS

Six randomized controlled trials were found on the use of favipiravir among patients with COVID-19 [26-31]. All 6 studies had some concerns in terms of risk of bias, but none of them had high risk of bias in any of the appraisal criteria. The overall quality of evidence was downgraded due to inconsistencies in combining the studies in some of the outcomes, limited sample size, and risk of bias.

Pooled results of three studies monitoring clinical improvement on day 7 showed a modest effect favoring favipiravir compared to standard care, however, clinical improvement on day 28 showed no clinical significance. Incidence of viral negative conversion was not significantly different between favipiravir and standard of care on day 3 as well as on day 7. However, time to negative conversion showed a minimal advantage towards favipiravir compared to standard care. Pooled results on the incidence of adverse events (i.e., hematologic effects, hepatobiliary disorders, gastrointestinal effects including diarrhea and nausea, skin disorders like rashes, to cardiac effects like bradycardia and chest pain) showed no significant difference between favipiravir and standard care.

CONSENSUS ISSUES

Given that there are on-going clinical trials on favipiravir, the recommendation explicitly stated that there was no recommendation on the use of favipiravir unless it will be used for clinical trials. In addition, there may be some implications regarding possible reimbursements and will encourage patients to join the clinical trial.

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

RECOMMENDATION

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

RECOMMENDATION
We suggest the addition of remdesivir to dexamethasone in patients with COVID-19 infection who have O2 saturation < 94% and/or requiring oxygen supplementation. (Low quality of evidence; Conditional recommendation) and are high risk for progression **For patients who progress to invasive mechanical ventilation while on remdesivir, the drug may be continued.*

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

KEY FINDINGS

Four randomized controlled trials on the use of remdesivir as treatment for COVID-19 were found [32-35]. Low quality evidence shows that remdesivir has limited effect on all cause-mortality, clinical improvement, and initiation of mechanical ventilation among confirmed COVID-19 patients. However, remdesivir appears to be beneficial in the time to clinical improvement especially among cases needing supplemental oxygen but not high flow oxygen/ mechanical ventilation. Remdesivir did not show increased risk for serious adverse events. Availability and cost of intervention should be considered before making recommendations regarding its use locally.

CONSENSUS ISSUES

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

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

RECOMMENDATION
We recommend the addition of tocilizumab to systemic steroids in patients with elevated biomarkers of inflammation (CRP), showing rapid respiratory deterioration

and/or requiring high doses of oxygen (high-flow nasal cannula, noninvasive or invasive mechanical ventilation) (Moderate quality of evidence; Strong recommendation)

RECOMMENDATION
We recommend against the use of tocilizumab in patients with COVID-19 infection who do not require oxygen supplementation. (Very low quality evidence, Strong recommendation)

KEY FINDINGS

Nine randomized controlled clinical trials (RCTs) [36-44] that evaluated the effectiveness of tocilizumab among confirmed hospitalized COVID-19 patients compared to placebo and/or standard of care was found. Low to moderate quality evidence shows that tocilizumab has a beneficial effect in hospitalized COVID-19 patients on clinical improvement, mortality reduction, and initiation of mechanical ventilation.

CONSENSUS ISSUES

The high cost and limited availability of tocilizumab should be considered in our local setting. The potential indiscriminate use, potential adverse effects (i.e., leukemia, TB reactivation), and lack of evidence of tocilizumab on COVID-19 patients who do not require oxygenation were additional factors considered by the panel in strongly recommending against the use of tocilizumab in patients not requiring oxygen.

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

RECOMMENDATION
We recommend against the use of convalescent plasma among patients with COVID-19 infection. (Moderate quality of evidence; Strong recommendation)

KEY FINDINGS

There were 13 published RCTs [45-57] that compared the effect of convalescent plasma therapy against placebo and/or standard of care among confirmed COVID-19 patients. Pooled estimates several patient-centric outcomes (i.e., all-cause mortality) on the use of convalescent plasma were not statistically significant. The incidence of adverse and serious adverse events (e.g., transfusion-related events) were not significantly different between the convalescent plasma group compared to those given standard care/placebo. Overall methodological quality of evidence for the included studies had moderate certainty of evidence for most of the reported outcomes (i.e., all-cause mortality, clinical improvement at D28, WHO progression score (level 7 or above) at D28, adverse events).

CONSENSUS ISSUES

The panel put a greater weight on the large RECOVERY trial that showed no significant reduction in mortality among moderate to critical hospitalized patients. The panel also noted that there is another large trial in UK (REMAP-CAP) that stopped its convalescent plasma arm for severe COVID-19 patients.

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

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

KEY FINDINGS

Currently, there are no randomized controlled trials that assessed the efficacy of ibuprofen as a treatment for COVID-19. Based on the two observational studies (one retrospective cohort and one case series) [58-59] that have not been peer-reviewed, there is limited evidence that ibuprofen treatment could improve COVID-19 symptoms and outcomes.

CONSENSUS ISSUES

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

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

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

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

KEY FINDINGS

To date, there is no available completed clinical trial directly investigating effectiveness or safety of virgin coconut oil as an adjunct treatment for COVID-19 patients of any age or disease severity. Indirect evidence was noted from two studies of VCO on other viruses such as human immunodeficiency viruses. [60-61]

CONSENSUS ISSUES

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

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

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

RECOMMENDATION
We recommend against the use of Lianhua as treatment among patients with COVID-19 infection. (Very low quality of evidence; Strong recommendation)

KEY FINDINGS

Limited evidence from 3 studies [62-64] with very low methodological quality shows that using Lianhua offers no clear benefit in improving the clinical status of patients with COVID-19. None of the studies provided effect estimates for the outcomes of mortality, development of ARDS, length of hospitalization, and the need for mechanical ventilation.

CONSENSUS ISSUES

The Consensus Panel considered the evidence from the presented trials to be of very low certainty, with only marginal benefit in terms of rate of recovery and time to symptom recovery and inconclusive evidence for harm due to imprecise confidence intervals. The accessibility issue and potential harm the drug might cause should be considered. Lianhua is currently a drug regulated by the Philippine Food and Drug Administration as it contains ephedra, a controlled substance. As a result, Lianhua could not be sold over the counter and may only be prescribed by physicians holding an S2 license. The ephedra content of Lianhua was reported by some physicians to be potentially harmful, especially in patients with cardiovascular disease.

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

RECOMMENDATION
We suggest against the use of ivermectin for the treatment of patients with mild-to-moderate COVID-19. (Very low quality of evidence; Conditional recommendation)

RECOMMENDATION
We recommend against the use of ivermectin for the treatment of patients with severe COVID-19. (Very low quality of evidence; Strong recommendation)

RECOMMENDATION
We suggest against the use of ivermectin combined with doxycycline for the treatment of patients with COVID-19. (Very low quality of evidence; Conditional recommendation)

KEY FINDINGS

Our search yielded 19 randomized controlled trials [65-83]. Ivermectin was compared to placebo or standard of care in 14 RCTs, lopinavir/ritonavir in 1 RCT, and hydroxychloroquine in 2 RCTs. Four RCTs investigated the effect of ivermectin in combination with doxycycline: 3 against placebo or standard of care and 1 against hydroxychloroquine with azithromycin.

No significant mortality benefit was found across all 5 comparisons. For RCTs that compared ivermectin against placebo/standard of care, a mortality reduction was noted only with the use of high dose ivermectin. Heterogeneity assessment revealed no effect of publication status, study quality, or disease severity on mortality.

Shorter time to viral clearance (3-5 days) was reported in studies that compared ivermectin with placebo/standard of care, hydroxychloroquine, and lopinavir/ritonavir. Clinical improvement on day 6-10 was also noted only in studies that used ivermectin combined with doxycycline. Significantly shorter time to symptom resolution was noted from 3 studies that used ivermectin-doxycycline versus placebo/standard of care; however, this combination was also found to result in significantly more adverse events.

Ivermectin did not have any significant effect on clinical deterioration, need for mechanical ventilation, proportion of patients attaining virologic clearance on day 7-14, duration of hospitalization, hospital discharge. The risk of serious and non-serious adverse events were not significantly higher among patients who received ivermectin.

These results must be interpreted in the context of very low certainty of evidence. The quality of evidence was downgraded due to varying degrees of risk of bias in most studies, serious imprecision due to a small number of events and sample sizes as well as wide confidence intervals in the estimates.

CONSENSUS ISSUES

The consensus panel noted that health equity may be decreased if budget will be allocated for ivermectin rather than efficacious medications and standard of care. The cost and availability of human grade ivermectin is another crucial consideration. The registered oral and parenteral preparations of ivermectin were registered for veterinary use only. Only the topical preparation of ivermectin is registered for human use. According to the Philippine Food and Drug Administration, drugs that were registered for veterinary use should not be utilized for human consumption.

In this update, the consensus panel made a conditional recommendation against the use of ivermectin as a treatment for mild and moderate COVID-19 cases since the current available evidence shows no clear benefit in terms of mortality reduction and clinical outcomes. Studies that showed a potential mortality benefit had significant methodological limitations and had results that are inconsistent with those reported in other trials. For severe and critical COVID-19 cases, the consensus panel made a strong recommendation against the use of ivermectin as there are currently other treatments with established effectiveness. The panel also recognized that while the current data showed no statistical difference between ivermectin and control in terms of adverse events, there is still limited data regarding the adverse effects that may be observed when ivermectin is administered in high doses or in doses similar to those given in in vitro studies. Results from the ongoing randomized clinical trials are still needed to establish ivermectin is a safe and effective treatment for COVID-19.

NOTE: The Consensus Panel agreed to make separate recommendations for patients with different disease severity. These recommendations were made without considering the dose of ivermectin.

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

RECOMMENDATION
We suggest against the use of colchicine in the treatment of COVID-19. (Low quality of evidence; Conditional recommendation)

KEY FINDINGS

We found 4 randomized controlled trials [84-87] that investigated the effect of colchicine compared to standard of care as treatment for patients with COVID-19. Colchicine did not show significant effect in terms of reducing all-cause mortality, need for mechanical ventilation, clinical deterioration. However, low quality evidence suggested that colchicine significantly shortened duration of hospitalization and duration of oxygen supplementation among patients with moderate to severe disease. Although adverse events, particularly diarrhea, were more frequently observed among participants treated with colchicine, the number of serious adverse events were comparable to those who received standard of care. All of the studies had risk of bias

issues as there were concerns in allocation concealment, blinding, attrition and selective reporting of outcome. The moderate risk of bias and imprecision in clinical outcomes such as all-cause mortality, mechanical ventilation, clinical deterioration and need for hospitalization contributed to downgrading of evidence to low certainty.

It is important to note that the effect estimates of important clinical outcomes were close to 1.0 for efficacy (no clear or appreciable benefit) among mild and moderate to severe COVID-19, and for serious adverse events (no clear harm) among patients with mild COVID-19. However, among patients with any severity of COVID-19, colchicine may cause more harm.

CONSENSUS ISSUES

Current evidence showed significantly more adverse events (e.g., pulmonary embolism, gastrointestinal effects, nausea, rash, and most commonly diarrhea) with no significant clinical benefit in COVID-19 patients treated with colchicine compared to those receiving placebo or standard of care. Results from ongoing studies such as the ACT Trial are needed to better assess the effectiveness of colchicine as a treatment for COVID-19.

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

RECOMMENDATION
We suggest against the use of interferon in the treatment of hospitalized patients with moderate to critical COVID-19. (Very low quality of evidence; Conditional recommendation)

KEY FINDINGS

There were 3 randomized controlled trials [88-90] on the efficacy and safety of interferon in the treatment of COVID-19. Overall quality of evidence was very low. The studies had serious risk of bias due to problems in allocation concealment and blinding. There were also imprecision and inconsistency attributed to non-uniformity in the dosage of interferon in one study and standard of care. There was a lack of significant benefit of interferon on all-cause mortality, progression to severe COVID-19 and clinical response by day 7. There was significant benefit on clinical response on day 14 and day 28. Serious adverse events among patients receiving interferon did not differ from those not receiving interferon.

CONSENSUS ISSUES

Current evidence shows no significant benefit with using interferon for treating COVID-19 infections. The high cost of this drug must be considered.

Should baricitinib with or without remdesivir be used in the management of hospitalized patients with COVID-19?

RECOMMENDATION
We suggest the use of baricitinib in combination with remdesivir in hospitalized COVID-19 patients who cannot take corticosteroids and require oxygen supplementation. (Low quality of evidence; Conditional recommendation)

RECOMMENDATION
There is insufficient evidence to recommend the use of baricitinib in combination with remdesivir and corticosteroids in hospitalized COVID-19 patients. (Very low quality of evidence)

RECOMMENDATION
There is no evidence to recommend the use of baricitinib alone in hospitalized COVID-19 patients.

KEY FINDINGS

One multinational double-blind placebo controlled randomized trial [91] investigated the effect of baricitinib with remdesivir versus remdesivir alone on 1,033 patients with moderate to severe COVID-19. Based on this RCT, baricitinib with remdesivir showed benefit in terms of shortening time to recovery by 1 day on average and reducing the incidence of new mechanical ventilation or ECMO. No significant effect on mortality was noted. Significantly fewer serious adverse events were documented with the group treated with baricitinib+remdesivir; however, the incidence of infections were increased in patients who were taking concomitant glucocorticoids. No other trials were found on baricitinib alone or in combination with other drugs. (i.e., glucorticoids).

CONSENSUS ISSUES

These recommendations were made in the context of dexamethasone being considered as a standard of care for severe or critical COVID-19 infection. The incremental benefit of giving baricitinib and remdesivir with dexamethasone remains to be a research gap. Thus, there is insufficient evidence to recommend the use of baricitinib in combination with remdesivir and corticosteroids in hospitalized COVID-19 patients. Caution must be exercised in administering baricitinib in patients who are already taking steroids due to the likelihood of the occurrence of immunosuppression. Results showed that patients who received glucocorticoids had a higher risk of having serious or non-serious infections than those who did not.

Due to supply problems in recent months, baricitinib is currently being used locally to replace tocilizumab in regimens with both remdesivir and dexamethasone. However, using baricitinib for COVID-19 qualifies as off-label use as it is approved only for use in rheumatoid arthritis.

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

RECOMMENDATION
There is insufficient evidence to recommend the use of inhaled corticosteroids as treatment for non-hospitalized patients with mild to moderate COVID-19 infection. (Very low quality of evidence)

KEY FINDINGS

Evidence on the use of inhaled corticosteroids for the treatment of COVID-19 included two randomized controlled trials [92, 93]. Among non-hospitalized patients with mild to moderate COVID-19, inhaled budesonide was not associated with a reduced risk in hospitalization, emergency department visit, or death. The Principle trial found a shorter time to clinical recovery with the use of inhaled budesonide compared to usual care. However, these two studies had serious risk of bias due to lack of blinding, unclear allocation concealment, and attrition bias.

CONSENSUS ISSUES

Further studies are needed to show the effectiveness of inhaled corticosteroids for the treatment of COVID-19 infection. Inhaled corticosteroids can be used to provide symptomatic relief for other concomitant conditions such as asthma and COPD.

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

RECOMMENDATION
We recommend against the use of lopinavir/ritonavir as treatment for COVID-19 infection. (Moderate quality of evidence; Strong recommendation)

KEY FINDINGS

Based on 5 randomized controlled trials [94—98] enrolling both suspected and confirmed COVID-19 patients, lopinavir/ritonavir combination did not significantly affect clinical improvement, all-cause mortality, viral negative conversion, need for mechanical ventilation, or WHO progression score level 7 or higher, when compared to standard of care. No difference in adverse events were also seen between lopinavir/ritonavir and control groups. The overall quality of evidence ranged from low to high across different outcomes.

CONSENSUS ISSUES

No issues were raised during the panel meeting.

Should bamlanivimab be used in the treatment of COVID-19?

RECOMMENDATION
We recommend against the use of bamlanivimab monotherapy as treatment for COVID-19 infection. (Very low quality of evidence; Strong recommendation)

RECOMMENDATION
We suggest against the use of bamlanivimab - etesevimab in the treatment of non-hospitalized COVID-19 patients with mild-to-moderate COVID-19 at high risk of progression to severe disease. (Low quality of evidence; Conditional recommendation)

KEY FINDINGS

Evidence on the use of bamlanivimab on COVID-19 comes from 2 randomized controlled trials [99, 100], namely the BLAZE 1-trial for ambulatory patients and the ACTIV-3/TICO trial for hospitalized patients. Among ambulatory patients with mild-to-moderate COVID-19, combination therapy with bamlanivimab and etesevimab as a single infusion resulted in a significant reduction in viral load compared to placebo at day 11. However, the use of bamlanivimab monotherapy was not associated with a reduction in viral load nor reductions in mortality, incidence of negative RT-PCR, time to sustained recovery, or hospital discharge. There were no significant differences in adverse events between the use of bamlanivimab and placebo.

CONSENSUS ISSUES

Bamlanivimab as monotherapy or in combination with etesevimab showed no significant benefit as treatment for COVID-19. Further studies are needed to show the effectiveness of bamlanivimab in the treatment of COVID-19 infection. In addition, the current cost of bamlanivimab remains high with an approximate cost of Php 60,000 to 120,000 per dose. Recommending its use will possibly promote inequity especially in remote areas. Its local availability should also be considered.

Should regeneron (monoclonal antibody cocktail of casirimibimab-imdevimab) be used in the treatment of COVID-19?

RECOMMENDATION
There is insufficient evidence to recommend the use of REGN-COV2 (casirivimab/imdevimab) as treatment for COVID-19 infection. (Low quality of evidence)

KEY FINDINGS

Interim data from one ongoing RCT [101] comparing REGN-COV2 monoclonal antibody cocktail (casirivimab plus imdevimab) with placebo showed a significant reduction in viral load after 7 days of treatment with REGN-COV2 among non-

hospitalized, non-severe patients. Lesser COVID-19 related medically attended visits were noted in the treatment group, but this did not reach statistical significance. The incidence of adverse events was balanced between the treatment and the placebo groups. Due to very serious imprecision, the certainty of evidence regarding the effectiveness of Regeneron remains low. There are currently 6 ongoing clinical trials on the use of REGN-COV2 as treatment of COVID-19.

CONSENSUS ISSUES

The study included in this review is only an interim analysis of data from 275 non-severe COVID-19 patients. Complete results from ongoing studies are needed to better determine the effectiveness of casirivimab plus imdevimab as treatment for COVID-19 infection. The availability and cost of this intervention must also be considered. No mortality and only serious adverse events such as hypertension and hypoxia were reported.

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

RECOMMENDATION
There is insufficient evidence to recommend the use of leronlimab as treatment for COVID-19. (Very low quality of evidence)

KEY FINDINGS

Very low-quality evidence based on three case series and one case study [102-105] was found on the use of leronlimab for the treatment of COVID-19. Among the patients with severe-critical COVID-19 given leronlimab, 26.3% died, 21.1% were still hospitalized, and 52.6% were discharged. There were reductions in serial IL-6 measurements before and several days after administration. No thromboembolic events were reported. Well-conducted randomized controlled trials are still needed to assess the effectiveness of leronlimab as treatment for COVID-19.

CONSENSUS ISSUES

Further trials are needed to recommend the use of leronlimab for the treatment of COVID-19. The cost and accessibility of this drug must also be considered.

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

RECOMMENDATION
We recommend against the use of steam inhalation alone in the treatment of COVID-19. (Very low quality of evidence; Strong recommendation)

KEY FINDINGS

Based on a single arm observational study [106] with high risk of bias, there is currently only very low quality evidence showing the possible benefit of steam inhalation in the prevention of developing symptomatic COVID-19 among exposed healthy individuals and reducing symptoms and number of days to negative SARS-COV-2 RT-PCR test of COVD-19 confirmed individuals. Meanwhile, there is indirect evidence highlighting the significant adverse effects of steam inhalation among individuals using it for symptomatic relief from the colds.

CONSENSUS ISSUES

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

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

RECOMMENDATION
We suggest against the use of baloxavir as treatment for patients with COVID-19 infection. (Very low quality of evidence; Conditional recommendation)

KEY FINDINGS

There was only one randomized controlled trial [107] included in this review. Treatment with baloxavir did not lead to significant reduction in the need for invasive mechanical ventilation, admission to intensive care unit, hospitalization and clinical improvement (very low quality of evidence). There was no report of mortality in any of treatment arms. Currently, there are two ongoing clinical trials on the efficacy of baloxavir as treatment for COVID-19.

CONSENSUS ISSUES

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

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

RECOMMENDATION

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

KEY FINDINGS

Based on the five retrospective cohort studies [108-112] included in this review, oseltamivir was associated with increased risk of mortality ((Odds Ratio (OR), 4.20; [95%CI 4.03, 4.38], very low quality of evidence). Moreover, it was associated with risk of disease progression (OR 5.22; [95% CI, 2.00, 13.02], low quality of evidence) as well as longer time to viral clearance (standard mean difference (SMD) of 1.65 days longer (95% CI 1.27, to 2.03, low quality of evidence). Currently, there are five ongoing clinical trials on the efficacy of oseltamivir as treatment for COVID-19.

CONSENSUS ISSUES

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

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

RECOMMENDATION
We suggest against the use of intravenous immunoglobulin as treatment for moderate to severe COVID-19. (Very low quality of evidence; Conditional recommendation)

KEY FINDINGS

Four RCTs [113-116] that were of low to very low quality found that the use of intravenous immunoglobulin (IVIg) did not significantly reduce mortality or risk of mechanical ventilation among patients with moderate to severe COVID-19. However, one very low quality RCT found higher incidence of virologic clearance as assessed by negative RT PCR with the use of IVIg. There was also no significant increase risk of adverse events with its use in COVID-19.

CONSENSUS ISSUES

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

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

RECOMMENDATION

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

KEY FINDINGS

We found 3 randomized controlled trials [117-119] evaluating the effectiveness and safety of mesenchymal stem cell (MSC) therapy in COVID-19 treatment. One RCT was at high risk of bias while the remaining 2 RCTs were of moderate quality. Validity issues included unclear allocation concealment, lack of blinding and incomplete outcome reporting. Based on very low quality evidence, umbilical cord-derived MSC (UC-MSC) therapy reduces mortality and hastens clinical improvement in adults with severe COVID-19. Limited by small sample sizes, adverse events were not significantly different between MSC and control groups.

CONSENSUS ISSUES

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

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

RECOMMENDATION
We suggest against the use of famotidine in the treatment of COVID-19. (Very low quality of evidence; Conditional recommendation)

KEY FINDINGS

Very low-quality evidence from seven retrospective cohort studies [120-126] was found on the use of famotidine for the treatment of COVID-19. There was no significant reduction in the risk of mortality, mechanical ventilation, and composite outcome of mortality or mechanical ventilation. However, there was a significant increase in the risk of the composite outcome of mortality, mechanical ventilation, and intensive care unit admission. Adverse events were not examined in these retrospective cohort studies.

CONSENSUS ISSUES

No issues were raised during the panel meeting.

