GUIDELINES

Interim Guidelines on the Screening, Assessment and Clinical Management of Pediatric Patients with Suspected or Confirmed Coronavirus Disease 2019 (COVID-19)

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INTRODUCTION

The emergence of the novel coronavirus SARS-CoV-2 and the subsequent declaration by the World Health Organization of the coronavirus disease 2019 (COVID-19) pandemic has greatly impacted the lives of many all over the world. As the total number of reported cases increase globally, the number of pediatric cases have also steadily increased over the past several months. This has led to an expansion of scientific and clinical knowledge on COVID-19 in children.

This rapid advice is the fourth version released by the Philippine Pediatric Society and the Pediatric Infectious Disease Society of the Philippines. It is intended to guide pediatricians, general and family practitioners, and other healthcare professionals caring for children on how to assess and treat pediatric patients with suspected or confirmed COVID-19. These guidelines were formulated based on information available at the time of its release, and shall be updated as new data becomes available.

This rapid advice is divided into four parts: part 1 discusses basic concepts on COVID-19 in children, including local epidemiology, disease transmission, risk factors, clinical manifestations, and pathogenesis; part 2 mainly focuses on screening and triaging of children; while part 3 discusses basic concepts of management. Part 4, a new section in this update, highlights disease prevention and control, and presents an overview of COVID-19 vaccines.

New in the Guidelines

Last Updated: February 6, 2021

- Updates on the epidemiology, transmission, and pathophysiology of COVID-19 in children
- Updated WHO case definitions for surveillance
- Updated WHO disease severity classification criteria, which now includes acute thrombosis and MIS-C
- Recommendations on the use of Antigen Test
- Revised recommendations on the use of Dexamethasone, Remdesivir, IVIG, Convalescent plasma, Zinc, and Vitamin D
- Updated recommendations on discontinuation of quarantine, isolation or transmission-based precautions
- New sections on disease prevention and control and an overview of COVID-19 vaccines

PART 1. COVID-19 IN CHILDREN

I. LOCAL EPIDEMIOLOGY AND BURDEN OF ILLNESS IN CHILDREN

As of February 6, 2021, the Department of Health has recorded 48,411 confirmed COVID-19 cases aged 19 years and below, which accounts for 9% of total cases in the country. Of these cases, 51.5% were males. The majority were between 15-19 years old, comprising 40.2% of total cases, followed by the 10-14 years age group at 23.8%, 0-4 years age group at 18.5%, and 5-9 years age group at 17.4%.

A total of 210 deaths were recorded among confirmed cases 19 years and below, giving a case fatality rate of 0.4%. Pediatric mortalities account for 1.9% of total mortalities in the country. Among the deaths, 54.8% were seen in the 0-4 years old age group, followed by the 15-19 years age group with 23.3% of total deaths, the 10-14 years age group with 14.8% of total deaths, and the 5-9 years age group with 7.1%.

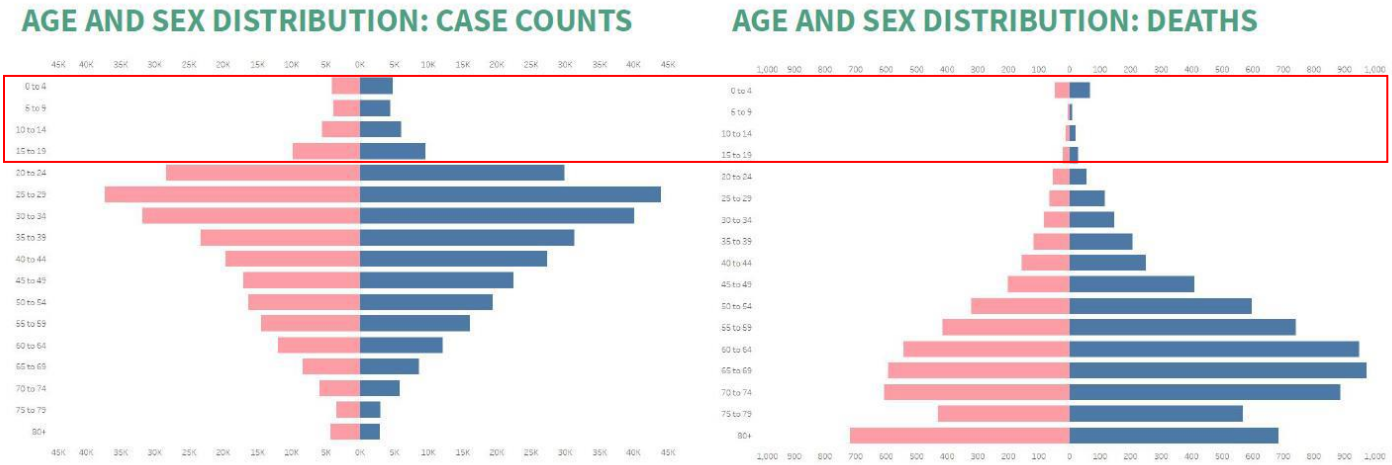


Figure 1. Age and sex distribution of COVID-19 cases and deaths as of 06 February 2021. The pediatric population is indicated by the red box.
(Source: Department of Health. Beat COVID-19 today Philippine situationer: full weekly report. Issue 286, February 7, 2021.)