References

1. Hernandez-Cardenas C, Thirion-Romero I, Rivera-Martinez N, Meza-Meneses P, Remigio-Luna A, Perez-Padilla R. Hydrochloroquine for the treatment of severe respiratory infection by COVID-19: A raondomized controlled trial. MedRxiv. 2021;
2. Johnston C, Brown E, Stewart J, Karita HC, Patricia K, John D, et al. Hydroxychloroquine with or without azithromycin for treatment of early SARS-CoV-2 infection among high-risk outpatient adults: A randomized clinical trial. EClinicalMedicine [Internet]. 2021; Available from: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00053-5/fulltext
3. Beltran Gonzales JL, Gamez MG, Enciso EAM, Maldonado RJE, Palacios DH. Efficacy and safety of Ivermectin and Hydroxychloroquine in patients with severe COVID-19. A randomized controlled trial [Internet]. MedRxiv. 2021 [cited 2021 Mar 9]. Available from: https://www.medrxiv.org/content/10.1101/2021.02.18.21252037v1
4. Abd-Elsalam S, Esmail ES, Khalaf M, Abdo EF, Medhat MA, El Ghafar MSA, et al. Hydroxychloroquine in the treatment of COVID-19: A multicenter randomized controlled study. Am J Trop Med Hyg. 2020;103(4):1635–9.
5. Ader F, Peiffer-Smadja N, Poissy J, Bouscamber-Duchamp M, Belhadi D, Diallo A, et al. Antiviral drugs in hospitalized patients with COVID-19 - the DisCoVeRy trial. MedRxiv [Internet]. 2021; Available from: https://www.medrxiv.org/content/10.1101/2021.01.08.20248149v1
6. Amaravadi R. The PATCH Trial (Prevention And Treatment of COVID-19 With Hydroxychloroquine) (PATCH) [Internet]. [cited 2020 Dec 28]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT04329923
7. Cavalcanti A, Zampeiri F, Rosa R, Azvedo L, Veiga V, Avezum A, et al. Hydroxychloroquine with or without Azithromycin in Mild to Moderate Covid 19. NEJM. 2020;383:2041–52.
8. Chen C-P, Lin Y-C, Chen T-C, Tseng T-Y, Wong H-L, Kuo C-Y, et al. A multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate coronavirus disease 2019 (COVID-19). PLoS One [Internet]. 2020;15(12):e0242763. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33264337
9. Chen J, Liu D, Liu L, Liu P, Xu Q, Xia L, et al. A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. Zhejiang Da Xue Xue Bao Yi Xue Ban [Internet]. 2020;49(2):215–9. Available from: http://www.zjujournals.com/med/EN/10.3785/j.issn.1008-9292.2020.03.03
10. Chen L, Zhang Z, Fu J, Feng Z, Zhang S, Han Q, et al. Efficacy and safety of chloroquine or hydroxychloroquine in moderate type of COVID 19 : a prospective open-label randomized controlled study. MedRxiv [Internet]. Available from: https://doi.org/10.1101/2020.06.19.20136093
11. Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. 2020.
12. Dubee V, Roy P, Vielle B, Parot-Schinkel E, Blanchet O, Darsonval A, et al. A placebo-controlled double blind trial of hydroxychloroquine in mild-to moderate COVID-19. Medrxiv.
13. Horby P, Mafham M, Staplin N, Emberson J, Wiselka M, Utiasnowski A. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020;383(21):2030–40.
14. Kamran S, Mirza Z, Azam R, Ullah N, Saeed F, Alamgir W. Clearing the fog : Is hydroxychloroquine effective in reducing Corona virus disease-2019 progression : A randomized controlled trial. MedRxiv [Internet]. Available from: https://doi.org/10.1101/2020.07.30.20165365
15. Lyngbakken M, Berdal J, Eskesen A, Kvale D, Olsen I, Rueegg C. A pragmatic randomized controlled trial reports lack of efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics. Nat Commun [Internet]. 2020;11:5284. Available from: https://doi.org/10.1038/s41467-020-19056-6

16. Mitja O, Carbacho-Monne M, Ubals M, Tebe C, Penafiel J, Tobias A. Hydrochloroquine for early treatment of adults with mild coronavirus disease 2019 : A randomized controlled trial. Clin Infect Dis. :ciaa1009.
17. Omrani A, Pathan S, Thomas S, Harris T, Coyle P, Thomas C, et al. Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe Covid-19. EClinical Med. 2020;29:100645.
18. Pan H, Peto R, Henao-Restrepo A, Preziosi M, Sathiyamoorthy V, Karim Q. Repurposed antiviral drugs for Covid-19 – Interim WHO Solidarity trial results. NEJM [Internet]. 2021;384(6):497–511. Available from: https://www.nejm.org/doi/pdf/10.1056/NEJMoa2023184?articleTools=true
19. Self W, Semler M, Leither L, Casey J, Angus D, Brower R, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19. A randomized clinical trial. JAMA. 2020;324(21):2165–76.
20. Skipper CP, Pastick KA, Engen NW, Bangdiwala AS, Abassi M, Lofgren SM, et al. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19 : A Randomized Trial. Ann Intern Med. 2020;173(8):623–31.
21. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydrochloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomized controlled trial. BMJ [Internet]. 2020;369. Available from: http://dx.doi.org/10.1136/bmj.m1849
22. Ulrich RJ, Troxel AB, Carmody E, Eapen J, Bäcker M, DeHovitz JA, et al. Treating COVID-19 with hydroxychloroquine (TEACH): A multicenter, double-blind randomized controlled trial in hospitalized patients. Open Forum Infect Dis. 2020;7(10):ofaa446.
23. Sekhavati E, Jafari F, SeyedAlinaghi S, Jamalimoghadamsiahkali S, Sadr S, Tabarestani M et al. Safety and effectiveness of azithromycin in patients with COVID-19: An open-label randomised trial. International Journal of Antimicrobial Agents. 2020;56(4):106143.
24. Furtado R, Berwanger O, Fonseca H, Corrêa T, Ferraz L, Lapa M et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. The Lancet. 2020;396(10256):959-967
25. RECOVERY Collaborative Group. Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10274):605-612.
26. Yan Lou, European Journal of Pharmaceutical Sciences, https://doi.org/10.1016/j.ejps.2020.105631
27. Ivashchenko AA, Dmitriev KA, Vostokova NV, Azarova VN, Blinow AA, Egorova AN, et al. AVIFAVIR for Treatment of Patients With Moderate Coronavirus Disease 2019 (COVID-19): Interim Results of a Phase II/III Multicenter Randomized Clinical Trial, Clinical Infectious Diseases, , ciaa1176, https://doi.org/10.1093/cid/ciaa1176
28. Dabbous HM, El-Sayed MH, Assal GE, Eghazaly H, Ebeid FFS, Sherief AF, et al. Safety and efficacy of favipiravir versus hydroxychloroquine in management of COVID-19: A randomised controlled trial. Scientific Reports. 2021; 11 (7282) https://doi.org/10.1038/s41598-021-85227-0
29. Balykova L.A., Granovskaya M.V., Zaslavskaya K.Ya., Simakina E.N., Agaf'ina A.S., Ivanova A.Yu., Kolontarev K.B., Pushkar D.Yu. New possibilities for targeted antiviral therapy for COVID-19. Results of a multicenter clinical study of the efficacy and safety of using the drug Areplivir. Infektsionnye bolezni: novosti, mneniya, obuchenie [Infectious Diseases: News, Opinions, Training]. 2020; 9 (3): 16–29. DOI: https://doi.org/10.33029/2305-3496-2020-9-3-16-29 (in Russian)
30. Ruzhentsova TA, Chukhliaev PV, Khavkina DA, Garbuzov AA, Oseshnyuk RA, Soluyanova TN, et. al. Phase 3 Trial of Coronavir (Favipiravir) in patients with mild to moderate COVID-19, https://ssrn.com/abstract=3696907
31. Udwadia ZR, Singh P, Barkate H, Patil S, Rangwala S, Pendse A, et, al. International Journal of Infections Diseases. 2021; 103:62-71 https://doi.org/10.1016/j.ijid.2020.11.142

32. W. H. O. Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med 2020.
33. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA 2020; 324(11): 1048-57.
34. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet 2020; 395(10236): 1569-78.
35. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl [9] Salvarani C, Dolci G, Massari M, et al. Effect of Tocilizumab vs Standard Care on Clinical
36. Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA Intern Med 2021; 181(1): 24-31.
37. Hermine O, Mariette X, Tharaux PL, et al. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. JAMA Intern Med 2021; 181(1): 32-40.
38. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med 2020; 383(24): 2333-44.
39. Wang D, Fu B, Peng Z, et al. Preprint. Tocilizumab ameliorates the hypoxia in COVID-19 moderate patients with bilateral pulmonary lesions: a randomized, controlled, open-label, multicenter trial. SSRN 2020.
40. Salama C, Han J, Yau L, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med 2021; 384(1): 20-30.
41. Gordon AC, Mouncey PR, Al-Beidh F, et al. Preprint: Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report. 2021.
42. Rosas I, Bräu N, Waters M, et al. Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia. medRxiv 2020.
43. Veiga VC, Prats J, Farias DLC, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ 2021; 372: n84.
44. Horby PWRCG. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. medRxiv 2021. J Med 2020; 383(19): 1813-26.
45. Libster R, Pérez Marc G, Wappner D, Coviello S, Bianchi A, Braem V et al. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. New England Journal of Medicine. 2021;
46. Simonovich V, Burgos Pratx L, Scibona P, Beruto M, Vallone M, Vázquez C et al. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. New England Journal of Medicine. 2020;.
47. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ. 2020;:m3939.
48. Ray Y, Paul S, Bandopadhyay P, D'Rozario R, Sarif J, Lahiri A et al. Clinical and immunological benefits of convalescent plasma therapy in severe COVID-19: insights from a single center open label randomised control trial. 2020.
49. AlQahtani M, Abdulrahman A, Almadani A, Alali S, Al Zamrooni A, Hejab A et al. Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease. 2020;.
50. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19. JAMA. 2020;324(5):460.
51. Gharbharan A, Jordans C, Geurtsvankessel C, den Hollander J, Karim F, Mollema F et al. Convalescent Plasma for COVID-19. A randomized clinical trial. 2020;.

52. Avendano-Sola C, Ramos-Martinez A, Munez-Rubio E, Ruiz-Antoran B, Malo de Molina R, Torres F et al. Convalescent Plasma for COVID-19: A multicenter, randomized clinical trial. 2020;.
53. Bajpai M, Kumar S, Maheshwari A, Chhabra K, kale P, Gupta A et al. Efficacy of Convalescent Plasma Therapy compared to Fresh Frozen Plasma in Severely ill COVID-19 Patients: A Pilot Randomized Controlled Trial. 2020;
54. Balcells M, Rojas L, Le Corre N, Martínez-Valdebenito C, Ceballos M, Ferrés M et al. Early Anti-SARS-CoV-2 Convalescent Plasma in Patients Admitted for COVID-19: A Randomized Phase II Clinical Trial. 2020;
55. Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, et al.. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. The Lancet 2021;397(10289):2049–59.
56. O'Donnell MR, Grinsztejn B, Cummings MJ, Justman JE, Lamb MR, Eckhardt CM, et al.. A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19. Journal of Clinical Investigation. Journal of Clinical Investigation; 2021;131(13).
57. Pouladzadeh M, Safdarian M, Eshghi P, Abolghasemi H, Bavani AG, Sheibani B, Moradi Choghakabodi P, Feghhi A, Ghafourian Boroujerdnia M, Forouzan A, Jalali Far MA, Kaydani GA, Rajaei E, Amin M, Torabizadeh M, Yousefi F, Hadaddezfuli R. A randomized clinical trial evaluating the immunomodulatory effect of convalescent plasma on COVID-19-related cytokine storm. Intern Emerg Med. 2021 Apr 10:1–11. doi: 10.1007/s11739-021-02734-8. Epub ahead of print. PMID: 33837906; PMCID:PMC8035885.
58. Wang D, Fu B, Peng Z, et al. Preprint. Tocilizumab ameliorates the hypoxia in COVID-19 moderate patients with bilateral pulmonary lesions: a randomized, controlled, open-label, multicenter trial. SSRN 2020.
59. Salama C, Han J, Yau L, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med 2021; 384(1): 20-30
60. Dayrit C. Coconut oil in health and disease: its and monolaurin's potential as cure for HIV/AIDS. 2000. Accessed from: http://coconutresearchcenter.org/wp-content/uploads/2015/11/article10526.pdf
61. Widhiarta KD. Virgin coconut oil for HIV-positive people. Cord. 2016; 3(1):50-57.
62. Hu K, Guan WJ, Bi Y, Zhang W, Li L, Zhang B, Liu Q, Song Y, Li X, Duan Z, Zheng Q, Yang Z, Liang J, Han M, Ruan L, Wu C, Zhang Y, Jia ZH, Zhong NS. Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: A multicenter, prospective, randomized controlled trial. Phytomedicine. 2020 May 16:153242. doi: 10.1016/j.phymed.2020.153242. Epub ahead of print. PMID: 32425361; PMCID: PMC7229744.
63. Xiao M, Tian J, Zhou Y, Xu X, Min X, Lv Y, Peng M, Zhang Y, Yan D, Lang S, Zhang Q, Fan A, Ke J, Li X, Liu B, Jiang M, Liu Q, Zhu J, Yang L, Zhu Z, Zeng K, Li C, Zheng Y, Wu H, Lin J, Lian F, Li X, Tong X. Efficacy of Huoxiang Zhengqi dropping pills and Lianhua Qingwen granules in treatment of COVID-19: A randomized controlled trial. Pharmacol Res. 2020 Nov;161:105126. doi: 10.1016/j.phrs.2020.105126. Epub 2020 Aug 8. PMID: 32781283; PMCID: PMC7414728.
64. Yao K, Liu, M, Li X, Huang J, Cai H. [Internet]. China: Yiling Group Company. [cited 2021 Feb 10]. Retrospective clinical analysis on the treatment of novel coronavirus-infected pneumonia with traditional Chinese medicine Lianhua Qingwen. Available from: http://www.yilinghospital.com/news/retrospective-clinical-analysis-on-treatment-of-novel-coronavirus-infected-pneumonia-with-traditional-chinese-medicine-lianhua-qingwen
65. Ahmed S, Karim MM, Ross AG, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis. 2021;103:214-216. doi:10.1016/j.ijid.2020.11.191
66. Chaccour C, Casellas A, Blanco-Di Matteo A, et al. The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial. EClinicalMedicine. 2021;32. doi:10.1016/j.eclinm.2020.100720

67. López-Medina E, López P, Hurtado IC, et al. Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial. JAMA - J Am Med Assoc. 2021;325(14):1426-1435. doi:10.1001/jama.2021.3071
68. Bukhari K, Asghar A, Ahmad Mangat S, Abdullah M, Fatima T, Mustafa A. Efficacy of ivermectin in COVID-19 patients with mild to moderate disease. medRxiv. February 2021:2021.02.02.21250840. doi:10.1101/2021.02.02.21250840
69. Gonzalez B, Lenin J, González Gámez M, et al. Efficacy and safety of ivermectin and hydroxychloroquine in patients with severe COVID-19: a randomized controlled trial. medRxiv. February 2021:2021.02.18.21252037. doi:10.1101/2021.02.18.21252037
70. Podder CS, Chowdhury N, Sina MI, Haque WMMU. Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study. IMC J Med Sci. 2021;14(2):11-18. doi:10.3329/imcjms.v14i2.52826
71. Babalola OE, Bode CO, Ajayi AA, et al. Ivermectin shows clinical benefits in mild to moderate COVID19: A randomised controlled double-blind, dose-response study in Lagos. QJM An Int J Med. February 2021. doi:10.1093/qjmed/hcab035
72. Shahbaznejad L, Davoudi A, Eslami G, et al. Effect of ivermectin on COVID-19: A multicenter double-blind randomized controlled clinical trial. Clin Ther. May 2021. doi:10.1016/j.clinthera.2021.04.007
73. Mahmud R, Rahman MM, Alam I, et al. Ivermectin in combination with doxycycline for treating COVID-19 symptoms: a randomized trial. J Int Med Res. 2021;49(5):1-14. doi:10.1177/03000605211013550
74. Hashim HA, Maulood MF, Rasheed AM, Fatak DF, Kabah KK, Abdulamir AS. Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq. medRxiv. October 2020:2020.10.26.20219345. doi:10.1101/2020.10.26.20219345
75. Chowdhury A, Shahbaz M, Karim M, Islam J, Dan G, He S. A comparative study on ivermectin-doxycycline and hydroxychloroquine-azithromycin therapy on COVID-19 patients. Eurasian J Med Oncol. 2021;5(1):63-70. doi:10.14744/ejmo.2021.16263
76. Chachar A, Ahmad Khan K, Asif M, Tanveer K, Khaqan A, Basri R. Effectiveness of ivermectin in SARS-CoV-2/COVID-19 patients. Int J Sci. 2020;9(09):31-35. doi:10.18483/ijsci.2378
77. Elgazzar A, Hany B, Youssef SA, Hafez M. Efficacy and safety of ivermectin for treatment and prophylaxis of COVID-19 pandemic. ResearchSquare. November 2020. doi:10.21203/rs.3.rs-100956/v2
78. Krolewiecki A, Lifschitz A, Moragas M, et al. Antiviral effect of high-dose ivermectin in adults with COVID-19: a pilot randomised, controlled, open-label, multicentre trial. SSRN Electron J. November 2020. doi:10.2139/ssrn.3714649
79. Mohan A, Tiwari P, Suri T, et al. Ivermectin in mild and moderate COVID-19 (RIVET-COV): a randomized, placebo-controlled trial. ResearchSquare. February 2021. doi:10.21203/rs.3.rs-191648/v1
80. Niaee MS, Gheibi N, Namdar P, et al. Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial. ResearchSquare. November 2020. doi:10.21203/rs.3.rs-109670/v1
81. Okumuş N, Demirtürk N, Çetinkaya RA, et al. Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients. ResearchSquare. February 2021. doi:10.21203/rs.3.rs-224203/v1
82. Ravikirti, Roy R, Pattadar C, et al. Ivermectin as a potential treatment for mild to moderate COVID-19 – A double blind randomized placebo-controlled trial. medRxiv. January 2021:2021.01.05.21249310. doi:10.1101/2021.01.05.21249310
83. Pott-Junior H, Bastos Paoliello MM, Miguel A de QC, et al. Use of ivermectin in the treatment of COVID-19: A pilot trial. Toxicol Reports. 2021;8:505-510. doi:10.1016/j.toxrep.2021.03.003
84. Tardif JC, Bouabdallaoui N, L'Allier PL, et al. for the COLCORONA Investigators. Efficacy of colchicine in non-hospitalized patients with COVID-19. doi: https://doi.org/10.1101/2021.01.26.21250494

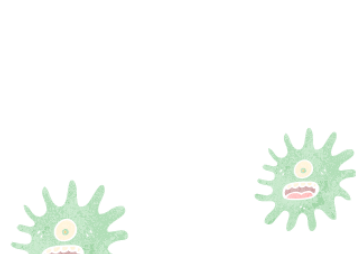
85. Lopes MIF, Bonjorno LP, Giannini MC, et al. Beneficial effects of colchicine for moderate to severe COVID-19: an interim analysis of a randomized, double-blinded, placebo controlled clinical trial. medRxiv 2020.doi:10.1101/2020.08.06.20169573
86. Deftereos SG, Giannopoulos G, Vrachatis DA, et al. Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019: the GRECCO-19 randomized clinical trial. JAMA Netw Open 2020;3:e2013136. doi:10.1001/jamanetworkopen.2020.13136
87. Salehzadeh, Farhad & Pourfarzi, Farhad & Ataei, Sobhan. (2020). The Impact of Colchicine on The COVID-19 Patients; A Clinical Trial Study. 10.21203/rs.3.rs-69374/v1.
88. Kazemzadeh H, Yekaninejad MS. A Randomized Clinical Trial of the Efficacy and Safety of Interferon β-1a in Treatment of Severe COVID-19. Antimicrob Agents Chemother. 2020 Aug 20;64(9):e01061-20. doi: 10.1128/AAC.01061-20. PMID: 32661006; PMCID: PMC7449227.
89. Monk PD, Marsden RJ, Tear VJ, Brookes J, Batten TN, Mankowski M, et al. Inhaled Interferon Beta COVID-19 Study Group. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Respir Med. 2021 Feb;9(2):196-206. doi: 10.1016/S2213-2600(20)30511-7. Epub 2020 Nov 12. PMID: 33189161; PMCID: PMC7836724. (Synairgen SG016 Phase 2 trial SNG001)
90. WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, Alejandria MM, Hernández García C, Kieny MP, Malekzadeh R, Murthy S, Reddy KS, Roses Periago M, Abi Hanna P, Ader F, Al-Bader AM, Alhasawi A, Allum E, Alotaibi A, Alvarez-Moreno CA, Appadoo S, Asiri A, Aukrust P, Barratt-Due A, Bellani S, Branca M, Cappel-Porter HBC, Cerrato N, Chow TS, Como N, Eustace J, García PJ, Godbole S, Gotuzzo E, Griskevicius L, Hamra R, Hassan M, Hassany M, Hutton D, Irmansyah I, Jancoriene L, Kirwan J, Kumar S, Lennon P, Lopardo G, Lydon P, Magrini N, Maguire T, Manevska S, Manuel O, McGinty S, Medina MT, Mesa Rubio ML, Miranda-Montoya MC, Nel J, Nunes EP, Perola M, Portolés A, Rasmin MR, Raza A, Rees H, Reges PPS, Rogers CA, Salami K, Salvadori MI, Sinani N, Sterne JAC, Stevanovikj M, Tacconelli E, Tikkinen KAO, Trelle S, Zaid H, Røttingen JA, Swaminathan S. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med. 2021 Feb 11;384(6):497-511. doi: 10.1056/NEJMoa2023184. Epub 2020 Dec 2. PMID: 33264556; PMCID: PMC7727327.
91. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med. 2021;384(9):795-807.
92. Ramakrishnan S, Nicolau D V., Langford B, et al. Inhaled Budesonide in the Treatment of Early COVID-19 Illness: A Randomised Controlled Trial. SSRN Electron J. 2021. doi:10.2139/ssrn.3777194
93. Yu L-M, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at higher risk of adverse outcomes in the community: interim analyses from the PRINCIPLE trial. medRxiv. January 2021:2021.04.10.21254672. doi:10.1101/2021.04.10.21254672
94. Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., . . . Wang, C. (2020). A trial of lopinavir–ritonavir in adults hospitalized with severe covid-19. New England Journal of Medicine, 382(19), 1787-1799. doi:10.1056/nejmoa2001282
95. Ader, F., Peiffer-Smadja, N., Poissy, J., Bouscambert-Duchamp, M., Belhadi, D., Diallo, A., . . . Mentre, F. (2021). Antiviral drugs in hospitalized patients With covid-19 - the DisCoVeRy trial. doi:10.1101/2021.01.08.20248149 [pre-print]
96. Li, Y., Xie, Z., Lin, W., Cai, W., Wen, C., Guan, Y., . . . Li, L. (2020 dec 18). Efficacy and safety of LOPINAVIR/RITONAVIR Or ARBIDOL in adult patients with Mild/Moderate COVID-19: An Exploratory randomized controlled trial. Med, 1(1), 105-113. doi:10.1016/j.medj.2020.04.001
97. Horby, P. W., Mafham, M., Bell, J. L., Linsell, L., Staplin, N., Emberson, J., . . . Landray, M. J. (2020 oct 5). Lopinavir–ritonavir in patients admitted to hospital With Covid-19 (RECOVERY): A RANDOMISED, CONTROLLED, OPEN-LABEL, Platform trial. The Lancet, 396(10259), 1345-1352. doi:10.1016/s0140-6736(20)32013-4

98. Pan, H., Peto, R., Karim, Q. A., Alejandria, M., Henao-Restrepo, A. M., García, C. H., . . . Swaminathan, S. (2021). Repurposed antiviral drugs FOR covid-19 –interim Who SOLIDARITY trial results. New England Journal of Medicine, 384th ser., 497-511. doi:Doi/10.1056/NEJMoa2023184
99. 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. 2021;325(7):632-644. doi:10.1001/jama.2021.0202
100. Lundgren JD, ACTIV-3/TICO LY-CoV555 Study Group*. A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19. N Engl J Med. 2021;384(10):905-914. doi:10.1056/NEJMoa2033130
101. Weinrich D, Sivapalasingam S. et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with COVID-19. NEJM 2021; 384(3): 238-51
102. Patterson BK, Seethamraju H, Dhody K, et al. CCR5 inhibition in critical COVID-19 patients decreases inflammatory cytokines, increases CD8 T-cells, and decreases SARS-CoV2 RNA in plasma by day 14. Int J Infect Dis. 2021;103:25-32. doi:10.1016/j.ijid.2020.10.101
103. Elneil S, Lalezari JP, Pourhassan NZ. Case study of a critically ill person with COVID-19 on ECMO successfully treated with leronlimab [published online ahead of print, 2021 Mar 23]. J Transl Autoimmun. 2021;100097. doi:10.1016/j.jtauto.2021.100097
104. Yang B, Fulcher JA, Ahn J, et al. Clinical Characteristics and Outcomes of COVID-19 Patients Receiving Compassionate Use Leronlimab [published online ahead of print, 2020 Oct 20]. Clin Infect Dis. 2020;ciaa1583. doi:10.1093/cid/ciaa1583
105. Agresti N, Lalezari JP, Amodeo PP, et al. Disruption of CCR5 signaling to treat COVID-19-associated cytokine storm: Case series of four critically ill patients treated with leronlimab. J Transl Autoimmun. 2021;4:100083. doi:10.1016/j.jtauto.2021.100083
106. la Marca G, Barp J, Frenos S, Mugelli A, Galli L, Calistri E, et al. Thermal inactivation of SARS COVID-2 virus: Are steam inhalations a potential treatment? Life Sci [Internet]. 2021 Jan 15 [cited 2021 Feb 22];265. Available from: https://pubmed.ncbi.nlm.nih.gov/33232690/
107. Lou Y, Liu L, Yao H. et al. Clinical outcomes and plasma concentrations of baloxavir marboxil and favipiravir in COVID-19 patients: an exploratory randomized, controlled trial. 2020. Eur J of Pharm Sci 157 105631.
108. Macilla-Galindo J, Garcia-Mendez J, Marquez-Sanchez J et a. All-cause mortality among patients treated with repurposed antivirals and antibiotics for COVID-19 in Mexico City: A real-world observational study. medRxiv 2020 preprint doi:https://doi.org/10.1101/2020.10.13.20211797.
109. Lee S, Park G, Moon Y, Sung K. Clinical characteristics and risk factors for fatality and severity in patients with coronavirus disease in Korea: A nationwide population-based retrospective study using the Korean Health Insurance Review and Assessment Service (HIRA) Database. Int J Environ Res Public Health 2020, 17, 8559; doi:10.3390/ijerph1728559.
110. Liu Q, Fang X, Tian L et al. Arbidol treatment with reduced mortality of adult patients with COVID-19 Wuhan, China: a retrospective cohort study. medRixv preprint doi:https://doi.rog/10.1101/2020.04.11.20056523.
111. Chen X, Zhang Y, Zhu B, et al. Association of clinical characteristics and antiviral drugs with viral RNA clearance in patients with COVID-19 in Guangzhou, China: a retrospective cohort study. medXriv preprint doi: https://doi.org/10.1101/2020.04.02.200589941.
112. Hu F, Yin G, Chen Y. et al. Corticosteroidsm, oseltamivir and delayed admission are independent risk factors for prolonged viral shedding in patients with coronavirus disease 2019. Clin Respir J. 2020; 14:1067-1075. Doi:10.1111/crj.13243
113. Gharebaghi N, Nejadrahim R, Mousavi SJ, Sadat-Ebrahimi S-R, Hajizadeh R. The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial. BMC Infect Dis. 2020;20(1):786. doi:10.1186/s12879-020-05507-4

114. Raman RS, Bhagwan Barge V, Anil Kumar D, et al. A Phase II Safety and Efficacy Study on Prognosis of Moderate Pneumonia in Coronavirus Disease 2019 Patients With Regular Intravenous Immunoglobulin Therapy. J Infect Dis. February 2021. doi:10.1093/infdis/jiab098
115. Sakoulas G, Geriak M, Kullar R, et al. Intravenous Immunoglobulin (IVIG) Significantly Reduces Respiratory Morbidity in COVID-19 Pneumonia: A Prospective Randomized Trial. medRxiv. January 2020:2020.07.20.20157891. doi:10.1101/2020.07.20.20157891
116. Tabarsi P, Barati S, Jamaati H, et al. Evaluating the effects of Intravenous Immunoglobulin (IVIg) on the management of severe COVID-19 cases: A randomized controlled trial. Int Immunopharmacol. 2021;90(January):107205. doi:10.1016/j.intimp.2020.107205
117. Shu L, Niu C, Li R, Huang T, Wang Y, Huang M, et al. Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells. Stem Cell Res Ther. 2020;11(1):1–11.
118. Lanzoni G, Linetsky E, Correa D, Messinger Cayetano S, Alvarez RA, Kouroupis D, et al. Umbilical cord mesenchymal stem cells for COVID-19 acute respiratory distress syndrome: A double-blind, phase 1/2a, randomized controlled trial. Stem Cells Transl Med. 2021;10(5):660–73.
119. Shi L, Huang H, Lu X, Yan X, Jiang X, Xu R, et al. Effect of human umbilical cord-derived mesenchymal stem cells on lung damage in severe COVID-19 patients: a randomized, double-blind, placebo-controlled phase 2 trial. Signal Transduct Target Ther. 2021;6(1).
120. Freedberg DE, Conigliaro J, Wang TC, Tracey KJ, Callahan MV, Abrams JA; Famotidine Research Group. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 Patients: a propensity score matched retrospective cohort study. Gastroenterology. 2020 Sep;159(3):1129-1131.e3. doi: 10.1053/j.gastro.2020.05.053.
121. Mura C, Preissner S, Nahles S, Heiland M, Bourne PE, Preissner R. Clinical evidence for improved outcomes with histamine antagonists and aspirin in 22,560 COVID-19 patients. medRxiv. 2021 Apr 5. doi: 10.1101/2021.03.29.21253914
122. Cheung KS, Hung IFN, Leung WK. Association between famotidine use and COVID-19 severity in hong kong: a territory-wide study. Gastroenterology. 2021 Apr;160(5):1898-1899. doi: 10.1053/j.gastro.2020.05.098.
123. Mather JF, Seip RL, McKay RG. Impact of famotidine use on clinical outcomes of hospitalized patients with COVID-19. Am J Gastroenterol. 2020 Oct;115(10):1617-1623. doi: 10.14309/ajg.0000000000000832.
124. Shoaibi A, Fortin SP, Weinstein R, Berlin JA, Ryan P. Comparative effectiveness of famotidine in hospitalized COVID-19 patients. Am J Gastroenterol. 2021 Apr;116(4):692-699. doi: 10.14309/ajg.0000000000001153
125. Yeramaneni S, Doshi P, Sands K, Cooper M, Kurbegov D, Fromell G. Famotidine use is not associated with 30-day mortality: a coarsened exact match study in 7158 hospitalized patients with coronavirus disease 2019 from a large healthcare system. Gastroenterology. 2021 Feb;160(3):919-921.e3. doi: 10.1053/j.gastro.2020.10.011.
126. Zhou J, Wang X, Lee S, Wu WKK, Cheung BMY, Zhang Q, Tse G. Proton pump inhibitor or famotidine use and severe COVID-19 disease: a propensity score-matched territory-wide study. Gut. Epub ahead of print: 04 December 2020. doi: 10.1136/gutjnl-2020-323668.

PHILIPPINE COVID-19 LIVING RECOMMENDATIONS

Critical Care and Respiratory Management



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

Should systemic corticosteroids be used in patients with COVID-19 infection?

RECOMMENDATION
We recommend the use of dexamethasone in patients with COVID-19 infection who require supplemental oxygenation (i.e., including high-flow device, non-invasive, invasive mechanical ventilation and ECMO). (High quality of evidence; Strong recommendation)

RECOMMENDATION
We recommend against the use of systemic corticosteroids among patients with COVID-19 infection who do not require oxygen supplementation. (Moderate to high quality of evidence; Strong recommendation)

KEY FINDINGS

Eleven randomized controlled trials [1-11] were found on the use of systemic corticosteroids for COVID-19, with only two high quality studies. Overall, the trend of benefit with the use of corticosteroids is leaning towards potential benefit for severe and critical patients in terms of mortality and clinical improvement at Day 14- 28 but did not reach statistical significance. The incidences of adverse events (e.g., severe neuromyopathy, fungemia) were not significantly different between the corticosteroids group compared to those given standards of care.

CONSENSUS ISSUES

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

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

RECOMMENDATION
We suggest the use of prophylactic anticoagulation among hospitalized patients with COVID-19 infection, unless with contraindications. (Very low quality of evidence; Conditional recommendation)

RECOMMENDATION
We suggest the use of prophylactic dose anticoagulation rather than therapeutic anticoagulation in critically ill patients with COVID-19 infection. (Low quality of evidence; Conditional recommendation)

KEY FINDINGS

Among patients with COVID-19, no significant difference was found between those who received anticoagulation compared to those who did not with regards risk to thromboembolic events, bleeding episodes and mortality based on six observational cohort studies [12-17]. The result of therapeutic anticoagulation versus prophylactic anticoagulation showed no significant effect on mortality from one RCT [18]. Bleeding episodes were noted to be significant among those receiving therapeutic dose anticoagulation. There were inconsistent findings for the need for mechanical ventilation, ventilator-free days, pulmonary function and success of weaning in groups who received anticoagulation. Observational studies had moderate to low risk of bias with issues mostly on the different doses and types of anticoagulation given, and the tendency of those more severely ill to receive a higher dose of anticoagulation.

CONSENSUS ISSUES

The common dosing for prophylactic anticoagulation are: (1) enoxaparin – 40 mg; (2) heparin – 5000 units based on the studies that specified the dose. The frequency depends on the creatinine clearance of the patients. Relative contraindications to be considered prior to giving anticoagulation include active and clinically significant bleeding, severe bleeding diathesis, severe thrombocytopenia, major trauma, previous intracranial hemorrhage, recent invasive procedure and major trauma, The recommendations for critically ill patients may change once the results of big trials come out.

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

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

KEY FINDINGS

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

CONSENSUS ISSUES

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

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

RECOMMENDATION
There is insufficient evidence on the use of hemoperfusion among patients with COVID-19 infection. (Very low quality of evidence)

KEY FINDINGS

There were no randomized controlled trials or any systematic reviews found to answer this question. Only one (1) prospective single-arm clinical trial and nine (9) case series / case reports [20-29] on the use of hemoperfusion among COVID-19 patients were retrieved. All the patients who have not undergone hemoperfusion eventually died, and 4 out of 5 who received hemoperfusion improved according to the study conducted by Rampino. However, no conclusion on the effectiveness of hemoperfusion as treatment for COVID-19 can be drawn. The results of the study of Ashgharpour showed that peripheral capillary oxygen saturations before hemoperfusion were 89.6% ± 3.94% and after the sessions it has improved to 92.13% ± 3.38, however the serum level of interleukin-6 did not show any clinical significance before and after sessions. Four (4) of the 10 patients in this study eventually expired.

CONSENSUS ISSUES

None raised during the panel meeting.

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

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

**without tissue hypoperfusion and fluid responsiveness*

KEY FINDINGS

Analysis of four randomized controlled trials [30-33], which included 1,106 hemodynamically stable mechanically ventilated patients with acute respiratory distress showed a trend towards decreased risk of mortality in the conservative fluid management strategy group. Furthermore, the use of conservative fluid management strategy resulted to significantly increased ventilator-free days, significant decrease in the length of intensive care unit stay and duration of mechanical ventilation. In terms of adverse events, the use of conservative fluid management strategy showed no significant difference in renal failure-free days and need for renal replacement therapy. The overall quality of studies included in this analysis was found moderate risk of bias with common issues on selection, performance, and reporting bias.

CONSENSUS ISSUES

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

Should proning be used in non-intubated patients with COVID-19 infection?

RECOMMENDATION
We suggest self-proning to improve oxygenation status of non-intubated hospitalized patients with COVID-19 infection requiring oxygen supplementation. (Very low quality of evidence; Conditional recommendation)

KEY FINDINGS

There is limited direct evidence showing physiological improvements in proning among patients diagnosed with COVID-19 regardless of whether they are receiving non-invasive supplemental oxygen modalities. The benefit of proning non-intubated patients in reducing the risk of mortality and intubation risk remains uncertain due to inconclusive results [34-36]. Patients who were placed in prone position experienced discomfort back pain and shoulder pain, accidental removal of peripheral IV lines. There were improvements in oxygenation among COVID-19 patients who were not yet intubated and experienced prone positioning.

CONSENSUS ISSUES

Self proning is recommended for patients with COVID-19 infection who are not qualified to be intubated. Based on the studies, self proning has no impact on mortality and intubation.

Should high flow nasal cannula be used in patients with COVID-19 infection?

RECOMMENDATION
We suggest the use of high-flow nasal cannula oxygenation rather than non-invasive ventilation (e.g., helmet CPAP, mask NIV) in patients with COVID-19 infection and acute hypoxemic respiratory failure who do not respond to conventional oxygen therapy. (Very low quality of evidence; Conditional recommendation)

KEY FINDINGS

Only one randomized controlled trial [37] evaluated the effectiveness of high flow nasal cannula (HFNC) and COT among adults with severe COVID-19, this study is of moderate risk of bias because of unclear randomization process, no allocation concealment, small sample size and unequal characteristics at baseline. Results showed that HFNC patients stayed almost one day shorter in the ICU and hospital length of stay was similarly shorter in the HFNC arm but not significantly different from the COT arm.

There is limited evidence on the effectiveness of HFNC vs. NIV in COVID-19 patients from four, moderate-quality retrospective cohort studies [38-41]. Pooled results from three studies showed a reduction in odds of mortality with the use of HFNC over NIV. Mean hospital stay of HFNC patients (19.2 13.3 days) did not differ significantly from those on mask NIV (21.5 +/- 15.1 days) and H-CPAP (19.8 +/- 12.1 days).

CONSENSUS ISSUES

The use of HFNC over conventional oxygen therapy (i.e., nasal cannula, venture mask or non-rebreather mask) is not congruent to usual clinical practice. The use for HFNC is preferred for patients who are not doing well with the conventional oxygen therapy. In addition, the trial employing severe COVID-19 patients, used HFNC even if it is not yet needed at the time.

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

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

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

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

KEY FINDINGS

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

Lung Protective Ventilation

Higher tidal volume was associated with the same or higher risk of 28-day mortality but there was no significant difference in ventilator-free days in multivariable models [42]. A smaller case-control study also [43] showed that barotrauma cases were observed to have significantly lower VT (median 5.4 vs. 11.7 mL/kg PBW, p = 0.005) and Pplat (median 27 vs. 32 cmH2O, p = 0.01) than the controls.

Higher PEEP and Low Tidal Volume Ventilation

Higher PEEP was not associated with 28-day mortality nor ventilator-free days in adults with COVID-19-related ARDS. A case-control study showed that PEEP was not statistically significantly different between patients with and without barotrauma. [42, 43]

Driving Pressure

There was no significant difference in 28-day mortality, in-hospital mortality, mechanical ventilation-free days, hospital stay and barotrauma were observed. [44]

CONSENSUS ISSUES

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

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

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

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

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

KEY FINDINGS

There were no studies directly comparing rapid sequence intubation (RSI) and delayed sequence intubation (DSI). For each modality, there were very low quality evidence, which had limitations in study design and indirectness. Both RSI and DSI improved the post-intubation oxygen saturations of the patients. The study on RSI [45] reported that 10.4% of the patients died within 24 hours of intubation. On the other hand, the study on DSI [46] reported no deaths within an unspecified time period. The study on RSI reported cardiac arrest in 2% of the patients and pneumothorax in 5.9% of the patients post intubation. Conversely, the study on DSI reported that none of the patients had cardiac arrest post intubation within an unspecified time period. The study on RSI reported that there was no evidence of cross infection in the anesthesiologists who intubated the COVID-19 patients.

CONSENSUS ISSUES

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

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

Should Extracorporeal Membrane Oxygenation (ECMO) be used in the management of ARDS among COVID-19?

RECOMMENDATION
We suggest the use of VV-ECMO for judiciously selected COVID-19 patients with severe ARDS based on the Extracorporeal Life Support Organization (ELSO) criteria. (Very low quality of evidence; Conditional recommendation)

KEY FINDINGS

We included seven observational studies [47-53] on the use of ECMO in the management of COVID-19. One of the cohort studies included a target trial emulation. There were no randomized controlled trials found. Mortality rates among patients on ECMO varied widely ranging from 17.1% to 58.3%. One study showed a significantly lower mortality rate among patients who received ECMO compared to those who did not. Reported harms were major bleeding, acute kidney injury requiring renal replacement therapy, pneumonia, other infections, and neurologic complications. Overall quality of studies was very low because these were observational studies.

CONSENSUS ISSUES

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

proning, mechanical ventilation and lung protective strategies) did not work and the patients are qualified for ECMO.

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

Should hyperbaric oxygen therapy be used in the management of COVID-19 patients?

RECOMMENDATION
There is insufficient evidence to recommend the use of hyperbaric oxygen therapy for the management of COVID-19 patients. (Very low quality of evidence)

KEY FINDINGS

Only one non-randomized clinical trial [54] was found on the use of hyperbaric oxygen therapy (HBOT) for COVID-19. HBOT significantly reduced the need for mechanical ventilation , but did not demonstrate significant benefit in terms of mortality. The few, minor adverse events experienced by the patients included epistaxis (which was not related to HBOT), ear pain, and claustrophobia. A serious adverse event in the interventional group occurred when a patient sustained a hypoxic arrest, demonstrating the high risk of transferring and caring for COVID-19 patients in a hyperbaric chamber. The overall quality of evidence was low due to imprecision and small sample size.

CONSENSUS ISSUES

The high cost of hyperbaric oxygen therapy must be considered before recommending its use for the treatment of COVID-19 infection. There is also limited availability of hyperbaric oxygen therapy machines in the Philippines. Its use may applied in the context of a clinical trial. The results of ongoing studies are needed to show the use of hyperbaric oxygen therapy for the treatment of COVID-19 infection.

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

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

KEY FINDINGS

Very low quality evidence was found on the use of etoposide as treatment for severe COVID-19: one case series and one case report [55, 56]. The case series showed an improvement in PaO2-FiO2 ratio (PFR) post-treatment of etoposide. Among the 14 patients studied in both studies, three patients expired while ten patients improved and were subsequently discharged. Adverse effects of etoposide include alopecia, gastrointestinal symptoms, acute hypersensitivity reactions, myelosuppression, and rarely, secondary malignancies such as acute myelocytic leukemia.

CONSENSUS ISSUES

There is not enough high-quality evidence to show that etoposide is useful for the management of COVID-19 patients with pneumonia in cytokine storm. There are significant adverse events with the use of etoposide, namely: alopecia, nausea, vomiting, myelosuppression, acute hypersensitivity reactions, hepatotoxicity, hypotension from rapid infusion, and secondary malignancies.

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

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

KEY FINDINGS

We found one randomized controlled trial [57] that investigated the effect of pulmonary rehabilitation (PR) among long COVID patients with residual respiratory symptoms. The study was found to have a moderate risk of bias due to absence of blinding for both patients and outcome assessors and unclear allocation process. They also enrolled only participants above 65 years of age. Based on moderate quality of evidence, pulmonary function tests of those who received pulmonary rehabilitation significantly improved. Quality of life and anxiety scales also significantly differed between groups, with improvement noted in the PR group compared to no PR. There was no significant difference for depression and activities of daily living between

groups and within groups before and after the intervention. The RCT did not report any adverse events; indirect evidence [58] from PR done on COPD patients likewise showed no to low number of adverse events which did not hinder the feasibility and safety of the procedure of pulmonary rehabilitation.

CONSENSUS ISSUES

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

References

1. Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, Gómez-Barquero J, Abadía-Otero J, García-Ibarbia C et al. GLUCOCOVID: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. 2020. [Preprint]
2. Du. 2020; unpublished. Covid-19 Living Data [Internet]. Covid-nma.com. 2021 [cited 1 February 2021]. Available from: https://covid-nma.com/living_data/infos_participants.php?i=167
3. Perner A. 2020, unpublished. Covid-19 Living Data [Internet]. Covid-nma.com. 2021 [cited 1 February 2021]. Available from: https://covid-nma.com/living_data/infos_participants.php?i=174
4. Villar J. 2020, unpublished. Covid-19 Living Data [Internet]. Covid-nma.com. 2021 [cited 1 February 2021]. Available from: https://covid-nma.com/living_data/infos_participants.php?i=168
5. Dequin P, Heming N, Meziani F, Plantefève G, Voiriot G, Badié J et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19. JAMA. 2020;324(13):1298.
6. Edalatifard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A, Mostafaei S et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. European Respiratory Journal. 2020;56(6):2002808.
7. Farahani R, Mosaed R, Nezami-Asl A, chamanara M, Soleiman-Meigooni S, Kalantar S et al. Evaluation of the efficacy of methylprednisolone pulse therapy in treatment of Covid-19 adult patients with severe respiratory failure: randomized clinical trial. Research Square. 2020;.
8. Jeronimo C, Farias M, Val F, Sampaio V, Alexandre M, Melo G et al. Methylprednisolone as adjunctive therapy for patients hospitalized with coronavirus disease 2019 (COVID-19; Metcovid): A Randomized, Double-blind, Phase IIb, Placebo-controlled Trial. Clinical Infectious Diseases. 2020;.
9. Angus D, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19. JAMA. 2020;324(13):1317.

10. Tomazini B, Maia I, Cavalcanti A, Berwanger O, Rosa R, Veiga V et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19. JAMA. 2020;324(13):1307.
11. Horby P, Lim W, Emberson J, Mafham M, Bell J, Linsell L et al. Dexamethasone in hospitalized patients with Covid-19 — Preliminary Report. New England Journal of Medicine. 2020;.
12. Ayerbe L, Risco C, Ayis S. The association between treatment with heparin and survival in patients with Covid-19. J Thromb Thrombolysis. 2020;50(2):298-301. https://doi.org/10.1007/s11239-020-02162-z.
13. Gonzalez-Porras JR, Belhassen-Garcia M, Bernus AL, Vaquero-Roncero LM. Low molecular weight heparin in adults inpatient COVID-19. https://doi.org/10.2139/ssrn.3586665
14. Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol. 2020;76(1):122-124. https://doi.org/10.1016/j.jacc.2020.05.001.Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094-1099. https://doi.org/10.1111/jth.14817
15. Rossi R, Coppi F, Talarico M, Boriani G. Protective role of chronic treatment with direct oral anticoagulants in elderly patients affected by interstitial pneumonia in COVID-19 era. Eur J Intern Med. 2020;77:158-160. https://doi.org/10.1016/j.ejim.2020.06.006
16. Tremblay D, van Gerwen M, Alsen M, et al. Impact of anticoagulation prior to COVID-19 infection: a propensity score–matched cohort study. Blood. 2020;136(1):144-147. https://doi.org/10.1182/blood.2020006941
17. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost. 2020;18(7):1743-1746. https://doi.org/10.1111/jth.14869.
18. Lemos ACB, do Espírito Santo DA, Salvetti MC, Gilio RN, Agra LB, Pazin-Filho A, et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). Thromb Res [Internet]. 2020;196:359–66. Available from: https://doi.org/10.1016/j.thromres.2020.09.026
19. Buetti, N., Mazzuchelli, T., Lo Priore, E., Balmelli, C., Llamas, M., Pallanza, M., Elzi, L., Consonni, V., Trimboli, P., Forni-Ogna, V. and Bernasconi, E., 2020. Early administered antibiotics do not impact mortality in critically ill patients with COVID-19. Journal of Infection, 81(2), pp.e148-e149. Available at: <www.sciencedirect.com/.../journal-of-infection/vol/81/issue/2> [Accessed 5 April 2021].
20. Asgharpour M, Mehdinezhad H, Bayani M,Zavareh MSH, Hamidi SH, Akbari R. et. al. Effectiveness of extracorporeal blood purification (hemoadsorption) in patients with severe coronavirus disease 2019 (COVID-19). BMC Nephrology. 2020; 21: 356, https://doi.org/10.1186/s12882-020-02020-3
21. Katagiri D, Ishikane M, Asai Y, et al. Direct hemoperfusion using a polymyxin B immobilized polystyrene column for COVID-19. J Clin Apher. 2020;1–9. https://doi.org/10.1002/jca.21861
22. Rampino T, Gregorini M, Perotti L, Ferrari F, Pattonlero EF, Grignano M. Hemoperfusion with CytoSorb as adjuvant therapy in critically ill patients with SARS-CoV2 pneumonia. Blood Pufi; 2020 Nov, DOI: 10.1159/000511725
23. Shadvar K, Tagizadiyeh A, Gamari AA, Soleimanpour H, Mahmoodpoor A. Hemoperfusion as a potential treatment for critically ill COVID-19 patients with cytokine storm. Blood Purif, 2020 Nov 10. DOI: 10.1159/000511391
24. Hajian S, Rastgoo N. The effect of hemoperfusion on the recovery of COVID-19 in hospitalized patients; case series and review study. Immunopathol Persa. 2021;7(2):e13. DOI:10.34172/ipp.2021.13.
25. Ishiwari M, Togashi Y, Takoi H, Kikuchi R, Kono Y, Abe S. Polymyxin B haemoperfusion treatment for respiratory failure and hyperferritinaemia due to COVID-19. Respirology Case Reports, 2020: 8(9), e00679, doi: 10.1002/rcr2.679

26. Kusaba Y, Izumi S, Takasaki J, Suzuki M, Katagiri D, Katsuno T, et. al. Successful Recovery from COVID-19-associated Acute Respiratory Failure with Polymyxin B-immobilized Fiber Column-direct Hemoperfusion. Intern Med 2020; 59: 2405-2408, doi: 10.2169/internalmedicine.5413-20
27. Moradi H, Abbasi S. Hemoperfusion as a Supportive Treatment in a COVID-19 Patient with Late Pulmonary Thromboembolism: A Case Report. International Medical Case Reports Journal. 2020: 13: 341-345.
28. Nihei Y, Nagasawa H, Fukao Y, Khara M, Ueda S, Gohda T, Suzuki Y. Continuous extracorporeal treatments in a dialysis patient with COVID-19. CEN Case Reports; 2020 Oct, https://doi.org/10.1007/s13730-020-00538-x
29. Vardanjani AE, Ronco C, Rafiel H, Golitaleb M, Pishvael MH, Mohammad M. Early Hemoperfusion for Cytokine Removal May Contribute to Prevention of Intubation in Patients Infected with COVID-19. Blood Purif. 2020 June, DOI: 10.1159/000509107
30. Hu W, Lin CW, Liu BW, Hu WH, Zhu Y. Extravascular lung water and pulmonary arterial wedge pressure for fluid management in patients with acute respiratory distress syndrome. Multidiscip Respir Med. 2014 Jan 16;9(1):3.
31. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL, National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006 Jun 15;354(24):2564-75.
32. Martin GS, Mangialardi RJ, Wheeler AP, Dupont WD, Morris JA, Bernard GR. Albumin and furosemide therapy in hypoproteinemic patients with acute lung injury. Crit Care Med. 2002 Oct;30(10):2175-82.
33. Martin GS, Moss M, Wheeler AP, Mealer M, Morris JA, Bernard GR. A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. Crit Care Med. 2005 Aug;33(8):1681-7.
34. Ferrando C, Mellado-Artigas R, Gea A, Arruti E, Aldecoa C et al. Awake prone positioning does not reduce the risk of intubation in COVID-19 treated with high-flow nasal oxygen therapy: a multicenter, adjusted cohort study. Critical Care. 2020; 24:597.
35. Jagan N, Morrow LE, Walters RW, Klein LP, Wallen TJ, et al. The POSITIONED Study: Prone positioning in non-ventilated coronavirus disease 2019 patients- a retrospective analysis. Critical Care Exploration. 2020; 2:e0229.
36. Padrao EMH, Valente FS, Besen B, Rahhal H, Mesquita PS et al. Awake prone positioning in COVID-19 hypoxemic respiratory failure: exploratory findings in a single-center retrospective cohort study. Academic Emergency Medicine 2020: 27(12):1249-1259
37. Teng XB, Shen Y, Han MF, Yang G et al. The value of high flow nasal cannula oxygen therapy in treating novel coronavirus pneumonia. Eur J Clin Invest. 2020.
38. Alharty A, Faqihi F, Noor A, Soliman I, Brindley PG, Karakitsos D et al. Helmet continuous positive airway pressure in the treatment of COVID-19 patients with acute respiratory failure could be an effective strategy: a feasibility study. Journal of Epidemiology and Global Health. 2020; 10(3):201-203.
39. Duan J, Chen B, Liu X, Shu W. Zhao W, Li J et al. Use of high-flow nasal cannula and non-invasive ventilation in patients with COVID-19: a multicenter observational study. American Journal of Emergency Medicine. 2020.
40. Franco C, Facciolongo N, Tonelli R, Dongili R, Vanello A, Pisani L et al. Feasibility and clinical impact of out-of ICU non-invasive respiratory support in patients with COVID-19 related pneumonia. European Respiratory Journal. 2020
41. Galton T, Bellani G, Foti G, Frazer MJ, Fuchs B, Cereda M. Early clinical experience in using helmet continuous positive airway pressure and high-flow nasal cannula in overweight and obese patients with acute hypoxemic respiratory failure from coronavirus disease 2019. Critical Care Explorations 2020.

42. Botta M, Tsonas AM, Pillay J, Boers LS, Algera AG, Bos LDJ, et al. Ventilation management and clinical outcomes in invasively ventilated patients with COVID-19 (PRoVENT-COVID): a national, multicentre, observational cohort study. Lancet Respir Med. 2020;19(20):1–10.
43. Udi J, Lang CN, Zotzmann V, Krueger K, Fluegle A, Bamberg F, et al. Incidence of Barotrauma in Patients With COVID-19 Pneumonia During Prolonged Invasive Mechanical Ventilation – A Case-Control Study. J Intensive Care Med. 2020;
44. Romano MLP, Maia IS, Laranjeira LN, Damiani LP, Paisani DDM, Borges MDC, et al. Driving Pressure-limited Strategy for Patients with Acute Respiratory Distress Syndrome A Pilot Randomized Clinical Trial. Ann Am Thorac Soc. 2020;17(5):596–604.
45. Yao W, Wang T, Jiang B, Gao F, Wang L, Zheng H et al. Emergency tracheal intubation in 202 patients with COVID-19 in Wuhan, China: lessons learnt and international expert recommendations. British Journal of Anaesthesia. 2020;125(1):e28-e37.
46. Weingart S, Trueger N, Wong N, Scofi J, Singh N, Rudolph S. Delayed Sequence Intubation: A Prospective Observational Study. Annals of Emergency Medicine. 2015;65(4):349-355.
47. Barbaro RP, MacLaren G, Boonstra PS, Iwashyna TJ, Slutsky AS, Fan E, et al. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. Lancet. 2020;396(10257):1071-8.
48. Marullo AG, Cavarretta E, Biondi Zoccai G, Mancone M, Peruzzi M, Piscioneri F, et al. Extracorporeal membrane oxygenation for critically ill patients with coronavirus-associated disease 2019: an updated perspective of the European experience. Minerva Cardioangiol. 2020;68(5):368-72.
49. Shaefi S, Brenner SK, Gupta S, O'Gara BP, Krajewski ML, Charytan DM, et al. Extracorporeal membrane oxygenation in patients with severe respiratory failure from COVID-19. Intensive Care Medicine. 2021;47(2):208-21.
50. Schmidt M, Hajage D, Lebreton G, Monsel A, Voiriot G, Levy D, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. Lancet Respir Med. 2020;8(11):1121-31.
51. Jacobs JP, Stammers AH, St Louis J, Hayanga JWA, Firstenberg MS, Mongero LB, et al. Extracorporeal Membrane Oxygenation in the Treatment of Severe Pulmonary and Cardiac Compromise in Coronavirus Disease 2019: Experience with 32 Patients. Asaio j. 2020;66(7):722-30.
52. Yang X, Cai S, Luo Y, Zhu F, Hu M, Zhao Y, et al. Extracorporeal Membrane Oxygenation for Coronavirus Disease 2019-Induced Acute Respiratory Distress Syndrome: A Multicenter Descriptive Study. Crit Care Med. 2020;48(9):1289-95.
53. Supady A, DellaVolpe J, Taccone FS, Scharpf D, Ulmer M, Lepper PM, et al. Outcome Prediction in Patients with Severe COVID-19 Requiring Extracorporeal Membrane Oxygenation—A Retrospective International Multicenter Study. Membranes. 2021;11(3):170.
54. Gorenstein S, Castellano M, Slone E, Gillette B, Liu H, Alsamarraie C et al. Hyperbaric oxygen therapy for COVID-19 patients with respiratory distress: treated cases versus propensity-matched controls. Undersea and Hyperbaric Medical Society [Internet]. 2020 [cited 25 March 2021];47(3). Available from: https://pubmed.ncbi.nlm.nih.gov/32931666/
55. Montero-Baladia, M., et al. "Etoposide treatment adjunctive to immunosuppressants for critically ill COVID-19 patients." The Journal of Infection, 81(3) (2020), 452-482. https://doi.org/10.1016/j.jinf.2020.06.006
56. Patel, M., Dominguez, E., Sacher, D., Desai, P., Chandar, A., Bromberg, M., Caricchio, R., Criner, G. J., & Temple University COVID-19 Research Group (2021). Etoposide as Salvage Therapy for Cytokine Storm Due to Coronavirus Disease 2019. Chest, 159(1), e7-e11. https://doi.org/10.1016/j.chest.2020.09.077
57. Liu K, Zhang W, Yang Y, Zhang J, Li Y, Chen Y. Respiratory rehabilitation in elderly patients with COVID-19: A randomized controlled study. Complement Ther Clin Pract [Internet]. 2020;39:101166. Available from: https://doi.org/10.1016/j.ctcp.2020.101166" https://doi.org/10.1016/j.ctcp.2020.101166

58. He M, Yu S, Wang L, Lv H, Qiu Z. Efficiency and safety of pulmonary rehabilitation in acute exacerbation of chronic obstructive pulmonary disease. Med Sci Monit. 2015 Mar 18;21:806-12. doi: 10.12659/MSM.892769. PMID: 25783889; PMCID: PMC4374486.