II. SARS-CoV-2 VIROLOGY

The incubation period of the SARS-CoV-2 virus is on average 5-6 days but can last up to 14 days (up to 21 days in some literature). Transmission of disease may occur during the pre-symptomatic and symptomatic phase of illness – infectiousness begins from 2.3 days before symptom onset and peaks at 0.7 days before symptom onset, and lasts up to 10 days (longer in patients with severe illness). The virus may be detected for a median of 20 days up to 37 days after symptom onset, but infectiousness has been observed to decline significantly 8 days after the onset of symptoms, and live virus could no longer be cultured after day 9 of illness. A modelling study by Johansson et al. has postulated that approximately 59% of all transmission come from asymptomatic transmission: 35% from presymptomatic individuals and 24% from individuals who never develop symptoms (asymptomatic infection).

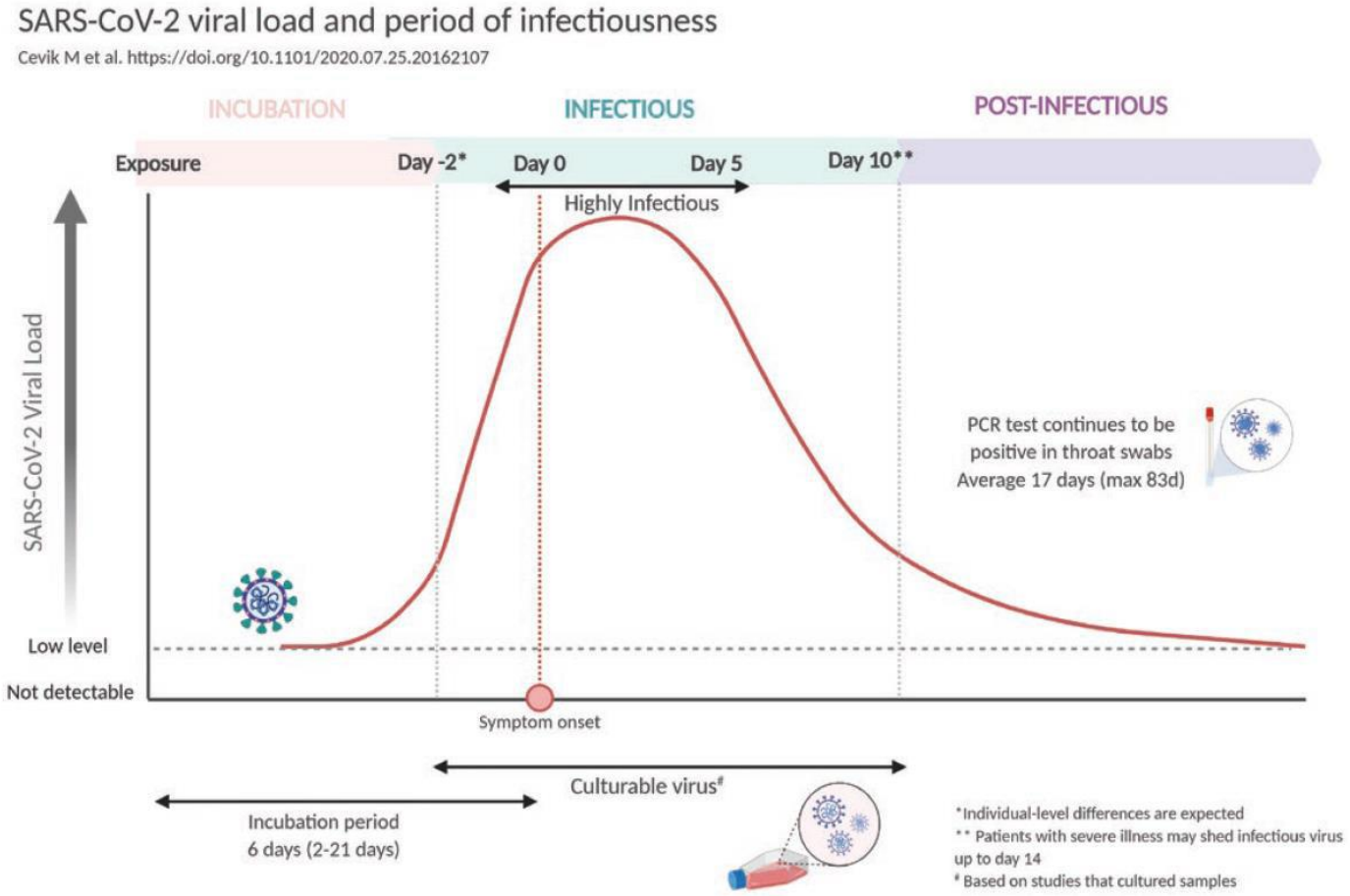


Figure 2. SARS-CoV-2 viral load dynamics and period of infectiousness. Incubation period (time from exposure to symptom onset) of 6 days (2–21 days), peak viral load levels documented from day 0 (symptom onset) to day 5, infectious period starts before symptom onset up to 10 days (this may be extended in patients with severe illness), and RNA shedding continues for a prolonged period of time but culturable virus has been identified up to day 9 of illness. (*Source: Cevik M et al. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission dynamics should inform policy. Clinical Infectious Diseases. Advanced online publication. DOI: 10.1093/cid/ciaa1442.)*

Several variants of SARS-CoV-2 have appeared due to mutations in the spike protein of the virus. The United Kingdom (UK) variant B.1.1.7 was initially detected in southeast England and has since been detected in many countries around the world, including the Philippines. This variant has been shown to be 56% more transmissible than preexisting variants, and 35% more likely to cause death. The South African variant B.1.351 shares some mutations with the UK variant, and has already been detected in multiple countries outside South Africa. The Brazilian variant P.1 was first identified in Japan in travelers from Brazil. The mutations in the P.1 variant have been shown to affect the ability of antibodies (from natural infection or vaccination) to recognize and neutralize the virus, but more definitive evidence is needed.

III. TRANSMISSION

COVID-19 is primarily transmitted through inhalation of infected respiratory droplets, or by contact of the mucosal surfaces of the eyes, nose and mouth after touching contaminated objects and surfaces. Airborne transmission may occur when viral particles are aerosolized through aerosol-generating procedures typically performed in health facilities. Daily activities like breathing, speaking and singing have also been demonstrated to generate aerosols.

Other possible modes of transmission have been reported in literature. Prolonged viral shedding in stool of infected children has been documented, but there is limited evidence at present on whether viral RNA shed in stools is infectious and whether fecal viral shedding plays a role in the dissemination of infection.