PHILIPPINE COVID-19 LIVING RECOMMENDATIONS

Non-Pharmacologic Interventions

Evidence and Recommendations for the Non-Pharmacologic Interventions for COVID-19

Should cloth masks be used in the prevention and control of COVID-19 infection?

RECOMMENDATION
We recommend that healthcare workers not directly taking care of COVID-19 patients, and other persons with high risk of exposure to COVID-19 should use properly fitted surgical masks instead of cloth masks. (Moderate quality of evidence; Strong recommendation)

RECOMMENDATION
We suggest using a cloth mask that fits snugly on the face and made of at least two layers of cotton (e.g., t-shirt fabric) or non-woven nylon with aluminum nose bridge by the general public with low risk of exposure to COVID-19 in outdoor or indoor areas to prevent COVID-19 infections. (Low quality of evidence; Conditional recommendation)

KEY FINDINGS

There is low-certainty evidence on the effectiveness of cloth masks compared with medical masks in preventing COVID-19 infections among the general population. There are no completed clinical trials or observational studies directly evaluating cloth masks compared with surgical masks in preventing SAR-CoV-2 transmission among healthcare workers or community dwellers. However, there is indirect evidence from a randomized controlled trial (RCT) investigating the use of surgical masks in the general public to prevent SARS-CoV-2 infection [1].

CONSENSUS ISSUES

The consensus panel agreed to base these recommendations on the exposure level to SARS-CoV-2 instead of population subgroups (i.e., general public versus healthcare workers). The ethical implications of recommending cloth masks instead of medical masks for the general public in cases where there are no shortages of medical masks was also considered.

A separate review question is needed to determine the appropriateness of cloth masks for vulnerable populations (e.g., immunocompromised patients, elderly, those with comorbidities), as the current evidence did not provide sufficient data to allow subgroup analysis for these vulnerable populations.

Although cloth masks are more practical to use than medical grade masks, the type of cloth and number of layers required should be specified. Guidelines on its proper disposal and reuse are also needed to reduce the risk of transmission. The need to

educate the public on the proper wearing of mask was deemed to be equally important as well to achieve its intended protection against COVID-19.

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

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

KEY FINDINGS

No direct evidence was found assessing the effectiveness of ionizing air filters in reducing SARS-CoV-2 infections. Five experimental studies [2-6] reported using an ionizing air purifier in reducing airborne particles, mostly in uninhabited laboratory settings. Ionizing air purifiers can efficiently remove the fine and ultrafine particles. However, its effectiveness in eliminating airborne organisms for infection control is lacking. Ozone, a dangerous respiratory irritant produced by some ionizing air purifiers, is a health risk to users. Overall, most of the studies were at high risk of bias, with common issues on selecting tested ionizing air purifiers and the assessor's blinding.

CONSENSUS ISSUES

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

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

RECOMMENDATION
We recommend against the use of footbaths for the prevention and control of COVID-19 transmission. (Very low quality of evidence; Strong recommendation)

KEY FINDINGS

No evidence was found evaluating the effectiveness of footbaths in preventing or controlling COVID-19 infections. The only study that could possibly explain the concomitant use of foot baths was the presence of SARS-CoV-2 particles found on the front of shoes of a health professional in Singapore [7]. However, the risk of

transmission through this route was low since the viral particle was isolated only in that one PPE swab and was not replicated in any of the other samples taken within the facility. Furthermore, viral culture was not done to demonstrate the viability of that viral particle found on the shoe.

CONSENSUS ISSUES

No issues were raised during the consensus panel meeting.

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

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

KEY FINDINGS

There are no existing or ongoing studies investigating the effectiveness and safety of sanitation tents for preventing and/or controlling COVID-19 infections. Indirect evidence from a rapid systematic review [8] of 6 laboratory studies and 1 in-vitro case control study showed effective viral inactivation after application of various cleaning products. However, disinfecting substances pose significant health risks, especially when used outside their manufacturer's recommendation or with repeated, prolonged exposure [9].

CONSENSUS ISSUES

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

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

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

KEY FINDINGS

No direct evidence was found evaluating the effectiveness of ultraviolet lamps in the prevention and control of COVID-19 infections in public spaces in locations with sustained community transmission. Indirect evidence of low quality showed some benefit in reducing the incidence of viral infection in a hospital ward [10-14]. However, the evidence for its potential harm such as skin erythema, ocular itching, blurring and conjunctival injections, was more significant [15].

CONSENSUS ISSUES

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

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

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

KEY FINDINGS

No direct evidence was found assessing the effectiveness of HEPA filters in preventing and controlling COVID-19 infection in public spaces and locations with sustained community transmission. Low quality evidence from 3 laboratory experiments and 1 case series demonstrated that HEPA filters appear to significantly improve air quality [16-19].

CONSENSUS ISSUES

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

lifespan. Despite the use of HEPA filters, minimum health standards should still be observed.

What are effective decontamination techniques for N95 reuse?

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

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

KEY FINDINGS

Eight quasi-experimental studies [20-27] reported the effects of six decontamination techniques (i.e., alcohol, autoclave, moist heat, HPV, PAF, UVGI) on SARS-CoV-2 laden N95 masks. There is low evidence on use of Hydrogen Peroxide Vapor (HPV), Ultraviolet Germicidal Irradiation (UVGI), moist heat and peracetic acid dry fogging system (PAF) as options for N95 mask decontamination. These decontamination methods resulted in ≥4.79 log10 reductions in SARS-CoV-2. Except for autoclave, they preserved the quality fit of N95 masks after 10 decontamination cycles. There is very low evidence against the use of autoclave and alcohol for N95 mask decontamination as these methods alter N95 integrity and degrade filtration efficacy.

CONSENSUS ISSUES

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

Regarding local availability, some noted that HPV is usually not afforded in resource-limited settings, making UVGI a preferable option due to its lower cost. In practice, however, HPV is considered more effective in decontamination. Its mist can reach all the spaces once halo fogging is done, which is beneficial to N95 mask since it has many pores. In contrast, UVGI can only disinfect the area reached by the UV light. Although HPV is available in the country, its use will entail the need for a special

decontamination room and a machine. Some noted that HPV is usually not affordable in resource-limited settings. The panel also stressed the importance of checking the condition of the N95 mask before decontamination and not just solely rely on the manufacturer's recommendation. Likewise, the proper procedure before decontamination should also be emphasized.

On the recommendation against the use of autoclave, it was clarified that although it can destroy the virus, the physical and functional integrity of the N95 mask is affected.

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

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

KEY FINDINGS

Five observational studies [28-32] investigated the effectiveness of PPE use in reducing SARS-CoV-2 transmission among healthcare workers involved in surgical aerosol-generating procedures (AGP).

Very low evidence suggests the protective effect of an appropriate PPE on surgeons engaged in AGP procedures of suspected or confirmed COVID-19 patients. Consistent N95 mask use reduced the odds of SARS-CoV-2 infections significantly than inconsistent N95 use among healthcare workers involved AGP. Consistent gown use significantly reduced the odds of SARS-CoV-2 infections than inconsistent gown use amongst healthcare workers performing AGP. Consistent glove use reduced the odds of SARS-CoV-2 significantly than inconsistent glove use among healthcare workers performing AGP. Very low evidence suggests the protective effects of N95 mask, gown, gloves, face shield/goggles, apron, and scrub hat in reducing SARS-CoV-2 transmission among healthcare workers performing AGP procedures.

CONSENSUS ISSUES

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

strict adherence to protocols and the appropriate use of this minimum PPE to prevent COVID-19 infection.

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

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

KEY FINDINGS

There are no available direct evidence comparing the effectiveness of N95 versus surgical mask in COVID-19 infection among healthcare workers in the outpatient setting. Meta-analysis comparing the two among healthcare workers in general showed no significant difference in their effectiveness in preventing clinical and laboratory viral infection [33]. One RCT [34] investigated the difference of N95 and surgical mask in protecting healthcare workers in different outpatient setting from viral respiratory infection and noted no significant difference between the two. Indirect evidence also shows more adverse skin reactions for those wearing N95 respirators as compared to surgical masks [35, 36]. The use of face shield on the other hand in addition to face mask provided added protection from acquiring COVID-19 among community healthcare workers in India based on a before and after study [37]. The use of gowns and gloves are standards of care in medicine whenever handling patient's body fluids and this recommendation is still applicable in the current setting.

CONSENSUS ISSUES

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

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

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

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

KEY FINDINGS

Three studies [38-40] and a case report [41] were found on the use of PPE among health care workers to prevent COVID infection. Moderate certainty evidence from three studies showed that the use of Level 2 PPE (disposable hat, medical protective mask (N95 or higher standard), goggles (anti-fog) or protective mask (anti-fog), medical gown clothing or white coats covered by medical protective clothing, disposable gloves and disposable shoe covers), N95 respirators and face shields protected health care workers in hospital settings from COVID-19 infections. On the other hand, very low certainty evidence showed no significant protective effect from the use of face/surgical masks, gowns, and/or disposable gloves if used individually.

CONSENSUS ISSUES

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

Should facemask plus face shield be used rather than facemask alone to reduce SARS COV2 transmission?

RECOMMENDATION
We suggest the use of face mask plus protective eyewear in the form of face shield or goggles for the general public in areas with sustained community transmission of SARS-COV2. (Very low quality of evidence; Conditional recommendation)

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

KEY FINDINGS

There was no available direct evidence for face shield plus face mask versus face mask alone against COVID-19 in the general public. One case-control study [42] ascertained the effectiveness of face shield in reducing the risk of SARS COV 2 among healthcare workers (HCW). The use of face shield/goggles in addition to other personal protective equipment offered significant protection during usual care of patients with COVID-19 infection compared to non-use of face shield/goggles, but this protection was not evident during the performance of aerosol-generating procedures. The study is of low quality being non-randomized and unadjusted for potential confounders.

A reduction in the proportion of SARS-COV-2 -affected healthcare workers was demonstrated in two pre- and post- surveillance studies [43,44] after routine use of face shield was required in one hospital in the United States and in one community in India. The addition of face shield to standard masks and personal protective equipment was associated with lower SARS-COV infection compared to standard practice of personal protective equipment alone. The studies were of very low quality with high risk of bias.

Overall, the use of face shield in addition to face mask was associated with significant reduction of viral transmission of SARS-COV2 among healthcare workers compared to face mask alone.

CONSENSUS ISSUES

The panel remarked that none of the studies considered ventilation. Eye protection is more for droplet transmission while airborne transmission would require better fitting masks.

Regarding the recommendation for the general public, it was clarified that the term "face mask" may also pertain to cloth mask, considering the concurrent recommendation of the Philippine COVID-19 Living CPG, which states that:

> "We suggest using a cloth mask that fits snugly on the face and made of at least two, layers of cotton (e.g., t-shirt fabric) or non-woven nylon with aluminum nose bridge for, the general public with low risk of exposure to COVID-19 in outdoor or indoor areas to, prevent COVID-19 infections. (Low quality of evidence; Conditional recommendation)"

The recommendation for health care workers is specific for areas with sustained community transmission of SARS-COV-2 so that it will not be misconstrued that the use of face shield plus medical face mask will be part of the standard PPE even without the pandemic.

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

RECOMMENDATION
We suggest against the use of protective physical barrier enclosures (ex. aerosol box) for the prevention of COVID-19 among health care providers who perform aerosol generating medical procedures*. (Very low quality of evidence; Conditional recommendation) **Proper PPEs should be used by health care providers when performing aerosol-generating procedures.*

RECOMMENDATION
We suggest the use of protective physical barriers in the prevention of COVID-19 in areas where physical distancing cannot be adhered to (e.g., offices, reception desk)**. (Very low quality of evidence; Conditional recommendation) ***Adequate ventilation, physical distancing, use of facemasks and personal hygiene should still be maintained to prevent COVID-19 infections. Regular cleaning and disinfection of physical barriers should be practiced.*

KEY FINDINGS

Two case series [45, 46] reported that there were no COVID-19 infections among health care providers who used protective barrier enclosures during aerosol generating procedures on COVID-19 patients. One systematic review [47] reported that barrier devices were effective at either preventing or reducing the number of particles escaping the system only when negative pressure suction was applied. As for physical barriers (i.e., sneeze guards), we did not find any studies on its efficacy in preventing COVID-19 infections. Two computational fluid-particle dynamics [48, 49] simulation studies, however, showed that physical barriers could potentially reduce aerosol transmission within shared spaces such as classrooms or airplane cabins.

CONSENSUS ISSUES

Protective physical barrier enclosures refer to passive protective barriers that were used to protect the health care workers during the early stages of the pandemic when PPE supplies were limited. The physical barrier enclosure can be used as an additional layer of protection in situations where the HCP does not have adequate PPE for aerosol generating procedures. However, these barriers should be used with suction or negative pressure devices to reduce the risk of transmission from secondary aerosols that are trapped underneath the plastic barrier. Previous studies showed that aerosols can still escape a physical barrier enclosure. In addition, concerns related to efficiency and usability of such barriers have also been reported, such as: (1) longer intubation time; (2) difficulty in maneuvering the arms because of the rigidity of the box; (3) view of the anesthesiologist or ER doctor is blocked by the plastic or acrylic

box). The Philippine Society of Anesthesiologists (PSA) also no longer recommends the use of physical barrier enclosures.

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

Should surfaces be disinfected to prevent COVID-19 infection?

RECOMMENDATION
We recommend the practice of cleaning and disinfecting surfaces using the appropriate disinfecting chemical agents such as 0.5% sodium hypochlorite solution (bleach) or 70% alcohol to prevent COVID-19 infection. (Low quality of evidence; Strong recommendation) For high touch surfaces and high traffic areas, such as in the workplace, disinfection should be done before shift, intermittently during shift and after the shift. For household disinfection, once daily disinfection on high touch surfaces is recommended.

KEY FINDINGS

No randomized controlled studies were found directly addressing this question. Indirect evidence from a rapid systematic review [50] provided data on the effects of cleaning products on SARS-CoV-2 inactivation. Laboratory studies showed that SARS-CoV-2 is inactivated by common disinfectants within 1 minute when used according to their manufacturer's specifications and precautionary measures. However, disinfectants such as 0.1% sodium hypochlorite and 70% alcohol are potential irritants to the skin, ocular tissue, and respiratory tract and should be handled with proper protection and precaution.

CONSENSUS ISSUES

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

References

1. Bungaard H, Bundgaard JS, Raaschu-Pedersen DET, Buchwald CV, Todsen T, Norsk JB et al. Effectiveness of adding a mask recommendation to other public health measures to prevent SARS-CoV-2 infection in Danish mask wearers. Annals of Internal Medicine 2020. Accessed from: doi:10.7326/m20-6817

2. Berry D, Mainelis G, Fennell D. Effect of an Ionic Air Cleaner on Indoor/Outdoor Particle Ratios in a Residential Environment. Aerosol Science and Technology. 2007 Apr;41(3):315–28.
3. Grinshpun SA, Mainelis G, Trunov M, Adhikari A, Reponen T, Willeke K. Evaluation of ionic air purifiers for reducing aerosol exposure in confined indoor spaces. Indoor Air. 2005 Aug;15(4):235–45.
4. Hyun J, Lee S-G, Hwang J. Application of corona discharge-generated air ions for filtration of aerosolized virus and inactivation of filtered virus. Journal of Aerosol Science. 2017 May;107:31–40.
5. Shi S, Zhu S, Lee ES, Zhao B, Zhu Y. Performance of wearable ionization air cleaners: Ozone emission and particle removal. Aerosol Science and Technology. 2016 Mar 3;50(3):211–21.
6. Huang R, Agranovski I, Pyankov O, Grinshpun S. Removal of viable bioaerosol particles with a low-efficiency HVAC filter enhanced by continuous emission of unipolar air ions. Indoor Air. 2008 Apr;18(2):106–12.
7. Ong SWX, Tan YK, Chia PY, et al. Air, Surface Environmental, and Personal Protective Equipment Contamination by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) From a Symptomatic Patient. JAMA. 2020; Published online: March 4. DOI:10.1001/jama.2020.3227.
8. Shimabukuro PMS, Duarte ML, Imoto AM, Atallah ÁN, Franco ESB, Peccin MS, Taminato M. Environmental cleaning to prevent COVID-19 infection. A rapid systematic review. Sao Paulo Med J. 2020 Nov-Dec;138(6):505-514. doi: 10.1590/1516-3180.2020.0417.09092020. PMID: 33206913.
9. Aseni Wickramatillake, Changa Kurukularatne, SARS-CoV-2 human disinfection chambers: a critical analysis, Occupational Medicine, Volume 70, Issue 5, July 2020, Pages 330–334, https://doi.org/10.1093/occmed/kqaa078
10. Hickerson RP, Conneely MJ, Tsutsumi SKH, Wood K, Jackson DN, Ibbotson SH,Eadie E. Minimal, superficial DNA damage in human skin from filtered far-ultraviolet-C (UV-C). Br J Dermatol. 2021 Jan 16. doi: 10.1111/bjd.19816. Epub ahead of print. PMID: 33452809.
11. Derraik JGB, Anderson WA, Connelly EA, Anderson YC. Rapid Review of SARS-CoV-1 and SARS-CoV-2 Viability, Susceptibility to Treatment, and the Disinfection and Reuse of PPE, Particularly Filtering Facepiece Respirators. Int J Environ Res Public Health. 2020 Aug 22;17(17):6117. doi: 10.3390/ijerph17176117. PMID: 32842655; PMCID: PMC7504573.
12. Buonanno M, Ponnaiya B, Welch D, Stanislauskas M, Randers- Pehrson G, Smilenov L, et al. Germicidal efficacy and mammalian skin safety of 222-nm UV light. Radiat Res 2017;187:483-91.
13. Pavia M, Simpser E, Becker M, Mainquist WK, Velez KA. The effect of ultraviolet-C technology on viral infection incidence in a pediatric long-term care facility. Am J Infect Control 2018;46:720-2.
14. Ramos CCR, Roque JA, Sarmiento DB, Suarez LEG, Sunio JTP, Hilario AL. Use of ultraviolet-C in environmental sterilization in hospitals: A systematic review on efficacy and safety. International Journal of Health sciences. 2020Nov;14(6):52–65.
15. Lyons, A.B., Narla, S., Torres, A.E., Parks-Miller, A., Kohli, I., Ozog, D.M., Lim, H.W. and Hamzavi, I.H. (2021), Skin and eye protection against ultraviolet C from ultraviolet germicidal irradiation devices during the COVID-19 pandemic. Int J Dermatol. https://doi.org/10.1111/ijd.15255
16. Qian H, Li Y, Sun H, Nielsen PV, Huang X, Zheng X (2010). Particle removal efficiency of the portable HEPA air cleaner in a simulated hospital ward. Building Simulation. 3:215-224.
17. Gedic IE and Alar T (2020). Protective measures undertaken during chest tube thoracostomy in COVID-19 outbreak. Indian Journal of Thoracic and Cardiovascular Surgery. https://doi.org/10.1007/s12055-020-01090-0
18. J.P. Gibbons, J. Hayes , C.J. Skerritt , J.M. O'Byrne , C.J. Green . Custom solution for personal protective equipment (PPE) in the orthopaedic setting: retrofitting Stryker Flyte T5 PPE system. Journal of Hospital Infection 108 (2021) 55e63.
19. Perry JL, Agui JH, Vijayakumar R. Submicron and Nanoparticulate Matter Removal by HEPA-Rated Media Filters and Packed Beds of Granular Materials. USA: National Aeronautics and

Space Administration. NASA/TM-2016-218224. May 2016. Downloaded from https://ntrs.nasa.gov/search.jsp?R=20170005166.
20. Fischer RJ, Morris DH, van Doremalen N, Sarchette S, Matson MJ, Bushmaker T, et al. Assessment of N95 respirator decontamination and re-use for SARS-CoV-2 [Internet]. Infectious Diseases (except HIV/AIDS); 2020 Apr [cited 2021 Jan 29]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.04.11.20062018
21. Smith JS, Hanseler H, Welle J, Rattray R, Campbell M, Brotherton T, et al. Effect of various decontamination procedures on disposable N95 mask integrity and SARS-CoV-2 infectivity. J Clin Trans Sci. 2020 Jun 11;1–5.
22. Kumar A, Kasloff SB, Leung A, Cutts T, Strong JE, Hills K, et al. N95 Mask Decontamination using Standard Hospital Sterilization Technologies [Internet]. Infectious Diseases (except HIV/AIDS); 2020 Apr [cited 2021 Jan 31]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.04.05.20049346
23. Daeschler SC, Manson N, Joachim K, Chin AWH, Chan K, Chen PZ, et al. Effect of moist heat reprocessing of N95 respirators on SARS-CoV-2 inactivation and respirator function. CMAJ. 2020 Oct 13;192(41):E1189–97.
24. Ibáñez-Cervantes G, Bravata-Alcántara JC, Nájera-Cortés AS, Meneses-Cruz S, Delgado-Balbuena L, Cruz-Cruz C, et al. Disinfection of N95 masks artificially contaminated with SARS-CoV-2 and ESKAPE bacteria using hydrogen peroxide plasma: Impact on the reutilization of disposable devices. Am J Infect Control. 2020 Sep;48(9):1037–41.
25. Simmons SE, Carrion R, Alfson KJ, Staples HM, Jinadatha C, Jarvis WR, et al. Deactivation of SARS-CoV-2 with pulsed-xenon ultraviolet light: Implications for environmental COVID-19 control. Infect Control Hosp Epidemiol. 2020 Aug 3;1–4.
26. Ozog DM, Sexton JZ, Narla S, Pretto-Kernahan CD, Mirabelli C, Lim HW, et al. The effect of ultraviolet C radiation against different N95 respirators inoculated with SARS-CoV-2. Int J Infect Dis. 2020 Nov;100:224–9.
27. Czubryt MP, Stecy T, Popke E, Aitken R, Jabusch K, Pound R, et al. N95 mask reuse in a major urban hospital: COVID-19 response process and procedure. Journal of Hospital Infection. 2020 Oct;106(2):277–82.
28. Chatterjee R, Bajwa S, Dwivedi D, Kanji R, Ahammed M, Shaw R. COVID-19 Risk Assessment Tool: Dual application of risk communication and risk governance. Progress in Disaster Science. 2020 Oct;7:100109.
29. Heinzerling A, Stuckey MJ, Scheuer T, Xu K, Perkins KM, Resseger H, et al. Transmission of COVID-19 to Health Care Personnel During Exposures to a Hospitalized Patient — Solano County, California, February 2020. MMWR Morb Mortal Wkly Rep. 2020 Apr 17;69(15):472–6.
30. Khalil MM, Alam MM, Arefin MK, Chowdhury MR, Huq MR, Chowdhury JA, et al. Role of Personal Protective Measures in Prevention of COVID-19 Spread Among Physicians in Bangladesh: a Multicenter Cross-Sectional Comparative Study. SN Compr Clin Med. 2020 Aug 28;1–7.
31. Liu M, Cheng S-Z, Xu K-W, Yang Y, Zhu Q-T, Zhang H, et al. Use of personal protective equipment against coronavirus disease 2019 by healthcare professionals in Wuhan, China: cross sectional study. BMJ. 2020 Jun 10;369:m2195.
32. Periyasamy P, Ng BH, Ali UK, Rashid ZZ, Kori N. Aerosolized SARS-CoV-2 transmission risk: Surgical or N95 masks? Infect Control Hosp Epidemiol. 2020 Sep 15;1–2.
33. Smith JD, MacDougall CC, Johnstone J, Copes RA, Schwartz B, Garber GE. Effectiveness of N95 respirators versus surgical masks in protecting health care workers from acute respiratory infection: A systematic review and meta-analysis. CMAJ [Internet]. 2016 May 17 [cited 2021 Apr 2];188(8):567–74. Available from: https://pubmed.ncbi.nlm.nih.gov/26952529/
34. Radonovich LJ, Simberkoff MS, Bessesen MT, Brown AC, Cummings DAT, Gaydos CA, et al. N95 respirators vs medical masks for preventing influenza among health care personnel: A randomized clinical trial. JAMA - J Am Med Assoc. 2019;322(9):824–33.

35. Trepanowski N, Larson AR, Evers-Meltzer R. Occupational dermatoses among front-line health care workers during the COVID-19 pandemic: A cross-sectional survey. J Am Acad Dermatol. 2021 Jan 1;84(1):223–5.
36. Foo CCI, Goon ATJ, Leow Y-H, Goh C-L. Adverse skin reactions to personal protective equipment against severe acute respiratory syndrome-a descriptive study in Singapore.
37. Bhaskar ME, Arun S. SARS-CoV-2 Infection among Community Health Workers in India before and after Use of Face Shields. Vol. 324, JAMA - Journal of the American Medical Association. American Medical Association; 2020. p. 1348–9.
38. Wang Q, Huang X, Bai Y, et al. Epidemiological characteristics of COVID-19 in medical staff members of neurosurgery departments in Hubei province: a multicentre descriptive study. medRxiv 2020; published online April 24. DOI:10.1101/2020.04.20.20064899 (preprint).
39. Al Mohajer M, Panthagani KM, Lasco T, Lembcke B, Hemmige V. Association between universal face shield in a quaternary care center and reduction of SARS-COV2 infections among healthcare personnel and hospitalized patients. Int J Infect Dis. 2021 Apr; 105:252-255. doi: 10.1016/j.ijid.2021.02.060. Epub 2021 Feb 18. PMID: 33610788; PMCID: PMC7891045.
40. Wang X, Pan Z, Cheng Z. Association between 2019-nCoV transmission and N95 respirator use. J Hosp Infect 2020; May;105(1):104-105. doi: 10.1016/j.jhin.2020.02.021. Epub 2020 Mar 3. PMID: 32142885; PMCID: PMC7134426.
41. Heinzerling A, Stuckey MJ, Scheuer T, Xu K, Perkins KM, Resseger H, Magill S, Verani JR, Jain S, Acosta M, Epson E. Transmission of COVID-19 to Health Care Personnel During Exposures to a Hospitalized Patient - Solano County, California, February 2020. MMWR Morb Mortal Wkly Rep. 2020 Apr 17;69(15):472-476. doi: 10.15585/mmwr.mm6915e5. PMID: 32298249; PMCID: PMC7755059.
42. Khalil MdM, Alam MM, Arefin MK, Chowdhury MR, Huq MR, Chowdhury JA, et al. Role of Personal Protective Measures in Prevention of COVID-19 Spread Among Physicians in Bangladesh: a Multicenter Cross-Sectional Comparative Study. SN Compr Clin Med. 2020 Oct;2(10):1733–9.
43. Mohajer M, Panthagani KM, Lasco T, Lembcke B, Hemmige V. Association between universal face shield in a quaternary care center and reduction of SARS-COV-2 infections among healthcare personnel and hospitalized patients. International Journal of Infectious Diseases. 2021 Apr;105:252–5.
44. Bhaskar ME, Arun S. SARS-CoV-2 Infection Among Community Health Workers in India Before and After Use of Face Shields. JAMA. 2020 Oct 6;324(13):1348.
45. Giampalmo M, Pasquesi R, Solinas E. Easy and Accessible Protection against Aerosol Contagion during Airway Management. Anesthesiology. 2020;133(3):686-7.
46. Convissar D, Chang CY, Choi WE, Chang MG, Bittner EA. The Vacuum Assisted Negative Pressure Isolation Hood (VANISH) System: Novel Application of the Stryker Neptune™ Suction Machine to Create COVID-19 Negative Pressure Isolation Environments. Cureus. 2020;12(5):e8126.
47. Price C, Ben-Yakov M, Choi J, Orchanian-Cheff A, Tawadrous D. Barrier enclosure use during aerosol-generating medical procedures: A scoping review. Am J Emerg Med. 2021;41:209-18.
48. Abuhegazy M, Talaat K, Anderoglu O, Poroseva SV. Numerical investigation of aerosol transport in a classroom with relevance to COVID-19. Phys Fluids (1994). 2020;32(10):103311. doi:10.1063/5.0029118
49. Talaat K, Abuhegazy M, Mahfoze OA, Anderoglu O, Poroseva SV. Simulation of aerosol transmission on a Boeing 737 airplane with intervention measures for COVID-19 mitigation. Phys Fluids (1994). 2021 Mar 1;33(3):033312. doi: 10.1063/5.0044720. Epub 2021 Mar 16. PMID: 33897238; PMCID: PMC8060968.
50. Takagi G, Yagishita K. Principles of Disinfectant Use and Safety Operation in Medical Facilities During Coronavirus Disease 2019 (COVID-19) Outbreak [published online ahead of print, 2020 Jul 18]. SN Compr Clin Med. 2020;1-4. doi:10.1007/s42399-020-00413-x

PHILIPPINE COVID-19 LIVING RECOMMENDATIONS

Vaccines and Prophylactic Interventions

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

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

RECOMMENDATION
We recommend the use of the following vaccines to prevent symptomatic SARS-CoV-2 infection in adults: (Moderate quality of evidence; Strong recommendation) a. BNT162b2 (Pfizer/BioNTech) (given as 0.3ml (30ug) intramuscular injections, in 2 doses, 21 days apart) b. mRNA-1273 (Moderna) (given as 0.5ml (100ug) intramuscular injections, in 2 doses, 28 days apart) c. ChAdOx1 (AstraZeneca) (given as 0.5 ml (5 x 106 vp) intramuscular injections, in 2 doses, at least 12 weeks apart) d. Gam-COVID-Vac (Gamaleya) (given as rAd-26 0.5ml intramuscular injection, then rAd-5S 0.5 ml intramuscular injection 21 days after) e. Ad26.COV2.S (Janssen/Johnson&Johnson) (given as 0.5ml single dose intramuscular injection) We recommend the use of CoronaVac (Sinovac) (given as 0.5ml (600SU) intramuscular injection, in 2 doses, at 28 days apart) to prevent symptomatic SARS-CoV-2 infection among adults. (Low quality of evidence; Strong recommendation)

CONSENSUS ISSUES

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

Regarding Coronavac, a strong recommendation was made despite the low quality of evidence because the panel considered its availability and the high vaccine efficacy in preventing severe COVID-19. Although a 14-day dosing interval was used in the trial, the recommendation of a 28-day dosing interval was based on the submission of the manufacturer to the Hongkong Food and Health Bureau. A longer interval showed higher vaccine efficacy rates based on the immunogenicity data (seroconversion on 14-days versus 28-days) and the result of the subgroup analysis (<21 days versus >21 days). It was likewise explained that in general, increasing the interval between the doses of vaccines provides better immunogenicity by giving ample time for the population of lymphocytes in the lymph nodes to be replenished, thus resulting to a more robust immune response.

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

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

CONSENSUS ISSUES

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

The panel did not make a recommendation for or against the use of CoronaVac in the elderly due to the very low quality of evidence wherein the interim analysis showed imprecision because of the very wide confidence interval for symptomatic COVID-19 and there is no disaggregation of data into mild, moderate or severe COVID-19 in older adults >60 y/o. There is also no data on harm.

RECOMMENDATION
We recommend the use of BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya), CoronaVac (Sinovac) and Ad26.COV2.S (Janssen/ Johnson&Johnson) vaccines in pregnant and lactating women after consultation with a physician. (Very low quality of evidence; Strong recommendation)

CONSENSUS ISSUES

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

of the benefits and risks of the vaccination, specific to its timing of administration during the pregnancy. Physicians should be educated on these risks and benefits for the delivery of proper advice.

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

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

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

CONSENSUS ISSUES

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

RECOMMENDATION
We recommend the use of BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya), CoronaVac (Sinovac) and Ad26.COV2.S (Janssen/ Johnson&Johnson) vaccines to prevent SARS-CoV-2 infection in immunocompromised patients (i.e., diagnosed with HIV, hepatitis B and C, those with cancer undergoing chemotherapy, transplant patients receiving immune-suppression) after medical clearance from a physician. (Low quality of evidence; Strong recommendation)

CONSENSUS ISSUES

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

RECOMMENDATION
We recommend the use of BNT162b2 (Pfizer/BioNTech)vaccine in children 12 years old and above to prevent SARS-CoV-2 infection. (Moderate quality of evidence, Strong recommendation)

RECOMMENDATION
There is no evidence on the use of mRNA-1273 (Moderna), ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya), Ad26.COV2.S (Janssen/ Johnson&Johnson) and CoronaVac (Sinovac) among children <18 years old to prevent SARS-CoV-2 infection.

CONSENSUS ISSUES

The updated recommendation on the use of the vaccines in children was based mainly on the preliminary results in the BNT162b2 clinical trial data from its adolescent population, demonstrating clear benefit over harm.

ChAdOx1 also included children in the trial protocol, however, the results are still pending. Based on existing protocols, children are excluded in the clinical trials of mRNA-1273, GamCOVID-Vac, Ad26.COV2.S and CoronaVac. There is no statement of planned recruitment for the younger population.

RECOMMENDATION
We recommend against the use of these vaccines for those who have known allergies to the contents / excipients of the vaccine, such as polysorbate (ChAdOx1 (Astrazeneca), Gam-COVID-Vac (Gamaleya) and Ad26.COV2.S (Janssen/ Johnson&Johnson)) and polyethylene glycol or PEG200 DMG (BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna)). (Moderate to high quality of evidence; Strong recommendation)

CONSENSUS ISSUES

It was clarified that the recommendation was specific for polysorbate and PEG because these two (2) excipients are notorious for hypersensitivity reactions based on different regulatory authorities. CoronoVac does not contain any of these, but the

Philippine Society of Allergy, Asthma and Immunology (PSAAI) has been receiving reports on allergic reactions to CoronaVac and this is currently being investigated.

KEY FINDINGS

As of May 13, 2021 preliminary Phase 3 trial data on the safety and efficacy of six COVID-19 vaccines have been made publicly available. The BNT162b2 (Pfizer/BioNTech), the mRNA-1273 (Moderna), the ChAdOx1 (AstraZeneca), the Gam-COVID-Vac (Gamaleya), and the Ad26.Cov2.S (Janssen/Johnson&Johnson) vaccines demonstrated satisfactory vaccine efficacy against symptomatic COVID-19 infection among adults in the short term with moderate certainty. Limited available information provides low certainty evidence that the CoronaVac (Sinovac) vaccine also provides satisfactory protection against symptomatic COVID-19 infection among adults. Updated trial report showed that BNT162b2 (Pfizer/BioNTech) is highly efficacious and safe against symptomatic COVID-19 infection for children aged 12 to 15 years old. Data on the efficacy against severe COVID-19 infection and asymptomatic COVID-19 infection are still inconclusive, except for Ad26.CoV2.S, which demonstrated, with moderate certainty, good efficacy in preventing moderate and/or severe COVID-19 infection and acceptable protection against asymptomatic COVID-19 infection 28 days after vaccination. Efficacy data on preventing death from COVID-19 infection are still inconclusive due to the low number of events recorded in these preliminary reports. Very limited clinical trial data are available to inform vaccine efficacy against the different variants of SARS-CoV-2 [1-11].

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

Real world evidence supports clinical trial findings on the efficacy of BNT162b2, mRNA-1273, ChAdOx1, Gam-COVID-Vac and CoronaVac [12-60]. As of April 17, no RWE data on effectiveness is available for Ad26.Cov2.S A rare phenomenon, the vaccine-induced immune thrombotic thrombocytopenia has been found to have a possible link with the use of ChAdOx1 and Ad26.COV2.S. However, regulatory authorities have maintained a positive benefit-risk ratio for the continued use of these vaccines. No safety signals have been identified with the mRNA vaccines. Cases of anaphylaxis have been reported with the mRNA vaccines and with ChAdOx1 but they remain in very low numbers. Deaths after vaccination are also rare and often assessed as not related. Many case reports on various adverse events following COVID-19 vaccination have increasingly appeared in the literature.

OTHER CONSENSUS ISSUES RAISED

The panel agreed to place in a separate document (i.e., guidance or standard operating procedure) the recommendations on (1) advising the recipients regarding

adverse reaction and adverse events as well as the (2) implementation of a pharmacovigilance program and regular evidence review upon vaccine use.

There was a concern raised on the policy of other countries that they will only consider a person "vaccinated" if s/he is immunized with a vaccine that has Emergency Use Authorization (EUA) in their country. This will affect the outbound Overseas Filipino Workers and may drive brand preference.

It was emphasized that while we are certain that COVID-19 vaccines reduce severe disease, hospitalization, and death, there are still unanswered questions on the duration of protection. Wearing masks is still necessary since there is information on protection but not yet on the prevention of transmission.

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

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

KEY FINDINGS

One observational study [61] reported lower odds of getting a positive test result for COVID-19 among those taking melatonin compared to those who were not. The study was found to be with serious risk of bias because of absence of randomization and allocation concealment and the lack of details which precluded assessment of blinding and follow-up. For safety, one systematic review [62] reported that overall, melatonin supplements have a good safety profile. However, there are some adverse effects that are dose- and timing-related, and one study stated that caution should be exercised in the use of melatonin in patients with hypertension.

CONSENSUS ISSUES

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

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

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

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

KEY FINDINGS

A retrospective cohort study [63] on frail, elderly nursing home residents (N=66) reported that fewer patients died among those who received 80,000 IU of Vitamin D during the week following the diagnosis of COVID-19, or within one month prior to diagnosis, when compared to patients who received other medications. There was no direct evidence on the safety of Vitamin D supplementation as prevention for COVID-19.

CONSENSUS ISSUES

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

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

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

KEY FINDINGS

No direct published evidence was found on the use of zinc supplements in the prevention of COVID-19. Among non-COVID adult participants, zinc acetate doses of 100 to 150 mg/day taken for months had few adverse effects. Excessive intake of zinc may lead to gastrointestinal disturbances [64]. When taken together with other supplements, zinc may reduce copper and iron levels in the body.

CONSENSUS ISSUES

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

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

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

KEY FINDINGS

Two randomized controlled clinical trials [65, 66] on the use of hydroxycholoroquine (HCQ) as pre-exposure prophylaxis for COVID-19 showed tendency for reduction in the risk of developing COVID-19 infection. However, there was significant increase in the risk of adverse events.. Three RCTs [67-69] were found on the use of HCQ for post-exposure prophylaxis for COVID -19 no significant reduction in the risk of developing COVID-19 infection and a trend toward increase in the risk of adverse events. Most of the studies were found to be at risk for bias with common issues in ascertainment bias and one study without blinding.

CONSENSUS ISSUES

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

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

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

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

KEY FINDINGS

There is currently no available direct evidence on the use of lopinavir/ritonavir in the prevention of COVID-19 among healthy individuals, particularly those exposed to confirmed COVID-19 individuals. There is very low quality indirect evidence of lopinavir/ritonavir as post-exposure prophylaxis for an outbreak of MERS-CoV [70].

CONSENSUS ISSUES

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

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

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

KEY FINDINGS

There are no direct studies assessing the benefit or harm of saline nasal irrigation use among healthy individuals as a preventive strategy for COVID-19. Only indirect evidence [71] from an observational study using saline spray compared to no nasal spray in the prevention of common colds showed shorter duration of symptoms of nasal blockage and discharge but no difference in number of respiratory infections.

CONSENSUS ISSUES

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

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

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

KEY FINDINGS

Based on a single arm observational study [72] with high risk of bias, there is currently only very low quality evidence showing the possible benefit of steam inhalation in the prevention of developing symptomatic COVID-19 among exposed healthy individuals and reducing symptoms and number of days to negative SARS-COV-2 RT-PCR test of COVD-19 confirmed individuals. Meanwhile, there is indirect evidence highlighting the significant adverse effects of steam inhalation among individuals using it for symptomatic relief from the colds.

CONSENSUS ISSUES

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

Should antiseptic gargles be used for the prevention of COVID-19?

RECOMMENDATION
There is insufficient evidence to recommend the use of antiseptic mouthwash or gargle to prevent COVID-19 in healthy individuals. (Very low quality of evidence)

KEY FINDINGS

There is no direct evidence on the use of antiseptic gargle or mouthwash in preventing COVID-19 among healthy individuals. There is indirect evidence that showed conflicting results as to whether antiseptic gargle or mouthwash decreased viral load [73-76]. There is also indirect evidence on the adverse effects of mouthwashes used in the home setting [77].

CONSENSUS ISSUES

The panel did not provide a recommendation on the use of antiseptic mouthwashes/ gargles because the indirect evidence found included COVID-19 positive patients instead of healthy individuals. Furthermore, the surrogate outcomes reported were more on the decrease in forward transmission (clearance of SARS CoV2 virus) rather than the prevention of a healthy individual from contracting the infection. Of note was one completed study in Canada which involved COVID-19 negative individuals, the result of which is not yet available.

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

RECOMMENDATION
We recommend against the use of ivermectin as COVID-19 prophylaxis for the general population. (Very low quality of evidence; Strong recommendation) We recommend against the use of ivermectin for COVID-19 as post-exposure prophylaxis for household contacts of confirmed COVID-19 patients. (Very low quality of evidence; Strong recommendation) We recommend against the use of ivermectin for COVID-19 as prophylaxis for healthcare workers. (Very low quality of evidence; Strong recommendation)

KEY FINDINGS

Four very low quality randomized controlled trials [78-81] were found on the use of ivermectin as COVID-19 prophylaxis. All RCTs were found to have very serious risk of bias in terms of lack of blinding, analysis of incomplete outcome data, and selective reporting. One RCT showed lower rates of developing COVID-19 related symptoms. Moreover, two RCTs showed lower RT-PCR-confirmed COVID-19 infection rates in the ivermectin group compared to non-intervention group. However, one of these two RCTs administered a co-intervention in the ivermectin group, which poses serious validity issues. Lastly, one cluster RCT showed inconclusive RT-PCR-confirmed results for ivermectin. Mild adverse events were reported such as gastrointestinal upset, fatigue, sleepiness, pruritus, numbness, and burning sensation, all of which did not necessitate discontinuation of therapy.

CONSENSUS ISSUES

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

The panel recognized the great potential for its misuse or overuse. The panel also stressed that there is a need to have concrete evidence on safety, as well as on the appropriate dose and dosing frequency, which the current very low quality evidence did not provide. Another issue raised was that only a compassionate special permit (CSP) has been granted to two specific hospitals that applied for the permit, despite

the current registration of ivermectin products as veterinary treatment for internal and external animal parasites. Hence, there may be legal implications when a positive recommendation to use it as a prophylaxis is issued. The human-grade ivermectin, on the other hand, is still applying for emergency use authorization (EUA) from the Philippine Food and Drug Administration. Considering the vaccine hesitancy of the public, a concern was raised by the panel that if a recommendation to an alternative to the vaccine as prophylactic agent will be made, then people will most likely opt not to get vaccinated, undermining the national vaccination program of the government.

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

RECOMMENDATION
We suggest against the use of BCG vaccine for the prevention of COVID-19 infection. (Very low quality of evidence; Conditional recommendation)

KEY FINDINGS

A systematic review of the literature on April 2, 2021 did not yield any completed randomized trial on the efficacy and safety of BCG vaccination in the prevention of COVID-19 infection. Five retrospective cohort studies [82-86] and one case control study [87] were included in this review and all showed high risk of bias and conflicting results. As of March 6, 2021, 22 studies that address this issue have been registered, 21 of which are randomized controlled trials.

CONSENSUS ISSUES

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

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

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

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

KEY FINDINGS

Very low quality evidence from one retrospective cohort study [88] was found on the use of aspirin prophylaxis for COVID-19 induced coagulopathy among COVID-19 patients. There was a significant reduction in the risk of mortality. COVID-19 induced coagulopathy and adverse events were not examined in this study.

CONSENSUS ISSUES

None was raised during the panel meeting.

References

1. Polack F, Thomas S, Kitchin N, Absalon J, Gurtman A, Lockhart S. Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603–15.
2. Baden L, El Sahly H, Essink B, Kotloff K, Frey S, Novak R. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2020;
3. Voysey M, Clemens S, Madhi S, Weckx L, Folegatti P, Aley P. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397(10269):99–111.
4. Ramasamy M, Minassian A, Ewer K, Flaxman A, Folegatti P, Owens D. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. Lancet. 2020;396(10267):1979–93.
5. Voysey M, Clemens S, Madhi S, Weckx L. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet [Internet]. 2021; Available from: https://doi.org/10.1016/S0140-6736(21)00432-3
6. Emary KR, Golubchick T, Aley PK, Ariani C, Angus B, Sagida B, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. Lancet [Internet]. 2021;397:1351–62. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00628-0/fulltext
7. Madhi S, Baillie V, Cutland C, Voysey A, Koen L, Fairlie K. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant [Internet]. New England Journal of Medicine. 2021. Available from: https://www.nejm.org/doi/pdf/10.1056/NEJMoa2102214?articleTools=true

8. Logunov D, Dolzhikova I, Shcheblakov D, Tukhavtulin A, Zubkhova O. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet [Internet]. 2021; Available from: https://doi.org/10.1016/%0DS0140-6736(21)00234-8
9. Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19 [Internet]. N Engl J Med. 2021 [cited 2021 Apr 23]. Available from: https://www.nejm.org/doi/pdf/10.1056/NEJMoa2101544?articleTools=true
10. Palacios R, Batista A, Albuquerque CS, Patiño E, Santos J, Conde M. Efficacy and Safety of a COVID-19 Inactivated Vaccine in Healthcare Professionals in Brazil: The PROFISCOV Study [Internet]. SSRN. 2021 [cited 2021 Apr 12]. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3822780
11. Bueno S, Abarca K, Gonzales P, Galvez N, Soto G, Duarte L. Interim report : Safety and immunogenicity of an inactivated vaccine against SARS-CoV-2 in healthy chilean adults in a Phase 3 clinical trial [Internet]. MedRxiv. 2021. Available from: April 1, 2021
12. Amit S, Regev-Rochay G, Afek A, Kreiss Y, Leshem E. Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients [Internet]. Lancet. 2021 [cited 2021 Mar 9]. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00448-7/fulltext
13. Britton A, KM JS, Edens C, SA N, SM B, Shang N, et al. Effectiveness of the Pfizer-BioNTech COVID-19 Vaccine Among Residents of Two Skilled Nursing Facilities Experiencing COVID-19 Outbreaks - Connecticut, December 2020-February 2021. MMWR Morb Mortal Wkly Rep [Internet]. 2021;70(11):396–401. Available from: http://www.epistemonikos.org/documents/4ea6bdb3868dac76a2b6ac17f346c4f0545b9e81
14. Cabezas C, Coma E, Mora-Fernandez N, Li X, Martinez-Marcos M, Fina-Aviles F, et al. Effects of BNT162b2 mRNA Vaccination on COVID-19 Disease, Hospitalisation and Mortality in Nursing Homes and Healthcare Workers: A Prospective Cohort Study Including 28,594 Nursing Home Residents, 26,238 Nursing Home Staff, and 61,951 Healthcare Workers i. SSRN [Internet]. 2021; Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3815682
15. Chodick G, Tene L, Patalon T, Gazit S, Ben-Tov A, Cohen D, et al. The effectiveness of the first dose of BNT162 b 2 vaccine in reducing SARS-CoV-2 infection 13-24 days after immunization: real-world evidence. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/1ff25b4cb7b9b006523f8e022be2ea21eecc0c79
16. Dagan N, Barda N, Kepten E, Miron O, Perchick S, Katz M, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med [Internet]. 2021; Available from: https://doi.org/10.1056/NEJMoa2101765
17. Guijarro C, Galan IM, Perez-Fernandez E, Martinez-Ponce DC, Goyanes MJ, Castilla V, et al. Dramatic drop of new SARS-CoV-2 infections among health care workers after the first dose of the BNT162b2 mRNA Covid-19 Vaccine. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/bd8ac8fc1f5bc489ab082fdbfe6150e2e7d6f7bc
18. Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, et al. Nationwide Vaccination Campaign with BNT162b2 in Israel Demonstrates High Vaccine Effectiveness and Marked Declines in Incidence of SARS-CoV-2 Infections and COVID-19 Cases, Hospitalizations, and Deaths. SSRN [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/0ccf39331a250aaef0bc7b095d16cf3c976ec55a
19. Hall V, Foulkes S, Saei A, Andrews N, Oguti B, Charlett A, et al. Effectiveness of BNT162b2 mRNA vaccine against infection and COVID-19 vaccine coverage in healthcare workers in England, multicentre prospective cohort study (the SIREN study). SSRN. 2021.
20. Jones N, Rivett L, Seaman S, RJ S, Warne B, Workman C, et al. Single-dose BNT162b2 vaccine protects against asymptomatic SARS-CoV-2 infection. Elife [Internet]. 2021;10. Available from: http://www.epistemonikos.org/documents/2f5773b3ef002738bd289b3fe8401696591231d5

21. Monge S, Olmedo C, Alejos B, Lapena M, Sierra MJ, Limia A. Direct and indirect effectiveness of mRNA vaccination against SARS-CoV-2 infection in long-term care facilities in Spain. medRxiv [Internet]. 2021; Available from: https://www.medrxiv.org/content/10.1101/2021.04.08.21255055v1
22. Moustsen-Helms IR, Emborg H-D, Nielsen J, Nielsen KF, Krause TG, Molbak K, et al. Vaccine effectiveness after 1st and 2nd dose of the BNT162b2 mRNA Covid-19 Vaccine in long-term care facility residents and healthcare workers - a Danish cohort study. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/53c4ee49af74968e43cc779456d74f51c3436dff
23. Rinott E, Youngster I, Lewis Y. Reduction in COVID-19 Patients Requiring Mechanical Ventilation Following Implementation of a National COVID-19 Vaccination Program - Israel, December 2020-February 2021. MMWR Morb Mortal Wkly Rep. 2021. p. 326–8.
24. Zacay G, Shasha D, Bareket R, Kadim I, Sikron FH, Tsamir J, et al. BNT162b2 Vaccine Effectiveness in Preventing Asymptomatic Infection with SARS-CoV-2 Virus: A Nationwide Historical Cohort Study. SSRN [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/47ca04d87dfe9db54fee471b364c6a07f0d129a0
25. Bernal JL, Andrews N, Gower C, Stowe J, Robertson C, Tessier E, et al. Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England [Internet]. MedRxiv. 2021 [cited 2021 Mar 9]. Available from: https://www.medrxiv.org/content/10.1101/2021.03.01.21252652v1
26. Glampson B, Brittain J, Kaura A, Mulla A, Mercuri L, Brett S, et al. North West London Covid-19 Vaccination Programme: Real-world evidence for Vaccine uptake and effectiveness. medRxiv [Internet]. 2021; Available from: https://www.medrxiv.org/content/10.1101/2021.04.08.21254580v1.full.pdf
27. Hyams C, Marlow R, Maseko Z, King J, Ward L, Fox K. Assessing the effectiveness of BNT162b2 and ChAdOx1nCoV-19 COVID-19 vaccination in prevention of hospitalisations in elderly and frail adults: a single centre test negative case-control study. SSRN. 2021.
28. Shrotri M, Krutikov M, Palmer T, Giddings R, Azmi B, Subbarao S, et al. Vaccine effectiveness of the first dose of ChAdOx1 nCoV-19 and BNT162b2 against SARS-CoV-2 infection in residents of Long-Term Care Facilities (VIVALDI study). medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/5132158a4d58353fd7b74cb64be8f2e6b67efaf7
29. Vasileiou E, Simpson CR, Robertson C, Shi T, Kerr S, Utkarsh A, et al. Effectiveness of first dose of COVID-19 vaccines against hospital admissions in Scotland: national prospective cohort study of 5.4 million people [Internet]. SSRN Electronic Journal. 2021 [cited 2021 Mar 9]. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3789264
30. Andrejko K, Pry JM, Myers JF, Jewell NP, Openshaw J, Watt J, et al. Early evidence of COVID-19 vaccine effectiveness within the general population of California. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/8040757f20fb5b63a6cd46ac066cb780ae6f8541
31. Mor V, Gutman R, Yang X, EM W, KW M, RA F, et al. Short-term impact of nursing home SARS-CoV-2 vaccinations on new infections, hospitalizations, and deaths. J Am Geriatr Soc [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/0d6978157e70cc56490b8161f0baa4d070da14fa
32. Pawlowski C, Lenehan P, Puranik A, Agarwal V, Venkataksrihnan A, Niesen M, et al. FDA-authorized COVID-19 vaccines are effective per real-world evidence synthesized across a multi-state health system [Internet]. MedRxiv. 2021 [cited 2021 Mar 5]. Available from: https://doi.org/10.1101/2021.02.15.21251623
33. Roghani A. The Influence of Covid-19 Vaccine on Daily Cases, Hospitalization, and Death Rate in Tennessee: A Case Study in the United States. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/1eed60fe61d77b4fd5f24cc34a5f3b91d2352773