Recent published data have shown evidence of transplacental transmission of SARS-CoV-2 from mother to infant. Evidence of placental and fetal infection with SARS-CoV-2 have been documented in a report by Stonoga et al., where placenta and cord blood tested positive for SARS-CoV-2 via PCR after delivery of a stillbirth fetus. A systematic review by Bwire et al. reported 11 infants born to mothers with COVID-19 who had detectable IgM and IgG antibodies but were tested negative for the virus after delivery. This indicates the possibility of natural passive immunity via the transplacental transfer of maternal antibodies. Transmission via breastmilk has also been investigated, and although viral RNA particles have been isolated in breastmilk, the viability of these viral particles have not been proven and transmission via breastmilk has yet to be confirmed.

Children have been shown to be infected via close contact with people infected with SARS-CoV-2. In a study on the spread of COVID-19 in family clusters with confirmed COVID-19 infection in children, 79% of households had an adult family member diagnosed with COVID-19 before the onset of symptoms in the COVID-19-infected child. In only 8% of households did the child develop symptoms first before any other household contact. This supports earlier findings that children are mainly infected within familial clusters. Pediatric index cases in household clusters were reported to range from 3.8% to 14% in several studies. In households with pediatric index cases, the secondary attack rates, defined as the proportion of confirmed infections among all household contacts, were reported to be 53% for index patients less than 12 years old, and 38% for index patients aged 12 to 17 years. Knowledge on the role of children in disease transmission is rapidly evolving, and more data is becoming available to determine how the disease is transmitted to and from children.

A systematic review by Bulfone et al. quantified the risk of SARS-CoV-2 transmission in outdoor settings to be at less than 10% of transmission, with less than 5% of cases related to outdoor occupations. The odds of transmission or super spreading are much lower outdoors, compared to estimates of indoor transmissions of 10.3 to 78% in various studies.

IV. RISK FACTORS

Several risk factors have been identified that predispose children to COVID-19 infection. In the systematic review by Hoang et al., a cohort of 655 patients were identified to have the following underlying conditions that predisposed the patients to COVID-19 infection:

- Immunosuppression (30.5%)
- Respiratory conditions (21%)
- Cardiovascular conditions (13.7%)
- Complex congenital malformations (10.7%)
- Hematologic conditions (3.8%)
- Neurologic conditions (3.4%)
- Obesity (3.4%)
- Prematurity (3.4%)
- Endocrine/metabolic conditions (2.1%)
- Renal conditions (1.7%)
- Gastrointestinal conditions (0.5%)

A more recent systematic review by Tsancov et al., which evaluated the risk of severe COVID-19 infection in children with pre-existing conditions, reported that children with pre-existing conditions are 1.8 times more likely to have severe COVID-19 infection and/or require intensive care. In addition, children with pre-existing conditions are 2.8 times more likely to die compared to children without pre-existing conditions. Obesity was reported to be the most common pre-existing condition in this study, and children who are obese are 2.9 times more likely to have severe COVID-19 infection. One proposed mechanism to explain this is that higher visceral adiposity induces higher levels of local and systemic inflammatory cytokines such as IL-6 and CRP, which predisposes to more severe infection.