34. Thompson M, Burgess J, Naleway A, Tyner H, Yoon S, Meece J, et al. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers - Eight U.S. Locations, December 2020-March. MMWR Morb Mortal Wkly Rep [Internet]. 2021;70(13):495–500. Available from: http://www.epistemonikos.org/documents/303b1dd4437be9fe0660353ae503f615be077c77
35. de Faria E, Guedes AR, Oliveira MS, Moreira MVG, Maia FL, Barboza AS, et al. Performance of vaccination with CoronaVac in a cohort of healthcare workers (HCW) - preliminary report. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/62d22737346dfe78bba89d35c0789a470838c139
36. Hitchings M, Ranzani OT, Torres MSS, Oliveira SB de, Almiron M, Said R, et al. Effectiveness of CoronaVac in the setting of high SARS-CoV-2 P.1 variant transmission in Brazil: A test-negative case-control study. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/554770e434a57651e335c3b16e4d26e62795ed0a
37. Luzuriaga JP, Marsico F, Garcia E, González V, Kreplak N, Pifano M, et al. Impact of vaccines against COVID-19 on the incidence of new SARS-COV2 infections in health care workers of the Province of Buenos Aires. 2021; Available from: https://preprints.scielo.org/index.php/scielo/preprint/view/2068/3406
38. Rivkees S, Roberson S, Blackmore C. Outcomes of COVID-19 Vaccination Efforts in Florida from December 14, 2020 to March 15, 2021 on Older Individuals. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/24ced7ae24bdd6585ffa245e35617596eb55618a
39. Dutta S, Kaur RJ, Charan J, Bhardwaj P, Sharma P, Ambwani S, et al. Serious adverse events reported from the COVID-19 vaccines: A descriptive study based on WHO database. medRxiv [Internet]. 2021; Available from: https://www.medrxiv.org/content/10.1101/2021.03.23.21253433v1.full.pdf
40. Mathioudakis A, Ghrew M, Ustianowski A, Ahmad S, Borrow R, LP P, et al. Self-Reported Real-World Safety and Reactogenicity of COVID-19 Vaccines: A Vaccine Recipient Survey. Life (Basel, Switzerland) [Internet]. 2021;11(3). Available from: https://www.mdpi.com/2075-1729/11/3/249
41. McMahon D, Amerson E, Rosenbach M, Lipoff J, Moustafa D, Tyagi A, et al. Cutaneous Reactions Reported after Moderna and Pfizer COVID-19 Vaccination: A Registry-Based Study of 414 Cases. J Am Acad Dermatol [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/640a98a9e5c75d5faf21bba63eb92d115d353023
42. Mortazavi S. Coronavirus Disease (COVID-19) Vaccination Associated Axillary Adenopathy: Imaging Findings and Follow-Up Recommendations in 23 Women. AJR Am J Roentgenol [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/47429f8c5d15be0f99b3845912d38d662c15035a
43. Shimabukuro T, Cole M, JR S. Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021. JAMA [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/9e146cd9b0b0e17214584b3f68682e41454a6034
44. Davido B, Mascitti H, Fortier-Beaulieu M, Jaffal K, P de T. “Blue toes” following vaccination with the BNT162b2 mRNA COVID-19 vaccine. J Travel Med [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/1066cc91c713cb890ee0b0a2e403b915a1141fbf
45. García-Grimshaw M, Ceballos-Liceaga SE, Hernández-Vanegas LE, Núñez I, Hernández-Valdivia N, Carrillo-García DA, et al. Systemic and Neurologic Adverse Events Among 704,003 First-Dose Recipients of the Pfizer-Biontech (BNT162b2) mRNA COVID-19 Vaccine in Mexico. SSRN [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/9623d8f06c619da3b9b56f54d7a4adecebbe09e0

46. Gee J, Marquez P, Su J, Calvert G, Liu R, Myers T, et al. First Month of COVID-19 Vaccine Safety Monitoring — United States, December 14, 2020–January 13, 2021 [Internet]. Vol. 70, Morbidity Mortality Weekly Report. 2021 [cited 2021 Mar 22]. p. 283–8. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7008e3-H.pdf
47. Kim S, Wi Y, Yun S, Ryu J, Shin J, Lee E, et al. Adverse Events in Healthcare Workers after the First Dose of ChAdOx1 nCoV-19 or BNT162b2 mRNA COVID-19 Vaccination: a Single Center Experience. J Korean Med Sci [Internet]. 2021;36(14):e107. Available from: http://www.epistemonikos.org/documents/48c6eb652f4eefc5627c4e815737f997ea13c49b
48. Monin-Aldama L, Laing A, Munoz-Ruiz M, McKenzie D, I del M del B, Alaguthurai T, et al. Interim results of the safety and immune-efficacy of 1 versus 2 doses of COVID-19 vaccine BNT162b2 for cancer patients in the context of the UK vaccine priority guidelines. medRxiv [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/310daffd483993141c2e7d5307c8d8daff474069
49. Riad A, Klugarova J, Koscik M, Klugar M, Riad A, Pokorna A, et al. Prevalence of covid-19 vaccine side effects among healthcare workers in the Czech Republic. J Clin Med [Internet]. 2021;10(7). Available from: http://www.epistemonikos.org/documents/2e6ace3dc0630f1bd3244d375cb81ac390de91f5
50. Waheed S, Bayas A, Hindi F, Rizvi Z, PS E. Neurological Complications of COVID-19: Guillain-Barre Syndrome Following Pfizer COVID-19 Vaccine. Cureus [Internet]. 2021;13(2):e13426. Available from: http://www.epistemonikos.org/documents/8de11dd4bd7fbf0a9cb2bb8ed619bf773c1774f1
51. CDC. Local Reactions, Systemic Reactions, Adverse Events, and Serious Adverse Events: Moderna COVID-19 Vaccine. CDC Website [Internet]. 2021; Available from: http://www.epistemonikos.org/documents/7c8223e8474331b949d0763a091fde114a9ca943
52. COVID-19 Response Team FDA. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Moderna COVID-19 Vaccine - United States, December 21, 2020-January 10, 2021. MMWR Morb Mortal Wkly Rep [Internet]. 2021;70(4):125–9. Available from: http://www.epistemonikos.org/documents/a06b60b5e02770c92d14b0f86fe85e708af3e13f
53. Julian J, Mathern D, Fernando D. Idiopathic Thrombocytopenic Purpura and the Moderna Covid-19 Vaccine – A Case Report. Ann Emerg Med [Internet]. 2021; Available from: https://www.annemergmed.com/article/S0196-0644(21)00122-0/pdf
54. Kadali R, Janagama R, Peruru S, Gajula V, Madathala R, Chennaiahgari N, et al. Adverse effects of COVID-19 mRNA-1273 vaccine: A randomized, cross-sectional study on healthcare workers with detailed self-reported symptoms. J Med Virol [Internet]. 2021; Available from: https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.26996?src=getftr
55. Greinacher A, Thiele T, Warkentin T, Weisser K, Kryle P, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Engl J Med. 2021.
56. Kaur U, Ojha B, Pathak BK, Singh A, Giri KR, Singh A, et al. A prospective observational safety study on ChAdOx1 nCoV- 19 corona virus vaccine (recombinant) use in healthcare workers-first results from India. medRxiv [Internet]. 2021; Available from: https://www.medrxiv.org/content/10.1101/2021.04.03.21254823v1.full.pdf
57. Mehta P, Mangion S, Benger M, Stanton B, Czuprynska J, Arya R, et al. Cerebral venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination - a report of two UK cases. Brain Behav Immun [Internet]. 2021; Available from: https://www.sciencedirect.com/science/article/pii/S088915912100163X?pes=vor
58. Schultz NH, Sorvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Aanodt A-H. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination [Internet]. N Engl J Med. 2021 [cited 2021 Apr 9]. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2104882
59. Wolf M, Bazner H, Luz B, Niehaus L, Bhogal P, Henkes H. Thrombocytopenia and intracranial venous sinus thrombosis after “covid-19 vaccine astrazeneca” exposure. J Clin Med [Internet]. 2021;10(8). Available from: https://www.mdpi.com/2077-0383/10/8/1599

60. Riad A, Sağıroğlu D, Üstün B, Attia S, Klugar M. Prevalence and Risk Factors of CoronaVac Side Effects: An Independent Cross-Sectional Study Among Healthcare Workers in Turkey [Internet]. SSRN. 2021 [cited 2021 Apr 24]. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3820571
61. Zhou Y, Hou Y, Shen J, Mehra R, Kallianpur A, Culver D et al. A network medicine approach to investigation and population-based validation of disease manifestations and drug repurposing for COVID-19. PLOS Biology. 2020;18(11):e3000970.
62. Foley H,Steel A. Adverse events associated with oral administration of melatonin: A critical systematic review of clinical evidence. Complementary Therapies in Medicine. 2019;42:65-81.
63. Annweiler C, Hanotte B, Grandin de l'Eprevier C, Sabatier JM, Lafaie L, Célarier T. Vitamin D and survival in COVID-19 patients: A quasi-experimental study. J Steroid Biochem Mol Biol. 2020;204:105771.
64. Hemilä H. Zinc lozenges and the common cold: a meta-analysis comparing zinc acetate and zinc gluconate, and the role of zinc dosage. JRSM Open. 2017;8(5):2054270417694291.
65. Abella et al. Efficacy and Safety of Hydroxychloroquine vs Placebo for Pre-exposure SARS-CoV-2 Prophylaxis Among Health Care Workers. JAMA Internal Medicine 2021;181(2):195-202 Available from: doi:doi:10.1001/jamainternmed.2020.6319 [Accessed 24th February 2021].
66. Rajasingham et al. Hydroxychloroquine as Pre-exposure Prophylaxis for Coronavirus Disease 2019 (COVID-19) in Healthcare Workers: A Randomized Trial. CID 2020. Available from: DOI: 10.1093/cid/ciaa1571 [Accessed 24th February 2021].
67. Barnabas et al. Hydroxychloroquine as Postexposure Prophylaxis to Prevent Severe Acute Respiratory Syndrome Coronavirus 2 Infection. Annals of Internal Medicine. Available from: https://doi.org/10.7326/M20-6519 [Accessed 24th February 2021].
68. Mitja et al. A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of Covid-19. N Engl J Med 2021; 384:417-427. Available from: DOI:10.1056/NEJMoa2021801 [Accessed 24th February 2021].
69. Boulware et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. N Engl J Med 2020; 383:517-525. Available from: DOI: 10.1056/NEJMoa2016638 [Accessed 24th February 2021].
70. Park SY, Lee JS, Son JS, Ko JH, Peck KR, Jung Y, et al. Post-exposure prophylaxis for Middle East respiratory syndrome in healthcare workers. J Hosp Infect [Internet]. 2019 Jan;101(1):42–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0195670118304845
71. Tano L, Tano K. A daily nasal spray with saline prevents symptoms of rhinitis. Acta Otolaryngol. 2004;124(9):1059–62.
72. Pawar S, Bhonsale D, Pawar D, Bhalla R, Mayekar R, Kude P, Bhonsale S (2020). Management of COVID positive medical staff: A medical college and public hospital experience with steam therapy
73. Gottsauner MJ, Michaelides I, Schmidt B, Scholz KJ, Buchalla W, Widbiller M, et al. A prospective clinical pilot study on the effects of a hydrogen peroxide mouthrinse on the intraoral viral load of SARS-CoV-2. Clin Oral Investig. 2020;24(10):3707–13.. Med. Med. Sci. 8(6): 056-058.
74. Pelletier JS, Tessema B, Frank S, Westover JB, Brown SM, Capriotti JA. Efficacy of Povidone-Iodine Nasal and Oral Antiseptic Preparations Against Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2). Ear, Nose Throat J. 2020;100:192–6.
75. Seneviratne CJ, Balan P, Ki KKK, Udawatte NS, Lai D LD et al. Efficacy of commercial mouth-rinses on SARS-CoV-2 viral load in saliva: Randomized Control Trial in Singapore. 2020;
76. Mohamed NA, Baharom N, Wan Sulaiman WS, Rashid ZZ, Ken WK, Ali UK, et al. Early viral Clearance among COVID-19 patients when gargling with povidone-iodine and essential oils – A clinical trial. medRxiv. 2020;
77. Tartaglia GM, Tadakamadla SK, Connelly ST, Sforza C, Martín C. Adverse events associated with home use of mouthrinses: a systematic review. Ther Adv Drug Saf. 2019;10:1–16.

78. Elgazzar A, Eltaweel A, Youssef SA, Hany B, Hafez M, Moussa H. Efficacy and Safety of Ivermectin for Treatment and Prophylaxis of COVID-19 Pandemic. Preprint [Internet]. 2021 [cited 2021 Mar 16]. Available from: https://www.researchsquare.com/article/rs-100956/v3 doi: https://doi.org/10.21203/rs.3.rs-100956/v3.
79. Shoumann WM, Hegazy AA, Nafae RM, Ragab MI, Samra SR, Ibrahim DA, et al. Use of Ivermectin as a potential chemoprophylaxis for COVID-19 in Egypt: A Randomised Clinical Trial. J Clin Diagn Res. 2021 Feb;15(2):OC27-32.
80. Chahla RE, Medina Ruiz L, Ortega ES, Morales MF, Barreiro F, George A, et al. A Randomized Trial – Intensive Treatment Based in Ivermectin and Iota-Carrageenan as Pre-exposure Prophylaxis for COVID-19 in Healthcare Agents. Preprint [Internet]. 2021 [cited 2021 Apr 21]. Available from https://www.medrxiv.org/content/10.1101/2021.03.26.21254398v1.
81. Seet RCS, Qek AML, Ooi DSQ, Sengupta S, Lakshiminarasappa R, Koo CY, et al. Positive impact of oral hydroxychloroquine and povidone-iodine throat spray for COVID-19 prophylaxis: An open-label randomized trial. International Journal of Infectious Diseases. 2021 Apr;106:314-322.
82. de Chaisemartin C, de Chaisemartin I. BCG vaccination in infancy does not protect against COVID-19. Evidence from a natural experiment in Sweden [Internet]. Clinical Infectious Diseases. 2020 [cited 2021 Apr 2]. Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1223/5896039
83. Hamiel U, Kozer F, Youngster I. SARS-CoV-2 Rates in BCG-Vaccinated and Unvaccinated Young Adults. JAMA [Internet]. 2020;323(22):2340–1. Available from: https://jamanetwork.com/journals/jama/fullarticle/2766182
84. Amirlak I, Haddad R, Hardy JD, Khaled NS, Chung MH. Effectiveness of booster BCG vaccination in preventing Covid-19 infection. MedRxiv. 2020.
85. Noval Rivas M, Ebinger J, Wu M, Sun N, Braun J. BCG vaccination history associates with decreased SARS-CoV-2 seroprevalence across a diverse cohort of healthcare workers. J Clin Invest. 2020;131(2).
86. Moorlag S, can Deuren R, van Werkhoven C, Jaeger M, Bedisarun P, Taks E. Safety and COVID-19 Symptoms in Individuals Recently Vaccinated with BCG: a Retrospective Cohort Study. Cell Rep. 2020;1(5):100073.
87. Sharma A, Ahmed A, Baig V, Shakad P, Dalela G, Kacker S. Characteristics and Outcomes of Hospitalized Young Adults with Mild to Moderate Covid-19 at a University Hospital in India. MedRxiv. 2020.
88. Meizlish ML, Goshua G, Liu Y, Fine R, Amin K, Chang E, DeFilippo N, Keating C, Liu Y, Mankbadi M, McManus D, Wang SY, Price C, Bona RD, Ochoa Chaar CI, Chun HJ, Pine AB, Rinder HM, Siner JM, Neuberg DS, Owusu KA, Lee AI. Intermediate-dose anticoagulation, aspirin, and in-hospital mortality in COVID-19: A propensity score-matched analysis. Am J Hematol. 2021 Apr 1;96(4):471-479. doi: 10.1002/ajh.26102. Epub 2021 Feb 22. PMID: 33476420; PMCID: PMC8013588.

PHILIPPINE COVID-19 LIVING RECOMMENDATIONS

Adjunct Interventions

Evidence and Recommendations for the Adjunct Interventions for COVID-19

Should zinc be given as an adjunct treatment to patients diagnosed with COVID-19 infection?

RECOMMENDATION
There is insufficient evidence to recommend the use of zinc as adjunct treatment for patients with COVID-19 infection both in the outpatient and in-patient setting. (Very low quality of evidence)

KEY FINDINGS

Zinc has an anti-viral effect through inhibition of SARS-Cov-1 replication as shown in in vitro studies. It has been suggested that zinc may reduce severity and duration of symptoms of other viral respiratory tract infections when used as an adjunct treatment.

One randomized controlled trial [1] was found that showed no significant difference on death, mechanical ventilation and recovery after 28 days in patients with COVID-19 when zinc was given as adjunct treatment together with HCQ, based on moderate quality of evidence. Another RCT [2] showed no significant reduction of symptoms in outpatient COVID-19 patients when given zinc gluconate. Three retrospective cohort [3-5] studies were found which when pooled, showed that adjunct zinc therapy significantly reduced the risk of mortality among COVID-19 patients, however this was from low quality of evidence. Indirect evidence [6] was found on the use of zinc for upper respiratory tract infections, and this reported no serious adverse effects but an increased risk for non-serious adverse effects such as nasal and throat irritation and GI discomfort.

CONSENSUS ISSUES

There were no issues raised during the consensus panel meeting.

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

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

KEY FINDINGS

There is one cohort study on the use of vitamin D/magnesium/vitamin B12 (DMB) supplementation on patients with COVID-19 infection [7]. Likelihood of subsequent oxygen therapy including ICU support was significantly less for those taking DMB. However, there was no significant difference when looking at oxygen therapy alone or

ICU support alone. There were no adverse events directly attributed to DMB use in the cohort study. There is very low certainty of evidence that suggests an association between excessive levels of Vitamin B12 and poorer outcomes in COVID-19 patients [8]. Overall, there is very low certainty of evidence due to risk of bias based on the observational design, as well as issues with directness (DMB was given in combination with vitamin D and magnesium) and imprecision (due to limited sample size).

CONSENSUS ISSUES

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

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

Should Vitamin C be used as adjunct treatment for COVID-19?

RECOMMENDATION
There is insufficient evidence to recommend the use of intravenous Vitamin C as adjunct treatment for patients with COVID-19 infection. (Low quality of evidence)

KEY FINDINGS

There were four randomized controlled trials included in this review [9-12]. Based on these studies, adjunctive treatment with vitamin C among COVID-19 patients did not lead to significant reduction in mortality, need for mechanical ventilation or hospital length of stay. Most of the studies included were found to be at low quality of evidence. There are currently 17 ongoing trials studying the efficacy of vitamin C as an adjunctive treatment for COVID-19.

CONSENSUS ISSUES

Since there is insufficient evidence to recommend the use of vitamin C as adjunct treatment for COVID-19 and the quality of evidence is rated low, this means that more randomized controlled trials on vitamin C as adjunct treatment for COVID-19 need to be done.

Intravenous administration was the route used by the included studies in this review. According to the search for pricing, intravenous vitamin C costs Php 430 for 40 ampules of 500mg/2ml but this pricing was from an online selling source; there were no data on pricing of intravenous vitamin C on pharmaceutical websites searched.

Should Vitamin D supplements be used as adjunct treatment for COVID-19?

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

KEY FINDINGS

Three RCTs were found on the use of vitamin D as adjunct treatment for patients with COVID-19 [13-15]. The effect of vitamin D supplements as adjunct treatment for patients with COVID-19 for the outcomes of mortality, progression of oxygen support and ICU admission was inconclusive. Across these outcomes, the studies were found to have low to very low certainty because of serious risk of bias (from unclear randomization and lack of blinding), inconsistency and imprecision. More patients supplemented with vitamin D had virologic clearance by day 21. No significant difference was found with duration of hospital length of stay, and duration of mechanical ventilation. Based on indirect evidence, vitamin D in excessive amounts may cause gastrointestinal complaints, hypercalcemia, hypercalciuria, and increased renal stone formation.

CONSENSUS ISSUES

There were no issues raised during the panel meeting.

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

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

KEY FINDINGS

There was only one very low quality randomized controlled trial [16] that compared melatonin with standard treatment, and it showed significant reduction in cough, dyspnea, and fatigue, and significantly shorter hospital stay and return to baseline health in those given melatonin. There was no significant difference in the proportion of patients discharged on day 14. No adverse events were observed in the use of melatonin among COVID-19 patients.

CONSENSUS ISSUES

There were no consensus issues raised during the panel meeting.

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

RECOMMENDATION
There is no evidence to recommend the use of virgin coconut oil as adjunct treatment for patients with COVID-19 infection.

KEY FINDINGS

Virgin coconut oil (VCO) is rich in lauric acid and pharmacologically active metabolite monolaurin. In vitro studies have found that VCO has anti-inflammatory, antioxidant, antibacterial, antifungal, and antiviral properties. In a clinical trial involving HIV and AIDS patients [17], VCO treatment led to an increase in CD4+ and lymphocyte counts as well as reduction in viral load. Currently, there are no published studies assessing the efficacy and safety of virgin coconut oil as an adjunctive treatment for COVID-19.

CONSENSUS ISSUES

There were no issues raised during the consensus panel meeting.

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

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

KEY FINDINGS

There is low certainty of evidence based on one randomized controlled trial [18] that compared omega-3-fatty acid supplementation of high-protein enteral feeding versus hi-protein enteral feeding alone in hospitalized patients with COVID-19, which showed significant reduction in mortality. The RCT did not report adverse events. Indirect evidence on adverse events from two meta-analyses [19, 20] of RCTs on critically ill ICU patients (non-COVID), mostly with ARDS, given fatty acid supplementation versus control, showed that gastrointestinal adverse events were common but did not differ significantly between groups.

CONSENSUS ISSUES

There were no reported adverse events in the study that assessed the effect of addition of 1000mg omega-3-fatty acid supplementation to enteral feeding of hospitalized patients with COVID-19. There was no significant difference in reported

adverse events between groups given fatty acid supplementation or placebo in critically-ill ICU patients (non-COVID).

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

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

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

KEY FINDINGS

One randomized controlled trial [21] comparing NAC to placebo with 135 participants was found to have no significant difference compared to control for mortality, invasive mechanical ventilation, ICU admission, length of hospital and ICU stay. A case series [22] of ten respirator-dependent patients who responded to IV NAC showed reduction in inflammatory markers wherein six patients rebounded once NAC was discontinued and eight were discharged while two remained hospitalized. Indirect evidence in a low-quality systematic review [23] of NAC vs placebo in patients with Acute respiratory distress syndrome failed to show any difference in the mortality, but significantly reduced ICU stay.

CONSENSUS ISSUES

The panel distinguished between the oral and intravenous (IV) preparations of N-acetylcysteine (NAC), noting in part the cost of the IV agent.

A study included in this review which compared NAC and placebo among suspected or confirmed COVID-19 patients found no significant difference on its primary and secondary outcomes (i.e., mortality, invasive mechanical ventilation and ICU admission). However, NAC may essentially still be used for its other clinical indications (i.e., as mucolytic) on patients with COVID-19, but not necessarily for the treatment of COVID-19.

There were also a few studies included in the review that compared IV-NAC and placebo among ARDS patients, and although it was also noted that NAC has no ancillary role on the treatment of ARDS, it is used for intubated patients for its mucolytic and immunomodulating properties.

Should RAAS blockers be continued in patients with COVID-19?

RECOMMENDATION
We recommend continuing maintenance RAAS blockers for hypertension among patients with COVID-19 infection. (Moderate quality of evidence; Strong recommendation)

KEY FINDINGS

Based on two randomized controlled trial [24, 25] with moderate certainty of evidence, there is probably little or no significant reduction in the risk of deaths and severe disease for patients with hypertension and COVID-19 who continued RAAS blockers compared to those who discontinued RAAS blockers.

CONSENSUS ISSUES

There were no issues raised during the consensus panel meeting.

Does the concurrent use of Ibuprofen worsen COVID-19 outcomes?

RECOMMENDATION
We suggest that ibuprofen may still be used as symptomatic treatment of patients with COVID-19 infection if clinically warranted. Concurrent use of ibuprofen is not associated with worsening of COVID-19 outcomes. (Very low quality of evidence; Conditional recommendation)

KEY FINDINGS

There has been concern on the use of ibuprofen in COVID-19. The point of entry for SARS-COV-2 is through angiotensin- converting enzyme 2 receptor, which is believed to be upregulated by ibuprofen. Based on six observational studies [26-31] assessed, there was no significant association between ibuprofen use and worse COVID-19 outcomes: composite outcome (death, acute respiratory distress syndrome, ICU admission, shock), Death , and progression of symptoms after propensity score matching. Five clinical trials on Ibuprofen use in COVID-19 are still on-going.

CONSENSUS ISSUES

There were no issues raised during the consensus panel meeting.

Should aspirin, taken as maintenance therapy for underlying medical conditions, be discontinued in patients with COVID-19?