V. CLINICAL MANIFESTATIONS OF COVID-19 IN CHILDREN

In a study by Dong et al. of 2,143 confirmed and suspected cases of pediatric COVID-19 in China, 4.4% were found to be asymptomatic, 50.9% had mild disease, and 38.8% had moderate disease, accounting for 94.1% of total cases. The rate of severe and critical cases was 5.2% and 0.6% respectively.

A systematic review of children with COVID-19 by Hoang et al. has described the most common symptoms seen (Table 1). The two most common manifestations are fever (59.1%) and cough (55.9%). No symptoms were seen in 19.3% of infected children.

Table 1. Clinical symptoms of COVID-19 in children (n=2,445)

Clinical symptoms	%
Fever	59.1
Cough	55.9
Rhinorrhea, nasal congestion	20.0
Myalgia, fatigue	18.7
Sore throat	18.2
Shortness of breath, dyspnea	11.7
Abdominal pain, diarrhea	6.5
Vomiting, nausea	5.4
Headache, dizziness	4.3
Pharyngeal erythema	3.3
Decreased oral intake	1.7
Rash	0.25
Asymptomatic	19.3

Several reports have been made about children testing positive for current or recent infection with SARS-CoV-2, and presenting with a severe inflammatory syndrome with Kawasaki disease-like features. This syndrome has since been named **Multisystem Inflammatory Syndrome in Children (MIS-C).** The case definition for this syndrome is as follows:

US Centers for Disease Control and Prevention (CDC) Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

- An individual aged < 21 years presenting with fever[a], laboratory evidence of inflammation[b], and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

Additional comments:

- Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

[a] Fever > 38.0°C for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours

[b] Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin.

VI. PATHOGENESIS OF COVID-19

The first step in infection is the virus attaching to a host cell, achieved through the spike (S) protein of the virus binding to its target receptor, the angiotensin-converting enzyme 2 (ACE2) receptor. The ACE2 receptor is expressed in airway epithelial cells, alveolar epithelial cells, vascular endothelial cells, and macrophages in the lung. SARS-CoV-2 reduces expression of ACE2 in lung cells, and loss of pulmonary ACE2 function is associated with acute lung injury. ACE2 also regulates the renin-angiotensin system (RAS), hence reduced ACE2 function influences blood pressure, fluid and electrolyte balance, and enhances inflammation and vascular permeability in the airways.

The binding of the virus to the ACE2 receptor triggers endocytosis of the virion, after which viral replication ensues, leading to viral assembly, maturation, and virus release.

SARS-CoV-2 infection triggers a local immune response, recruiting macrophages and monocytes that respond to infection, release cytokines, and prime adaptive T and B cell immune responses. This immune response is capable of resolving the infection in most cases. However, in some cases, a dysfunctional immune response occurs, which can cause severe lung and even systemic pathology. SARS-CoV-2 is capable of inducing death and injury of virus-infected cells and tissues in a phenomenon called pyroptosis, a highly inflammatory form of programmed cell death. This triggers a subsequent inflammatory response involving a cytokine storm that mediates widespread lung inflammation as well as systemic manifestations such as multiorgan failure, septic shock, and myocardial damage with circulatory failure.

Most children and adolescents present with mild to moderate symptoms, in contrast to adult patients with COVID-19 who present more commonly with severe manifestations, with older children approximating the risk in adults the older they are. Only a small percentage of patients develop severe and critical COVID-19. The

mortality rate in children was reported to be at 0.09% in one systematic review. Several theories have been formulated to attempt to explain the difference in severity and susceptibility of children compared to adults (table 3). Further studies are needed to find more evidence supporting these theories.

Table 3. Theories regarding the severity and susceptibility of children to COVID-19

Factor	Theory
ACE2 receptor	The ACE2 receptor is necessary for viral entry into cells. The development, function, or activity of this protein might be less in children. ACE2 receptors are upregulated in those with COPD or hypertension, which may partially explain more serious disease in those with comorbid conditions.
Role of other viruses	Children are susceptible to a wide variety of viral illnesses. Presence of these viruses on epithelial surfaces can limit infection of SARS-CoV-2 through competition. Also, cross-reactive antibodies resulting from other viral infections, including non-SARS coronaviruses, may be partially protective against SARS-CoV-2.
Reduced exposures	Children may have fewer opportunities than adults to be exposed to the virus or to those with COVID-19. Additionally, compared to adults, children have had less lifetime exposure to toxins such as cigarette smoke and air pollution, factors which may affect the health of an individual's epithelium.
Aging of the immune system	Natural involution of the thymus over time leads to a decline in circulating naïve T cells. Due to this normal process, immune systems in adults are less able to be adaptive than those of children.
Innate versus adaptive immune system	The innate immune system, which acts earlier than the adaptive immune response, is more active in children, and may prevent more serious illness.
Inflammation	There is evidence that the levels of various proinflammatory cytokines are higher in adults. This may mean that adults experience a more pronounced inflammatory response than children with a similar exposure to SARS-CoV-2.