RECOMMENDATION
There is insufficient evidence to recommend discontinuation of aspirin as maintenance therapy for underlying medical conditions in patients with COVID-19. (Very low quality of evidence)

KEY FINDINGS

Very low quality evidence from three retrospective cohort studies [32-34] was found on the continuation of aspirin as maintenance for underlying medical conditions among patients with COVID-19. There was no significant decrease in the odds of mortality in the use of aspirin. However, there was a significant increase in the odds of the composite outcome of mortality or discharge to hospice with continuation of aspirin. Thromboembolic and adverse events were not examined in these studies.

CONSENSUS ISSUES

Further studies are needed for the panel to make a recommendation on the discontinuation of aspirin as maintenance therapy in patients with COVID-19. There is certainty of benefit for continuing aspirin for underlying medical conditions. However, the benefit of its use among patients with COVID-19 is still uncertain.

References

1. Abd-Elsalam S, Soliman S, Esmail ES, Khalaf M, Mostafa EF, Medhat MA, et al. Do Zinc Supplements Enhance the Clinical Efficacy of Hydroxychloroquine?: a Randomized, Multicenter Trial. Biol Trace Elem Res [Internet]. 2020 Nov 27 [cited 2020 Dec 26];1–5. Available from: https://pubmed.ncbi.nlm.nih.gov/33247380/
2. Thomas S, Patel D, Bittel B, Wolski K, Wang Q, Kumar A, et al. Effect of High-Dose Zinc and Ascorbic Acid Supplementation vs Usual Care on Symptom Length and Reduction Among Ambulatory Patients With SARS-CoV-2 Infection. JAMA Netw Open [Internet]. 2021 Feb 12 [cited 2021 Feb 13];4(2):e210369. Available from: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2776305
3. Yao JS, Paguio JA, Dee EC, Tan HC, Moulick A, Milazzo C, et al. The Minimal Effect of Zinc on the Survival of Hospitalized Patients With COVID-19: An Observational Study. Chest [Internet]. 2020 [cited 2020 Dec 26]; Available from: https://pubmed.ncbi.nlm.nih.gov/32710890/
4. Carlucci PM, Ahuja T, Petrilli C, Rajagopalan H, Jones S, Rahimian J. Hydroxychloroquine and azithromycin plus zinc vs hydroxychloroquine and azithromycin alone: outcomes in hospitalized COVID-19 patients. medRxiv [Internet]. 2020 Jan 1 [cited 2020 Dec 26];2020.05.02.20080036. Available from: https://doi.org/10.1101/2020.05.02.20080036
5. Frontera JA, Rahimian JO, Yaghi S, Liu M, Lewis A, de Havenon A, et al. Treatment with Zinc is Associated with Reduced In-Hospital Mortality Among COVID-19 Patients: A Multi-Center Cohort Study. Res Sq [Internet]. 2020 Oct 26 [cited 2020 Dec 28]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/33140042
6. Hunter J, Arentz S, Goldenberg J, Yang G, Beardsley J, Myers SP, et al. Benefits and risks of zinc for adults during covid-19: rapid systematic review and meta-analysis of randomised controlled trials. medRxiv [Internet]. 2020 Jan 1;2020.11.02.20220038. Available from: http://medrxiv.org/content/early/2020/11/04/2020.11.02.20220038.abstract
7. Tan CW, Pock L, Kalimuddin S, Cherng BPZ, Teh YE, Thien SW et al. Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B12 in combination on progression to severe outcomes in older patients with coronavirus (COVID-19). Nutrition. 2020; 79-80. https://doi.org/10.1016/j.nut.2020.111017
8. Dalbeni A, Bevilacqua M, Teani I, Normelli I, Mazzaferri F, Chiarioni G. Excessive vitamin B12 and poor outcome in COVID-19 pneumonia. Nutr Metab Cardiovasc Dis. 2021 Mar

10;31(3):774-775. doi: 10.1016/j.numecd.2020.12.005. Epub 2020 Dec 11. PMID: 33549452; PMCID: PMC7834259.
9. Jamalimoghadamsiahkali S, Zaresade B, Koolaji S, SeyedAlinaghi S, Zendehdel A, Tabarestani M, Moghadam E, Abbasian L, Manshadi S, Salehi M, Hasannezhad M, Ghaderkani S, Meidani M, Salahshour F, Jafari F, Manafi N, Ghiasvand F. Safety and effectiveness of high-dose vitamin C in patients with COVID-19: a randomized open-label clinical trial. European Journal of Medical Research (2021) 26:20
10. Kumari P, Dembra S, Dembra P, Bhawna F, Gul A, Ali B, Sohail H, Kumar B, Memon M, Rizwan A. The role of vitamin C as adjuvant therapy in COVID-19. Cureus 2020, 12(11):e11779
11. Thomas S, Patel D, Bittel B, Wolski K, Wang Q, Kumar A, Il'Giovine Z, Mehra R, McWilliams C, Nissen S, Desai M. Effect of high dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection. The COVID A to Z randomized clinical trial. JAMA Network Open. 2021;4(2):e210369
12. Zhang J, Rao X, Li Y, Zhu Y, Liu F, Guo G, Luo G, Meng Z, De Backer D, Peng Z. Pilot trial of high dose vitamin C in critically ill COVID-19 patients. Ann Intensive Care 2021; 11:5
13. Castillo ME, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, Miranda JL, Bouillon R, et al. "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". J Steroid Biochem Mol Biol [Internet]. 2020;105751. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32871238
14. Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CSC, et al. Effect of vitamin D3 Supplementation vs Placebo on Hospital Length of Stay in Patients with Severe COVID-19: A Multicenter, Double-blind, Randomized Controlled Trial. medRxiv [Internet]. 2020 Jan 1;2020.11.16.20232397. Available from: http://medrxiv.org/content/early/2020/11/17/2020.11.16.20232397.abstract
15. Rastogi A, Bhansali A, Khare N, Suri V, Yaddanapudi N, Sachdeva N, et al . Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomized, placebo-controlled study (SHADE study). Postgrad Med J. 2020;0:1-4. doi:10.1136/postgradmedj-2020-139065.
16. Farnoosh G, Akbariqomi M, Badri T, Bagheri M, Izadi M, Saeedi-Boroujeni A, et al. Efficacy of a Low Dose of Melatonin as an Adjunctive Therapy in Hospitalized Patients with COVID-19: A Randomized, Double-blind Clinical Trial. Authorea Prepr [Internet]. 2020; Available from: https://www.authorea.com/doi/full/10.22541/au.160734344.45295921/v1?commit=5be3e7266256468d59e81ff82a1b125710ba7459
17. Dayrit C. Coconut oil in health and disease: its and monolaurin's potential cure for HIV/AIDS. Indian Coconut Journal 2000; (31):19-24 Available from: http://coconutresearchcenter.org/wp-content/uploads/2015/11/article10526.pdf
18. Doaei S, Gholami S, Rastgoo S, Gholamalizadeh M, Bourbour F. The effect of omega - 3 fatty acid supplementation on clinical and biochemical parameters of critically ill patients with COVID - 19 : a randomized clinical trial. J Transl Med [Internet]. 2021;1–9. Available from: https://doi.org/10.1186/s12967-021-02795-5
19. Dushianthan A, Cusack R, Burgess VA, Grocott MPW, Calder P. Immunonutrition for adults with ARDS: Results from a cochrane systematic review and meta-analysis. Respir Care. 2020;65(1):99–110.
20. Koekkoek W (Kristine), Panteleon V, van Zanten AR. Current evidence on ω-3 fatty acids in enteral nutrition in the critically ill: A systematic review and meta-analysis. Nutrition [Internet]. 2019;59:56–68. Available from: https://doi.org/10.1016/j.nut.2018.07.013
21. de Alencar JCG, Moreira CL, Müller AD, Chaves CE, Fukuhara MA, da Silva EA, Miyamoto MFS, Pinto VB, Bueno CG, Lazar F, Gomez LM, Menezes MCS, Marchini JFM, Marino LO, Brandão RA, Souza HP; COVID Register Group. Double-blind, randomized, placebo-controlled trial with N-acetylcysteine for treatment of severe acute respiratory syndrome caused by COVID-19. Clin Infect Dis. 2020 Sep 23:ciaa1443. doi: 10.1093/cid/ciaa1443. Epub ahead of print. PMID: 32964918; PMCID: PMC7543361.

22. Ibrahim H, Perl A, Smith D, Lewis T, Kon Z, Goldenberg R, Yarta K, Staniloae C, Williams M. Therapeutic blockade of inflammation in severe COVID-19 infection with intravenous N-acetylcysteine. Clin Immunol. 2020 Oct;219:108544. doi: 10.1016/j.clim.2020.108544. Epub 2020 Jul 22. PMID: 32707089; PMCID: PMC7374140.
23. Lu X, Ma Y, He J, Li Y, Zhu H, Yu X. N-acetylcysteine for adults with acute respiratory distress syndrome: A meta-analysis of randomized controlled trials. Hong Kong Journal of Emergency Medicine. 2019Jan9;26(5):288–98.
24. Cohen JB, Hanff TC, William P, Sweitzer N, Rosado-Santander NR, Medina C, et al. Continuation versus discontinuation of renin–angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. Lancet Respir Med. 2021;2(20):1–10.
25. Lopes RD, Macedo AVS, De Barros E Silva PGM, Moll-Bernardes RJ, Dos Santos TM, Mazza L, et al. Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and out of the Hospital in Patients Admitted with COVID-19: A Randomized Clinical Trial. JAMA - J Am Med Assoc. 2021;325(3):254–64.
26. Choi M, Ahn H, Ryu H, Kim B, Jang J, Jung M, Jeong S. Clinical Characteristics and Disease Progression in Early-Stage COVID-19 Patients in South Korea. Journal of Clinical Medicine 2020, 9(6), 1959.doi:10.3390/jcm9061959
27. Esba L, Alqahtani R, Thomas A. Ibuprofen and NSAID Use in COVID-19 Infected Patients Is Not Associated with Worse Outcomes: A Prospective Cohort Study. Infect Dis Ther Nov. 2, 2020. https://doi.org/10.1007/s40121-020-00363-w
28. Kragholm K, Gerds T, Fosbol E et al. Association Between Prescribed Ibuprofen and Severe COVID-19 Infection: A Nationwide Register-Based Cohort Study. Clin Transl Sci (2020) 13, 1103–1107; doi:10.1111/cts.12904
29. Perkins S, Holmes A, Nelson J, Hirschl J, Chopra Z, Medlin R, Fung C, Korley F. Clinical outcomes among COVID-19 patients taking non-steroidal anti-inflammatory drugs. Annals of Emergency Medicine Oct. 2020. Vol 76(4).
30. Rinnot E, Kozer E, Shapira Y, Bar-Haim A, Youngster I. Ibuprofen use and clinical outcomes in COVID-19 patients. Clinical Microbiology and Infection 26, 2020. 1259.e5e1259.e7
31. Samimagham H, Arabi M, Hooshyar D, Kazemijahromi M. The association of non-steroidal anti-inflammatory drugs with COVID-19 severity and mortality. Arch Clin Infect Dis. 2020 August; 15(4):e106847.
32. Viecca M, Radovanovic D, Forleo GB, Santus P. Enhanced platelet inhibition treatment improves hypoxemia in patients with severe Covid-19 and hypercoagulability. A case control, proof of concept study. Pharmacol Res 2020;158:104950.
33. Meizlish ML, Goshua G, Liu Y, Fine R, Amin K, Chang E, DeFilippo N, Keating C, Liu Y, Mankbadi M, McManus D, Wang SY, Price C, Bona RD, Ochoa Chaar CI, Chun HJ, Pine AB, Rinder HM, Siner JM, Neuberg DS, Owusu KA, Lee AI. Intermediate-dose anticoagulation, aspirin, and in-hospital mortality in COVID-19: A propensity score-matched analysis. Am J Hematol. 2021 Apr 1;96(4):471-479. doi: 10.1002/ajh.26102. Epub 2021 Feb 22. PMID: 33476420; PMCID: PMC8013588.
34. Ahmed HY, Papali A, Haile T, Shrestha GS, Schultz MJ, Lundeg G, Akrami KM, For The Covid-Lmic Task Force. Pragmatic Recommendations for the Management of Anticoagulation and Venous Thrombotic Disease for Hospitalized Patients with COVID-19 in Low- and Middle-Income Countries. Am J Trop Med Hyg. 2021 Jan 11;104(3 Suppl):99–109. doi: 10.4269/ajtmh.20-1305. Epub ahead of print. PMID: 33432908; PMCID: PMC7957232.

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Discussion

Outputs of the Philippine COVID-19 Living CPG Project

CLINICAL PRACTICE QUESTIONS

COVID-19 management issues and questions were collected from the Steering Committee members and Consensus Panelists during the organizational meetings and consensus panel meetings. Management trends and new issues were added to this list as they emerge or as suggested by health policymakers. The topics were reviewed and prioritized regularly. Priority topics were then assigned to the evidence reviewers for new evidence reviews or updating of existing reviews. A total of 139 priority topics were identified.

CONSENSUS MEETINGS, EVIDENCE SUMMARIES, AND RECOMMENDATIONS

For the entire project duration, there were a total of 90 evidence summaries presented and 136 recommendations generated in 26 consensus panel meetings. Refer to Appendix D for the breakdown per batch.

UPDATED EVIDENCE SUMMARIES AND RECOMMENDATIONS

Eleven questions were identified for updating in the third batch of evidence reviews. Due to the urgency of the policy change needed, four of these updates were already presented to the Consensus Panel and the recommendations were updated considering the new evidence. The other updates will be covered by Phase 2 of this Living CPG.

Applicability Issues

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

ORGANIZATIONAL CONSIDERATIONS TO IMPLEMENTATION

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

a limitation in the availability of screening tests. Specially trained personnel were needed to do the more specialized tests, such as pooled testing using RT-PCR.

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

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

RESOURCE IMPLICATIONS

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

Implementation Tools

Selected recommendations from the Philippine COVID-19 Living CPG have been used as a reference to the Unified COVID-19 Algorithms, specifically on testing and management. These algorithms were developed collaboratively by 15 professional organizations and stakeholder institutions. Their complete algorithms were published on the PSMID website (https://www.psmid.org/unified-covid-19-algorithms-5/). Healthcare providers, patients, and the public are encouraged to access these algorithms on the main webpage.

Process Evaluation

Using the native website tools and Google analytics, the PSMID website administrator was able to gather various metrics on website visits for the Philippine COVID-19 Living

CPG: click trends and download trends. Since the release on March 31, 2021, there have been 147,510 total clicks on the website. The spikes in website visits (Figure 6) during the ends of March and April coincided with the release of recommendations and new evidence summaries. Most of these visits were from the National Capital Region, Central Visayas (Region VII), and Davao Region (Region XI), which reflected the areas that had the greatest number of new cases and active cases during the project duration (Figure 7 and Table 6). Furthermore, the list of top evidence summaries clicks revealed the possible topics that CPG users needed the most guidance on (Table 7). Note that some of these topics remained to be contentious as of the present date, such as ivermectin, lianhua, and ionizing air purifiers.

Figure 6. Website click trend of the Philippine COVID-19 Living CPG.

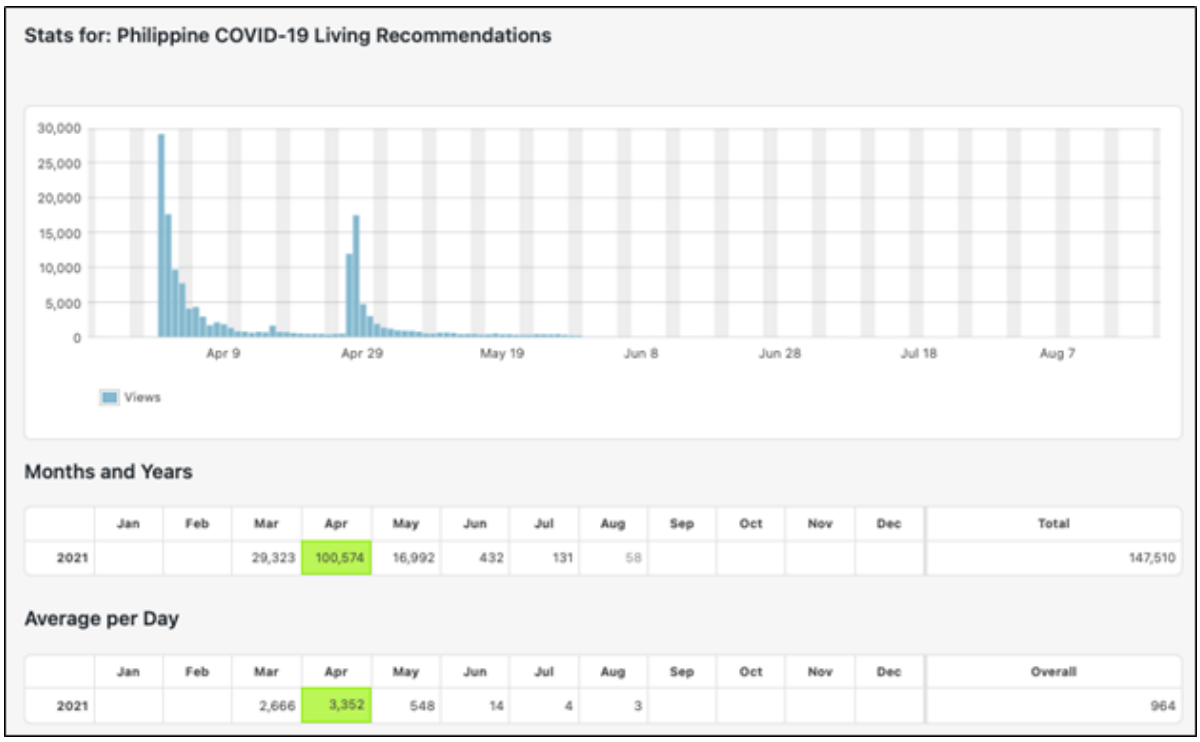

Figure 7. Geographical location of website visitors of the Philippine COVID-19 Living CPG.

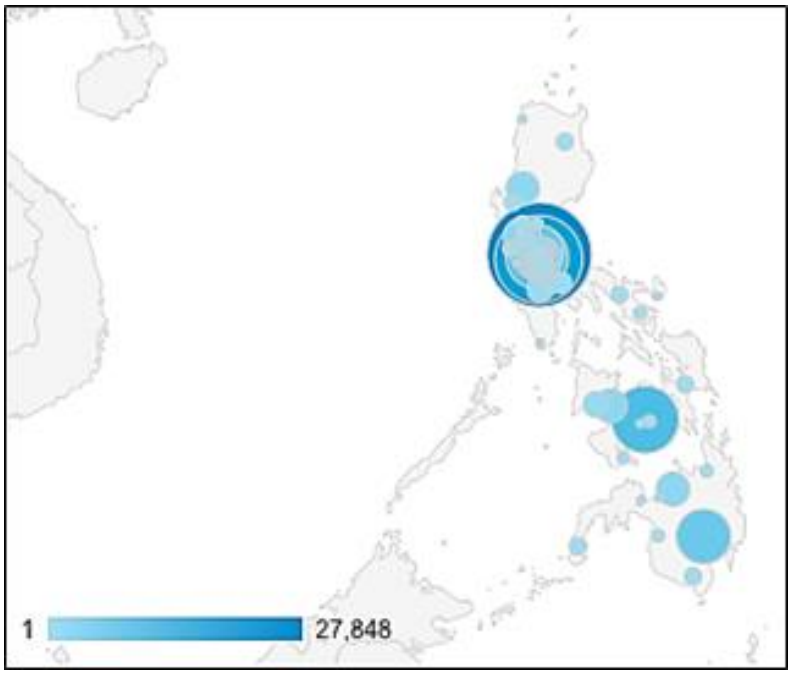

Table 6. Top locations of website visitors of the Philippine COVID-19 Living CPG.

City	n	Percentage
Quezon City	27,848	18.77
Makati	20,202	13.61
Cebu City	11,112	7.49
Manila	9,706	6.54
Meycauayan	7,994	5.39
Davao City	7,249	4.89
Pasig	3,944	2.66
Paranaque	3,772	2.54
Angeles	3,376	2.28
Antipolo	3,092	2.08
Others	10,191	7.14

Table 7. Top evidence summaries downloaded from the Philippine COVID-19 Living CPG.

Topic	n
Ivermectin as treatment	2784
Hemoperfusion	2676
Ivermectin as prophylaxis	1815
Remdesivir	1334
Saliva RT-PCR	1252
Virgin coconut oil	923
Lianhua	899
Azithromycin	699
Ionizing air purifiers	655
Tocilizumab	587

Research Implications

The novel coronavirus, now known as SARS-CoV-2, brought about a disease condition that is new to everyone. Despite the rapidly evolving evidence on COVID-19, many research gaps need to be filled in the management, prevention, and control of this disease. These were identified during the evidence reviews done in this CPG and were documented in the evidence summaries. The following discussion presents a synthesis of these research gaps.

As expected in a novel disease condition, many of the recommendations were answered with low to very low certainty of evidence. These areas are directed to a need for further primary research to be conducted.

While existing studies on the investigational treatment interventions have been able to identify the subset of patients that would benefit best (such as remdesivir with dexamethasone for patients on oxygen supplementation, or tocilizumab with dexamethasone for patients with elevated inflammatory biomarkers or rapid respiratory deterioration), there is still a need for further studies on dosing, frequency of administration, combinations with other drugs, etc. Aside from the successful experimental drugs, additional research on those drugs showing early promise is urgently required.

Diagnosis and treatment were sometimes overemphasized in the management of COVID-19. 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 (except for COVID-19 vaccines, which have been slowly building their knowledge base). These studies were also crucial to prove the lack of effectiveness of several interventions that many subscribe to.

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

Conclusions and Recommendations

The Philippine COVID-19 Living CPG identified 139 priority questions on COVID-19 management, infection prevention, and control, generated 90 evidence summaries, and came up with 136 recommendations. Thematic areas included in this CPG were screening and diagnosis, treatment, critical care, and respiratory management, non-pharmacologic interventions, vaccines and prophylactic interventions, and adjunct interventions. Four additional evidence summaries were used to update recommendations because of new evidence that was released during the interval period.

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

The main challenges in doing a living CPG for a new disease condition in a pandemic setting were the rapidly evolving evidence and the need to come out with point in time recommendations for clinicians and policymakers. Consensus panels needed to balance the quality and totality of the evidence with the net benefit and the contextual factors related to the implementation of the interventions, i.e., cost, equity, acceptability, and feasibility.

Flexibility and adaptability are key in developing a Living CPG, especially in this pandemic and virtual setting. The following refinements could help streamline the process of evidence synthesis, which would be valuable inputs for Phase 2 of the Philippine COVID-19 Living CPG:

1. Designate a dedicated search specialist for each panel to actively search relevant databases and websites such as COVID-19 NMA.
2. Continue holding capacity-building workshops on CPG development, systematic reviews, rapid reviews, and evidence-based medicine to increase the pool of skilled evidence reviewers.
3. Implement a structured worksheet containing the evidence to decision framework to guide the panelists on the factors to discuss and consider before voting for or against a recommendation is suggested. This will ensure that both the facilitator and the panelists cover important applicability and implementation issues of a recommendation, apart from the net benefit and certainty/quality of the evidence.

References

1. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. 2021. Retrieved August 20, 2021, from https://covid19.who.int/.
2. Philippine Department of Health. DOH COVID-19 Tracker. 2021. Retrieved August 20, 2021, from https://doh.gov.ph/covid19tracker.
3. National Task Force against COVID-19. 2020. National Action Plan against COVID-19. Retrieved August 20, 2021, from https://ndrrmc.gov.ph/attachments/article/4148/National-Action-Plan-against-COVID19-Phase-III.pdf.
4. DOH Cordillera CHD. 2021. Vaccines Administered in the Philippines as of June 10, 2021. Retrieved August 20, 2021, from https://caro.doh.gov.ph/vaccines-administered-in-the-philippines-as-of-june-10-2021/.
5. Department of Health Philippines. 2018. Manual for Clinical Practice Guideline Development.
6. Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available from guidelinedevelopment.org/handbook.
7. 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.
8. Akl EA, Meerpohl JJ, Elliott J, Kahale LA, Schünemann HJ; Living Systematic Review Network. Living systematic reviews: 4. Living guideline recommendations. J Clin Epidemiol. 2017 Nov;91:47-53. doi: 10.1016/j.jclinepi.2017.08.009. Epub 2017 Sep 11. PMID: 28911999.
9. Dans, AL, Dans, LF, Silvestre, MAA. Eds. Painless Evidence-Based Medicine, Second Edition. John Wiley & Sons Ltd. DOI: 10.1002/9781119196150
10. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses, 2012. Retrieved August 20, 2021, from http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf

Appendices

A Members of the Philippine COVID-19 Living CPG Task Force
B Summary of Declarations of Conflicts of Interests
C General Search Strategy for COVID-19
D Breakdown of Consensus Meetings, Evidence Reviews, and Recommendations per Batch

Appendix A. Members of the Philippine COVID-19 Living CPG Task Force

STEERING COMMITTEE

Jemelyn U. Garcia. MD, FPCP, FPSMID
Medical Specialist III, Research Institute for Tropical Medicine
Assistant Secretary, Philippine Society for Microbiology and Infectious Diseases

Ivan N. Villespin, MD, MBA, FPCP, FPCCP, FCCP
Associate Professor of Medicine, Faculty of Medicine and Surgery, University of Santo Tomas
Active Medical Staff, University of Santo Tomas Hospital
Immediate Past President, Philippine College of Chest Physicians

Maria Rosario Singh-Vergeire, MD, MPH, CESO II
Undersecretary of Health, Public Health Services Team, Department of Health

Mario M. Panaligan, MD, FPCP, FACP, FPSMID, FIDSA
Assistant Professor of Medicine, College of Medicine, University of the East, Ramon Magsaysay Memorial Medical Center, Inc.
Medical Specialist II and Head, Section of Infectious Diseases, Department of Medicine, Dr. Jose R. Reyes Memorial Medical Center
Infection Control Coordinator, St. Luke's Medical Center
Immediate Past President, Philippine College of Physicians and Philippine Society for Microbiology and Infectious Diseases

Noel L. Espallardo, MD, MSc, FPAFP
Board of Trustee, Philippine Academy of Family Physicians

Antonio L. Dans, MD, MSc, FPCP
Asia Pacific Center for Evidence Based Healthcare
Professor, College of Medicine, University of the Philippines

Aileen R. Espina, RMT, MD, MPH, MHA, FPAFP, CESE
Independent Consultant for Health Systems Strengthening and Disaster Risk Resilience
Member, Technical and Policy Committee, Philippine Society of Public Health Physicians

Evalyn A. Roxas, MD, MPH, FPCP, FPSMID
Clinical Associate Professor, Division of Infectious Diseases, Department of Medicine, University of the Philippines
Associate Professor, Department of Medical Microbiology, College of Public Health, University of the Philippines-Manila
President, Philippine Hospital Infection Control Society Inc.