The figure below illustrates some concepts behind the reduced susceptibility of children to COVID-19.

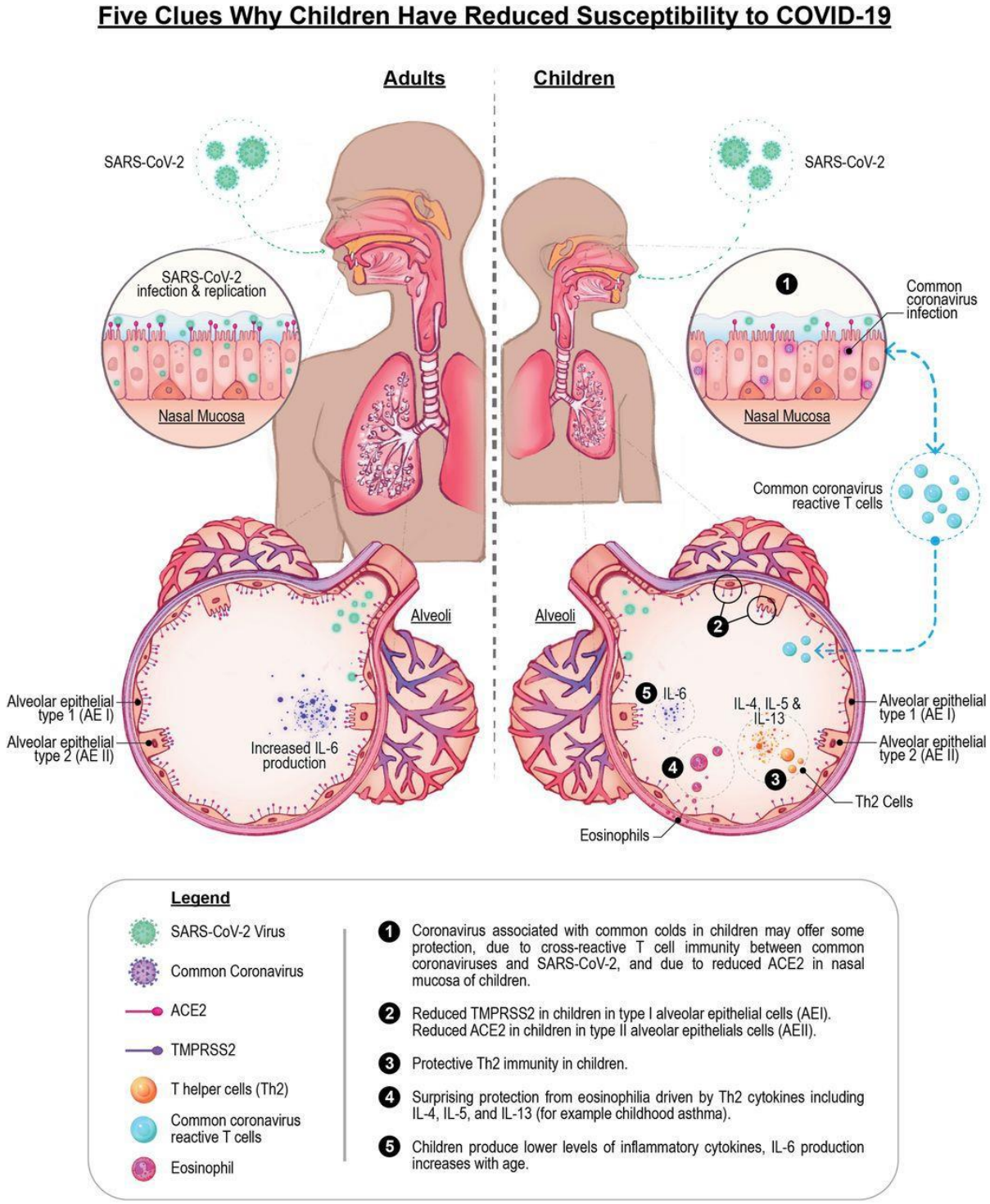


Figure 3. Illustrated concepts behind the reduced susceptibility of children to COVID-19

(Source: *Steinman J et al. Reduced development of COVID-19 in children reveals molecular checkpoints gating pathogenesis illuminating potential therapeutics. Proceedings of the National Academy of Sciences Oct 2020, 117 (40) 24620-24626. Accessed from https://www.pnas.org/content/117/40/24620)*

PART 2. SCREENING AND ASSESSMENT

I. SCREENING A CHILD FOR COVID-19

A. Investigate whether the child has had any symptoms of **influenza-like illness (ILI)** - sudden (within 3 days) onset of fever ≥ 38°C and cough or sore throat - for which no other plausible alternative etiology can be considered.

Likewise, determine if the child presents with features compatible with **Severe Acute Respiratory Infection (SARI)**, defined as an acute respiratory infection with onset during the previous 7 days requiring overnight hospitalization. A SARI case must meet the ILI definition AND any of the following:

a. shortness of breath or difficulty of breathing;
b. severe pneumonia of unknown etiology, acute respiratory distress, or severe respiratory disease possibly due to novel respiratory pathogens (such as COVID-19)

Symptoms frequently seen in children with COVID-19 are listed in Table 1 (see above). The two most common manifestations are fever (59.1%) and cough (55.9%).

B. Exposure evaluation

Assess the child's travel history or history of close contact:

1. Evaluate if the child has been in close contact with sick individuals or suspect, probable or positive COVID-19 patients, whether from home or during travel. *Contact* is defined by the WHO as a person who has experienced any one of the following exposures **during the 2 days before and the 14 days after the onset** of symptoms of a probable or confirmed case:
   a. Face-to-face contact with a probable or confirmed case within 1 meter and **for at least 15 minutes** (see note below);
   b. Direct physical contact with a probable or confirmed case;
   c. Direct care for a patient with probable or confirmed COVID-19 disease without using recommended personal protective equipment; OR
   d. Other situations as indicated by local risk assessments

   Note: The **Centers for Disease Control and Prevention (CDC)** recently released a revised definition of ***close contact*** (21 October 2020), which sets exposure for a **cumulative total of 15 minutes** or more over a 24-hour period. Factors to consider when defining close contact include (i) proximity; (ii) duration of exposure; (iii) symptomaticity of individuals involved; (iv) likelihood of generation of respiratory aerosols; and (v) other environmental factors.

   For confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample that led to confirmation was taken.
2. Take note if the child resides in or has travelled within the last 14 days to areas with localized transmission or local communities under quarantine. Check DOH updates to confirm if the child's community is classified as such. Note also if there is clustering of influenza-like illnesses in the home, neighborhood or area.

C. Clinical evaluation

Assess the child's clinical status, taking note of either rapid progression or worsening symptoms despite compliance with standard treatment and absence of defined etiology.

D. Laboratory evaluation

Ancillary laboratory tests may aid in the screening and triaging of children presenting with symptoms, and may aid in assessing the severity of symptoms and need for further management. (Common laboratory tests and characteristic findings are discussed in Part 3: Clinical Management.)

E. If either **exposure evaluation**, **clinical evaluation** or **ancillary laboratory tests** (particularly imaging procedures) is positive, **the diagnosis of COVID-19 should be considered** *(see algorithm on the screening, classification and management of pediatric patients with suspected COVID-19, page 49*).

F. If none of the features described above is present, the child is considered to have an **Acute**

Respiratory Infection. Screen for pre-existing comorbidities contributory to and/or causative of the current complaint (e.g. asthma, risk factors for aspiration). Take note also of pre-existing immunocompromising conditions that may predispose to a more severe condition (malignancy, congenital immunodeficiencies, HIV/AIDS, severe acute malnutrition, congenital heart/lung/kidney disease, intake of immunosuppressant drugs, etc.). If these exist, assess the need for inpatient care and manage accordingly. If none of these conditions are present, treat the child as having an acute respiratory infection and follow "Home Interventions" guidelines as described in Part 3.

II. CASE DEFINITIONS FOR COVID-19

After screening the child for COVID-19, classify the child according to the case definitions for COVID-19 (see also Appendix A for case definitions).

Table 4. Updated WHO Case Definitions for COVID-19 (16 December 2020)

Category	Criteria
SUSPECT CASE	**A.** A person who meets the clinical **AND** epidemiological criteria: Clinical criteria: 1. Acute onset of fever AND cough; OR 2. Acute onset of **ANY THREE OR MORE** of the following signs or symptoms: fever, cough, general weakness/fatigue,[1] headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting,[1] diarrhea, altered mental status. **AND** Epidemiological criteria: 1. Residing or working in an **area with high risk of transmission of the virus**: closed residential settings, humanitarian settings such as camp and camp-like settings for displaced persons, anytime within the 14 days prior to symptom onset; OR 2. Residing in or travel to an **area with community transmission** anytime within the 14 days prior to symptom onset; OR 3. Working in **any health setting**, including within health facilities and within the community, anytime within the 14 days prior to symptom onset. **B.** A patient with **severe acute respiratory illness** (SARI: acute respiratory infection with history of fever or measured fever of ≥ 38°C; and cough; with onset within the last 10 days; and requires hospitalization). **C.** Asymptomatic person not meeting epidemiologic criteria with a **positive SARS-CoV-2 Antigen-RDT**[2]
PROBABLE CASE	**A.** A patient who meets **clinical criteria** above **AND** is a **contact of a probable or confirmed case**, or linked to a **COVID-19 cluster**[3] **B.** A **suspect case with chest imaging** showing findings suggestive of COVID-19 disease[4] **C.** A person with recent onset of **anosmia** (loss of smell) or **ageusia** (loss of taste) in the absence of any other identified cause **D.** **Death**, not otherwise explained, in an adult with **respiratory distress** preceding death AND **was a contact of a probable or confirmed case** or linked to a **COVID-19 cluster**[3]
CONFIRMED CASE	A. A person with a positive **Nucleic Acid Amplification Test (NAAT)** B. A person with a **positive SARS-CoV-2 Antigen-RDT AND** meeting either the **probable case definition or suspect criteria A OR B** C. An **asymptomatic person with a positive SARS-CoV-2 Antigen-RDT** who is a **contact of a probable or confirmed case**