PROJECT LEAD CONVENORS

Marissa M. Alejandria, MD, MSc, FPCP, FPSMID
Professor, Department of Clinical Epidemiology, College of Medicine, University of the Philippines Manila
Director, Institute of Clinical Epidemiology, National Institutes of Health, University of the Philippines Manila
Clinical Professor, Division of Infectious Diseases, Department of Medicine, Philippine General Hospital
President, Philippine Society for Microbiology and Infectious Diseases

Leonila F. Dans, MD, MSc, FPPS, FPRA
Professor, Department of Clinical Epidemiology and Department of Pediatrics, University of the Philippines
Faculty, Asia Pacific Center for Evidence Based Healthcare

CONSENSUS PANELS

CONSENSUS PANEL FOR SCREENING AND DIAGNOSIS

Clemencia D. Bondoc, MD
Municipal Health Officer, Zarraga, Iloilo
National President, Association of Municipal Health Officers of the Philippines

Alpha Grace B. Cabic, MD, DPSP
Medical Specialist III/ Internal COVID Laboratory Operations, Laboratory Research Division, DOH-Research Institute for Tropical Medicine

Jocelyn Myra R. Caja, MD, FPSP, MHPEd
Chair, Department of Pathology, University of Santo Tomas Faculty of Medicine and Surgery
Former Board of Governors as Secretary, Treasurer, Asst. Treasurer, Philippine Society of Pathologists, Inc.,

Mary Ann D. Lansang, MD, MSc, FPCP, FPSMID
Clinical Professor, Department of Clinical Epidemiology, College of Medicine, University of the Philippines
Consultant, Infectious Diseases Section, Department of Medicine, The Medical City
Board of Advisers, Philippine Society for Microbiology and Infectious Diseases

Virginia de los Reyes, MD, FPCCP, FPCP, FPSSM, MHPED
Section Head, Section of Sleep Medicine, Department of Pulmonary, Critical Care and Sleep Medicine, Lung Center of the Philippines
Associate Professor, Ateneo School of Medicine and Public Health
Executive Board, Philippine College of Chest Physicians and American College of Chest Physicians

Jane Eflyn L. Lardizabal-Bunyi, RPh, MD, OHP, DFM, FPAFP, CSPSH
Assistant Professor III, Manila Central University – Filemon D. Tanchoco Medical Foundation
Active Non-Rotating Consultant, Manila Central University – Filemon D. Tanchoco Medical Foundation Hospital
National Treasurer, Philippine Academy of Family Physicians

Imelda B. Mateo, MD, MBAH, FPCP, FPCCP
Medical Center Chief II, DOH- Amang Rodriguez Memorial Medical Center
Treasurer, Philippine College of Physicians

Vernon M. Serafico, MD, FPCP
Asst. Training Officer, Department of Internal Medicine, De Los Santos Medical Center Private
Board of Trustee, Philippine Society of General Internal Medicine

CONSENSUS PANEL FOR TREATMENT

Maria Elinore Alba-Concha, MD, FPAFP
Chief Training Officer, Southern Philippines Medical Center
Member, Research and Publications Committee, Philippine Academy of Family Physicians

Mary Ann C. Bunyi, MD, FPPS, FPIDSP
Deputy Director, Office of Education, Training and Research Services, Philippine Children's Medical Center
Assistant Professor III, Department of Microbiology, College of Medicine, Pamantasan ng Lungsod ng Maynila

Karl Evans R. Henson, MD, FPCP, FPSMID
Clinical Assistant Professor, Division of Infectious Diseases, College of Medicine, University of the Philippines
Training Officer, Infectious Diseases Fellowship Training Program, The Medical City
Fellow, National Board Member, and Chair, Information Technology and Media Relations Committee, Philippine Society for Microbiology and Infectious Diseases

Erwin R. De Mesa, MD, FPOGS, FPIDSOG
Training Officer, Department of Ob-Gyn, De Los Santos Medical Center
Treasurer, Philippine Obstetrical and Gynecological Society
Immediate Past President, Philippine Infectious Diseases Society for Obstetrics and Gynecology

Faith Joan C. Mesa-Gaerlan, MD, MS, FPCEM
Clinical Associate Professor, College of Medicine, UP Mamnila
Training Officer, Department of Emergency Medicine, UP-Philippine General Hospital
Member, Advisory Council, Philippine College of Emergency Medicine

Roland M. Panaligan, MD, LLM, FPCP, FPCCP
Chair, Department of Medical Ethics, University of Santo Tomas Faculty of Medicine and Surgery
Training Officer, Adult Pulmonology Fellowship Training Program, Center for Respiratory Medicine, University of Santo Tomas Hospital
Chair, Council on Diagnostics and Therapeutics, Philippine College of Chest Physicians

Rommel B. Punongbayan, RMT, MD, MBA, FPCP, FPSMS, CSPSH, DPCOM
Medical Specialist II, Bulacan Medical Center
Vice President, Philippine Society of General Internal Medicine

Iris Conela A. Tagaro, MD, DPPS, MPM-MHSD
Medical Specialist III, DOH-Food and Drug Administration

CONSENSUS PANEL FOR CRITICAL CARE AND RESPIRATORY MANAGEMENT

Joseph Adrian L. Buensalido, MD, FPCP, FPSMID
Infectious Diseases Specialist/Consultant at Asian Hospital and Medical Center and Makati Medical Center Infection Prevention and Control
Associate Professor of Medicine and Deputy Training Officer, Division of Infectious Diseases, Department of Medicine, University of the Philippines - Philippine General Hospital
Fellow, Philippine Society for Microbiology and Infectious Diseases

Pauline F. Convocar, MD, MCHM, DPBEM, FPCEM, DPCOM
Vice Chair for Patient Services Quality Management System and Telemedicine, Department of Emergency Medicine, Southern Philippines Medical Center
Immediate Past President & Section on Advocacy Chair, Philippine College of Emergency Medicine

Ricardo A. Francisco, Jr, MD, MHA, FPCP, FPSN
Chief, Section of Nephrology, Veterans Memorial Medical Center (VMMC)
Member, Board of Trustees, Philippine Society of Nephrology

Chito C. Permejo, MD, FPCP, FPCC, FPSCCM
Medical Specialist III, Philippine Heart Center
Fellow, Philippine Society of Critical Care and Medicine

Mark Kristoffer U. Pasayan, MD, FPCP, FPSMID
Medical Specialist II, DOH-Research Institute for Tropical Medicine
Fellow, Philippine Society for Microbiology and Infectious Diseases

Albert L. Rafanan, MD, FPCCP, FPCP, FCCP, FASSM, FPSSM
Assistant Medical Director for Continuing Medical Education, Critical Care Committee Chairman, Center for Sleep Disorders
Head, Ching Hua Hospital, Cebu City Professor of Medicine, Cebu Doctors University College of Medicine
Member, Board of Trustees, Philippine College of Chest Physicians

Rowena Marie T. Samares, MD, FPAFP, FPSHPM
Chair, Department of Family Medicine, Silliman University Medical Center
Fellow, Philippine Academy of Family Physicians; Philippine Society of Hospice and Palliative Medicine
Secretary, Philippine Society of Hospice and Palliative Medicine

Paul Michael S. Tan, RN, MAN, PhD†
Senior Nurse, Cardiovascular Post Anesthesia Care Unit – St. Luke's Medical Center, Global City
Chairperson, Continuing Professional Education Accreditation (CPEA) Committee, Philippine Nurses Association

CONSENSUS PANEL FOR NON-PHARMACOLOGIC INTERVENTIONS

Regina P. Berba, MD, MSc, FPCP, FPSMID
Professor, University of the Philippines Manila
Head, Philippine General Hospital Infection Control Unit
Fellow, Philippine Society for Microbiology and Infectious Diseases

Vivien Fe F. Fadrilan-Camacho, MD, MPH, FPAFP
Associate Professor, Department of Environmental and Occupational Health, College of Public Health, University of the Philippines
Member, Technical and Policy Committee, Business Development Committee, Philippine Society of Public Health Physicians

Rodley Desmond Daniel M. Carza, MPH, RN
Chief, Policy and Technology Division, Heath Promotion Bureau, Department of Health, Philippines

Dominga Calalang-Gomez, RN
Retired Nurse VI, Philippine General Hospital
Founding President, Philippine Hospital Infection Control Nurses Association

Victoria Isla-Ching, RN, MGM-ESP
Former Manager, Hospital Infection Control Committee, The Medical City
Former Manager, Patient Safety Department, The Medical City
Board Member, Philippine Hospital Infection Control Society, Inc

Anna Sofia Victoria Tamayo Salazar Fajardo, MD, MBAH, DPCOM
Medical Director, Perpetual Help Medical Center - Biñan
National Vice President, Philippine College of Occupational Medicine
National Secretary, Philippine College of Occupational Medicine

Nenacia Ranali Nirena P. Mendoza, MD, FPAFP
Consultant and Mentor, Healthway Family Clinic Family and Community Medicine Residency Training Program
Member, Continuing Professional Development Committee; Research Committee; and Publication Committee, Philippine Academy of Family Physicians

Ruth S. Punzalan, MD, MPH, MMHoA, FPAFP
Municipal Health Officer, Tanza, Cavite
Vice President, Association of Municipal Health Officers of the Philippines

CONSENSUS PANEL FOR VACCINES AND PROPHYLACTIC INTERVENTIONS

Maria Rhona G. Bergantin, MD, MSc, FPCP, FPSMID
Associate Professor, University of Santo Tomas
Consultant Staff and Training Officer, Section of Infectious Diseases, Department of Medicine, University of Santo Tomas Hospital
Fellow, Philippine Society for Microbiology and Infectious Diseases

Karina S. Descartin, MD, MS, MPH, DIMPH, FRSPH
Senior Project Manager and Lead Preventionist, Project Firstline, State of Rhode Island Department of Health, on behalf of HCH Enterprises, LLC
Adjunct Professor, Epidemiology/Healthcare Quality and Safety, Jacksonville University-Brooks College of Healthcare Sciences
Member, Technical and Policy Committee, Philippine Society of Public Health Physicians

Dax Ronald O. Librado, MD, FPCP, FACP
Assistant Professor, Matias H. Aznar Memorial School of Medicine; Cebu Institute of Medicine; and CNU-Vicente Sotto Memorial Medical Center
President, Philippine Society of General Internal Medicine

Anna Guia Orejola Limpoco, MD, MSc, CM-FCM FPAFP
Associate Professor, Department of Family and Community Medicine, University of the Philippines
Fellow, Philippine Academy of Family Physicians

Edmyr M. Macabulos, MD, MPH, FPCOM
Associate Professor II, St. Luke's Medical Center College of Medicine-WHQM
Immediate Past National President, Philippine College of Occupational Medicine

Fatima Ignacio Gimenez, MD, FPPS, FPIDSP
Training Officer, Pediatric Infectious Disease Section, Philippine Children's Medical Center
Vice President, Pediatric Infectious Disease Society of the Philippines
Chairman, Immunization Committee, Philippine Pediatric Society
Philippine Foundation for Vaccination

Rosally P. Zamora, MD, FPCP, DPSMID
Associate Professor, University of the East Ramon Magsaysay Memorial Medical Center
Fellow, Philippine College of Physicians

Gian Carlo Sy Torres, PhD, MAN, RN
Faculty, University of Santo Tomas College of Nursing
Chair, Department of Public Affairs, Philippine Nurses Association

CONSENSUS PANEL FOR ADJUNCT INTERVENTIONS

Anthony F. Cortez, MD
Municipal Health Officer, RHU Bambang, Nueva Vizcaya
President, Association of Municipal Health Officers of the Philippines – Nueva Vizcaya

Katrina G. Gomez-Chua, MD, MPH
Primary Care Physician, ICH (Innovations for Community Health)
Member, Technical and Policy Committee, Philippine Society of Public Health Physicians

Ana Melissa S. Guererro, MD, MPH (HTA)
Division Chief, DOH Pharmaceutical Division
Head, DOH Health Technology Assessment Unit

Joan Mae M. Oliveros, MD, FPAFP
Faculty/Research & COPC Coordinator, Department of Family Medicine, Silliman Medical Center
Fellow, Philippine Academy of Family Physicians
Member/Peer Reviewer, Research Committee, Philippine Academy of Family Physicians

Maria Sonia Salamat, MD, MPH, FPCP, FPSMID
Medical Specialist III, Philippine General Hospital
Clinical Associate Professor, College of Medicine, University of the Philippines Manila
Member, Board of Councils, Philippine Society for Microbiology and Infectious Diseases, 2020

Julie Christie Gutierrez Visperas, MD, MHPEd, FPCP, FPCCP, FPSP
Head, Medical Intensive Care Unit and Pulmonary Vascular Unit, University of Santo Tomas Hospital
Hospital Assistant Professor 3, Department of Physiology and Department of Medicine, University of Santo Tomas, Faculty of Medicine and Surgery
Co-chair, Committee on Ethics and Quiz Committee, Philippine College of Physicians

Shirley P. Whisenhunt DNM, RN
Department Manager- Nursing Research, St. Luke's Medical Center-Global City
Chairman, Committee on Continuing Professional Development, Philippine Nurses Association

EVIDENCE REVIEW EXPERTS

Eva I. Bautista, MD, MSc, FPPS
Assistant Professor, College of Medicine, Far Eastern University-Nicanor Reyes Medical Foundation
Chair, Research Committee, National Children's Hospital

John Jefferson V. Besa, MD
Medical Officer III, Philippine General Hospital

Julian M. A. Buban
Medical Intern, Philippine General Hospital

Aldrich Ivan Lois D. Burog, MD, MSc (cand.)
Department of Clinical Epidemiology, College of Medicine, University of the Philippines Manila

Ian Theodore Cabaluna, RPh, MD, GDip (Epi)
Medical Officer, Wellbridge Health, Inc.
Department of Clinical Epidemiology, College of Medicine, University of the Philippines Manila

Marie Gene D. Cruz, MD
Internal Medicine Hospitalist, St. Luke's Medical Center - Global City

Patricia Maria Gregoria M. Cuaño, MD
Institute of Clinical Epidemiology, National Institutes of Health, University of the Philippines

Lea Roselle O. De Castro, MD
Internal Medicine Hospitalist, Chinese General Hospital Internal Medicine
Hospitalist, St. Luke's Hospital - BGC

Namnama P. Villarta-De Dios, MD, MSc, DPPS
Medical Specialist II, Department of Pediatrics, Amang Rodriguez Memorial Medical Center
Visiting Faculty, Ateneo School of Medicine and Public Health

Belen Lardizabal Dofitas, MD, FPDS, MSc Clin Epid
Associate Professor IV, College of Medicine, University of the Philippines Manila
Attending Physician, Philippine General Hospital
Vice-Chair for Research, Department of Dermatology, Philippine General Hospital

Valentin C. Dones III, PhD
Research Supervisor, Center for Health Research and Movement Science, University of Santo Tomas

Louie F. Dy
Medical Intern, Philippine General Hospital

Gina Antonina S. Eubanas, MD, FPDS, D Clin Epi
Assistant Professor, Department of Clinical Research, St. Luke's Medical Center, College of Medicine - WHQM
Head, Section of Dermatology, Department of Internal Medicine, Qualimed - Daniel Mercado Medical Center

Antonio L. Faltado Jr., MD, FPCP, FPSEDM
Chair, Research Ethics Board, and Head, Diabetes Center, Lipa Medix Medical Center

Anna Maria Vida P. Garcia, RPh, D Clin Epi
Clinical Scientist, ClinChoice Inc.

Rowena F. Genuino, MD, MSc
Professor, Department of Anatomy, College of Medicine, University of the Philippines
Consultant Dermatologist, Manila Doctors Hospital and Makati Medical Center

Germana Emerita V. Gregorio, MD, PhD
Consultant, Department of Pediatrics, University of the Philippines Manila College of Medicine Philippine General Hospital

Myzelle Anne J. Infantado, PTRP, MSc (cand.)
PT Consultant, ManilaMed Child Development Enrichment Center and New Beginnings Center for Child Development
Department of Clinical Epidemiology, College of Medicine, University of the Philippines Manila

Racquel Ibanez, MD, FPCP, FPCCP, D Clin Epi
Medical Specialist, Lung Center of the Philippines and National Center for Mental Health

Marquis Von Angelo Syquio Go Joson, MD
Department of Pediatrics, University of the Philippines - Philippine General Hospital

Anna Angelica Macalalad Josue, MD, FPCP, DPSEDM, MSc (cand)
Medical Specialist, Taguig Pateros District Hospital

Marie Carmela Lapitan, MD, MS, FPUA, FPCS
Research Professor, Institute of Clinical Epidemiology, University of the Philippines-National Institutes of Health
Clinical Professor, Department of Surgery, College of Medicine, University of the Philippines
Attending Surgeon, Department of Surgery, Philippine General Hospital

Christopher G. Manalo, MD, DPBEM
Medical Specialist II, Department of Emergency Medicine, Philippine General Hospital, University of the Philippines Manila
Emergency Physician, Department of Emergency Medicine, The Medical City
Department of Clinical Epidemiology, College of Medicine, University of the Philippines Manila

Patricia Pauline M. Remalante-Rayco, MD, FPCP, FPRA
Associate Professor, De La Salle Medical and Health Sciences Institute
Active Consultant, De La Salle University Medical Center and Perpetual Help Medical Center - Las Piñas

Evelyn O. Salido, MD, MSc, FPCP, FPRA
Chair, Division of Rheumatology, Philippine General Hospital

Maria Cristina Z. San Jose, MD, FPNA
Division Chair, Section of Adult Neurology, Department of Neurosciences, University of the Philippines - Philippine General Hospital
Head, Health Services Outcome Research Unit, St. Luke's Medical Center
Associate Professor, College of Medicine, University of the Philippines
Department of Clinical Epidemiology, College of Medicine, University of the Philippines Manila

Maria Vanessa V. Sulit, BSN, RN, MSc (Clinical Epidemiology)
Faculty Member & Workshop Coordinator, Asia-Pacific Center for Evidence-Based Healthcare, Inc.

Joey A. Tabula, MD, FPCP
General Internist, San Antonio, Zambales

Frangelo Conrad Tampus, MD
Junior Consultant, Lorenzo D Zayco District Hospital

Cary Amiel G. Villanueva, MD
Institute of Clinical Epidemiology, National Institutes of Health, University of the Philippines Manila

Paoline Nicole P. Villanueva, RMT, MD
Institute of Clinical Epidemiology, National Institutes of Health, University of the Philippines Manila

FACILITATORS

Screening and Diagnosis:
Lia Aileen M. Palileo-Villanueva, MD, MSc
Associate Professor, College of Medicine, University of the Philippines Manila
Vice Chair for Undergraduate Training, Department of Medicine, UP-Philippine General Hospital

Treatment:
Diana R. Tamondong-Lachica, MD, FPCP
Associate Professor, Division of Adult Medicine, UP-Philippine General Hospital

Critical Care and Respiratory Management:
Bernadette Heizel Manapat-Reyes, MD, MHPEd, FPCP, FPRA
Professor, Department of Medicine, College of Medicine, University of the Philippines
Head, Medical Education Unit, College of Medicine, University of the Philippines Manila

Non-Pharmacologic Interventions:
Carol Stephanie C. Tan-Lim, MD, MScCE
Diplomate, Philippine Pediatric Society and Philippine Society of Allergy, asthma and immunology

Vaccines and Prophylactic Interventions:
Maria Asuncion A. Silvestre, MD, FPSNbM
President, Kalusugan ng Mag-Ina, Inc. (KMI)
Member, Independent Review Group, Early Essential Newborn Care (EENC), WHO, WPRO

Adjunct Interventions:
Carlo Irwin Panelo, MD, MA
Professor, Department of Clinical Epidemiology, College of Medicine, University of the Philippines Manila

PROJECT STAFF

Project Manager:

Dan Louie Renz P. Tating, MS(cand), RN
Department of Clinical Epidemiology, College of Medicine, University of the Philippines

Technical Coordinators:

Howell Henrian G Bayona, MSc, CSP-PASP
Speech Pathologist, The Medical City Speech Pathologist, St. Luke's Medical Center-Global City
Department of Clinical Epidemiology, College of Medicine, University of the Philippines

Maria Teresa S. Tolosa, MD, FPDS, D Clin Epi
Assistant Professor, St. Lukes' Medical Center College of Medicine – WHQM
Assistant Professor, UERMMMCI College of Medicine
Department of Clinical Epidemiology, College of Medicine, University of the Philippines

Dan Louie Renz P. Tating, MS(cand), RN
Department of Clinical Epidemiology, College of Medicine, University of the Philippines

Associate Staff:

Maria Eleanor L. Candelaria, MPH, RN
Project Assistant, COVID-CPG, SIBOL UV/HPV and COVENANT Antibody Study
Research Associate, Institute of Health Policy and Development Studies-National Institutes of Health

Kate D. Dunlao, RPh
Institute of Clinical Epidemiology, National Institutes of Health, University of the Philippines Manila

Technical Writers:

Joyce Anne Ceria-Pereña, RPh, MPM
Project Development Officer V, Anti-Red Tape Authority

Mikarla M. Lubat, RND
Department of Epidemiology and Biostatistics, College of Public Health, University of the Philippines Manila

Kate D. Dunlao, RPh
Institute of Clinical Epidemiology, National Institutes of Health, University of the Philippines Manila

Copy Editors:

Cybele Lara R. Abad, MD, FPCP, FIDSA
Maria Regina Naval-Jacinto, MD

PSMID Website Administrator:

Chito L. Patiño

Appendix B. Summary of Declarations of Conflicts of Interests.

Name	Role in the CPG Project	Nature of Declared COI
Vivien Fe F. Fadrilan-Camacho, MD, MPH, FPAFP	Consensus Panelist, Non-Pharmacologic Interventions	Technical Consultant of three plants in Laguna on their COVID-19 risk assessment (Non-significant COI)
Rosally P. Zamora, MD, FPCP, DPSMID	Consensus Panelist, Vaccines and Prophylactic Interventions	TWG Member of the PSMID Adult Vaccination Committee (Non-significant COI)
Iris Conela A. Tagaro, MD, DPPS, MPM-MHSD	Consensus Panelist, Treatment	Clinical Research Head, Center for Drug Regulation and Research, Philippine FDA (Non-significant COI)
Regina P. Berba, MD, MSc, FPCP, FPSMID	Consensus Panelist, Non-Pharmacologic Interventions	Infection Control Lectures for Delex, BD and MSD (PhP 8,000 each lecture) Reviewed data for FDA EUA applications of Pfizer and Sinovac COVID-19 vaccines DOH research grant for Favipiravir clinical trial (with PhP 7,500 monthly honoraria) (Non-significant COI)
Marie Carmela Lapitan, MD, MS, FPUA, FPCS	Evidence Review Expert (on convalescent plasma, HCQ/CQ and azithromycin for treatment; COVID-19 vaccines and BCG vaccines for prevention)	Part-time Medical Expert for GSK Contractual reviewer for WHO and Cochrane response (Non-significant COI related to assigned review topics)
Racquel Ibanez, MD, FPCP, FPCCP, D Clin Epi	Evidence Review Expert (on prognostic factors and laboratory markers for COVID-19 severity and mortality)	Sub Investigator in a Clinical Trial on an antiviral sponsored by a pharmaceutical company (Non-significant COI related to assigned review topics)

Appendix C. General Search Strategy for COVID-19

Search strategy for COVID-19:

((("COVID-19" [Supplementary Concept] OR "COVID-19 diagnostic testing" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [Supplementary Concept] OR "COVID-19 vaccine" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR "2019-nCoV" OR "2019nCoV" OR "cov 2" OR "Covid-19" OR "sars coronavirus 2" OR "sars cov 2" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus 2" OR "COVID 19" OR "COVID-19" OR "2019 ncov" OR "2019nCoV" OR "corona virus disease 2019" OR "cov2" OR "COVID-19" OR "COVID19" OR "nCov 2019" OR "nCoV" OR "new corona virus" OR "new coronaviruses" OR "novel corona virus" OR "novel coronaviruses" OR "SARS Coronavirus 2" OR "SARS2" OR "SARS-COV-2" OR "Severe Acute Respiratory Syndrome Coronavirus 2") OR ((19[tiab] OR 2019[tiab] OR "2019-nCoV" OR "Beijing" OR "China" OR "Covid-19" OR epidem*[tiab] OR epidemic* OR epidemy OR new[tiab] OR "novel"[tiab] OR "outbreak" OR pandem* OR "SARS-CoV-2" OR "Shanghai" OR "Wuhan") AND ("Coronavirus Infections"[Mesh] OR "coronavirus"[MeSH Terms] OR coronavirus*[all] OR corona-virus*[all] OR cov[tiab] OR pneumonia-virus*[tiab]))) AND 2019/12/1:3000/12/31[PDAT])

Search filter for Randomized Controlled Trials:

(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])

Search filter for Systematic Reviews and Meta-Analyses:

(((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt]

Appendix D. Breakdown of Consensus Meetings, Evidence Reviews, and Recommendations per Batch.

CPG Panel	Date of Meetings	Evidence Summaries Presented*	Consensus Panel Recommendations Generated*
Screening and Diagnosis	Batch 1: February 20 and March 6, 2021	6	13
	Batch 2: April 9 and 26, 2021	7	15
	Batch 3: May 26, 2021	3	3
Treatment	Batch 1: February 19 and March 5, 2021	10	14
	Batch 2: April 8, 10 and 16, 2021	8	11
	Batch 3: May 29 and June 2, 2021	7	7
Critical Care and Respiratory Management	Batch 1: February 19 and March 6, 2021	7	11
	Batch 2: April 15, 2021	6	6
Non-Pharmacologic Interventions	Batch 1: February 26 and March 12, 2021	7	9
	Batch 2: April 17, 2021	3	3
	Batch 3: May 26, 2021	4	5
Vaccines and Prophylaxis	Batch 1: February 20 and March 12, 2021	9	10
	Batch 2: April 10, 2021	1	14
	Batch 3: May 28, 2021	1	1
Adjunct Interventions and Other Questions	Batch 1: February 20 and March 13, 2021	8	8
	Batch 2: April 16, 2021	3	6
Total (Batch 1)		47	65
Total (Batch 2)		28	55
Total (Batch 3)		15	16

**Does not include updated evidence summaries recommendations to avoid double counting*