[1] Signs separated with slash (/) are to be counted as one sign

[2] NAAT is required for confirmation (see diagnostic testing for SARS-CoV-2)

[3] A group of symptomatic individuals linked by time, geographic location and common exposures, containing at least one NAAT-confirmed case or at least two epidemiologically linked, symptomatic (meeting clinical criteria of Suspect case definition A or B) persons with positive AgRDTs (based on ≥97% specificity of test and desired >99.9% probability of at least one positive result being a true positive)

[4] Typical chest imaging findings suggestive of COVID-19 include the following:

- *Chest radiography: hazy opacities, often rounded in morphology, with peripheral and lower lung distribution*
- *Chest CT: multiple bilateral ground glass opacities, often rounded in morphology, with peripheral and lower lung distribution*
- *Lung ultrasound: thickened pleural lines, B lines (multifocal, discrete, or confluent), consolidative patterns with or without air bronchograms*

Source: World Health Organization. Public health surveillance for COVID-19. Interim guidance. 16 December 2020. Accessed at https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2

III. DISEASE SEVERITY CLASSIFICATION CRITERIA

A child for whom the diagnosis of COVID-19 is considered should further be classified according to disease severity. Table 5 lists categories specified in the recent update of the WHO COVID-19 clinical management living guidance (25 Jan 2021).

Table 5. COVID-19 Disease Severity

Mild disease		Symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia.
Moderate disease	Pneumonia	Child with clinical signs of non-severe pneumonia (cough or difficulty breathing + fast breathing and/or chest indrawing) and no signs of severe pneumonia. Fast breathing (in breaths/min): • < 2 months: ≥ 60 • 2–11 months: ≥ 50 • 1–5 years: ≥ 40 Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including SpO_2 ≥ 90% on room air While the diagnosis can be made on clinical grounds, chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.
Severe disease	Severe pneumonia	Child with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following: • Central cyanosis or SpO_2 < 90%; severe respiratory distress (e.g. fast breathing, grunting, very severe chest indrawing); general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions • Fast breathing (in breaths/min): ○ < 2 months: ≥ 60 ○ 2–11 months: ≥ 50 ○ 1–5 years: ≥ 40 Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO_2 < 90% on room air While the diagnosis can be made on clinical grounds, chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.
Critical disease	Acute respiratory distress syndrome (ARDS)	**Onset**: within 1 week of a known clinical insult (i.e. pneumonia) or new or worsening respiratory symptoms. **Chest imaging**: (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. **Origin of pulmonary infiltrates**: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. ECG) to exclude hydrostatic cause of infiltrates / edema if no risk factor present. **Oxygenation impairment in adolescents/adults**: a) Mild ARDS: 200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH_2O) b) Moderate ARDS: 100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg (with PEEP ≥ 5 cmH_2O) c) Severe ARDS: PaO_2/FiO_2 ≤ 100 mmHg (with PEEP ≥ 5 cmH_2O) **Oxygenation impairment in children**: note OI and OSI, use OI when available. If PaO_2 not available, wean FiO_2 to maintain SpO_2 ≤ 97% to calculate OSI or SpO_2/FiO_2 ratio: • Bilevel (NIV or CPAP) ≥ 5 cmH_2O via full face mask: PaO_2/FiO_2 ≤ 300 mmHg or SpO_2/FiO_2 ≤ 264

		• Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5 • Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3 • Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3
Critical disease	Sepsis	**Adolescents/adults**: acute life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate, or hyperbilirubinemia. **Children**: suspected or proven infection and ≥ 2 age-based systemic inflammatory response syndrome (SIRS) criteria, of which one must be abnormal temperature or white blood cell count.
	Septic shock	**Adolescents/adults**: persistent hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥ 65 mmHg and serum lactate level > 2 mmol/L. **Children**: any hypotension (SBP < 5th centile or > 2 SD below normal for age) or two or three of the following: altered mental status; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and heart rate < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or weak pulse; fast breathing; mottled or cool skin or petechial or purpuric rash; high lactate; reduced urine output; hyperthermia or hypothermia
	Acute thrombosis	Acute venous thromboembolism (i.e. pulmonary embolism), acute coronary syndrome, acute stroke.
	MIS-C	Preliminary case definition: children and adolescents 0–19 years of age with fever > 3 days **AND** two of the following: rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet); hypotension or shock; features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP); evidence of coagulopathy (by PT, PTT, elevated D-dimers), acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain); **AND** elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin. **AND** no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. **AND** evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19. See scientific brief, 15 May 2020 WHO: Multisystemic inflammatory syndrome in children and adolescents temporally related to COVID-19

Table Notes:
If altitude is higher than 1000 m, then the correction factor should be calculated as follows: PaO2/FiO2 x barometric pressure/760
When PaO_2 is not available, $SpO_2/FiO_2 \leq 315$ suggests ARDS (including in non-ventilated patients).
Oxygenation Index (OI) is an invasive measurement of the severity of hypoxemic respiratory failure and may be used to predict outcomes in pediatric patients. It is calculated as follows: percentage of fraction of inhaled oxygen multiplied by the mean airway pressure (in mmHg), divided by the partial pressure of arterial oxygen (in mmHg). Oxygen saturation index (OSI) is a non-invasive measurement and has been shown to be a reliable surrogate marker of OI in children and adults with respiratory failure. OSI replaces PaO_2 with oxygen saturation as measured by pulse oximetry (SpO_2) in the OI equation.
SIRS criteria: abnormal temperature (> 38.5°C or < 36°C); tachycardia for age or bradycardia for age if < 1 year; tachypnea for age or need for mechanical ventilation; abnormal white blood cell count for age or > 10% bands

Source: World Health Organization. COVID-19 clinical management living guidance. 25 Jan 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1

PART 3. CLINICAL MANAGEMENT

Since there is no specific antiviral proven to be effective for COVID-19 at this time, management remains focused on providing best supportive care, management of co-existing conditions and treatment of possible bacterial co-infections.

I. PATIENTS WITH MILD SYMPTOMS

COVID-19 testing MAY be done for these children if testing kits are available in the facility, but in settings where kits are limited, priority must be given to those with severe symptoms. The child can then be sent home after the specimen has been collected. In any circumstance that the child's condition deteriorates, or upon the discretion of the physician, advise inpatient management.

Home interventions for children with mild COVID-19

Children with non-severe disease – and in some cases with stable underlying comorbidities – do not require hospital interventions unless there is concern for rapid deterioration or an inability to promptly return to hospital. Laboratory confirmation of COVID-19 is not necessary for patients with mild symptoms because it will not change the management. Home management is recommended and should focus on appropriate supportive treatment, prevention of transmission of the virus to others, as well as monitoring for clinical deterioration, which will eventually prompt inpatient management (See Appendix B Sample Symptom Monitoring Form). Isolation to contain or prevent virus transmission within the household and community should be prioritized. Where feasible, a communication link with health care providers should be made for the duration of the home care until the child's symptoms have completely resolved.

Isolation

- Children should stay at home and be separated from other people in the household. NOTE: Should the home not be suitable for isolation or if the local authorities decide to admit the child and his/her family in a quarantine facility, the same isolation precautions should still be followed.
- Place the child in a well-ventilated single room (e.g. open windows, use electric fans for ventilation, may use air conditioner if available) ideally with its own bathroom, where feasible.
- Ventilation at home may be improved by the following: a) bringing in as much fresh air into the home as possible by opening doors and windows if it's safe to do so; b) using fans to improve air flow; c) filter the air in the home when a heating, ventilation and air conditioning system (HVAC) is in use; consider using a portable high-efficiency particulate air (HEPA) cleaner if an HVAC system is not available or extra filtration is intended.
- Confine activities of the child in his/her room. If not possible, limit shared space and movement of the child in the house.
- Assign one person who is in good health as primary caretaker of the child (see section on *Caregiver*).
- Other household members not caring for the child should stay in a different room, or if not feasible, must always maintain a distance of at least 1 meter from the child.
- Do not allow visitors until the child has completely recovered and has no signs or symptoms of respiratory tract infection.
- The child should use dedicated dishes, drinking glasses, cups, eating utensils, towels, and beddings.
- Children 2 years of age and older should be properly instructed on how to wear a mask. The child's mask should securely cover the nose and mouth. Masks should not be worn when eating or drinking, and should not be touched when worn. All household members should also wear a surgical face mask when in the same room as the child or when interacting inside the home.
- Children younger than 2 years old should NOT wear masks due to risk of suffocation. A mask is also not recommended: (1) if the child has difficulty breathing when a mask is worn; (2) if the child has a cognitive or respiratory impairment which makes tolerating a mask difficult; (3) if the mask is a possible choking or strangulation hazard; and (4) if wearing a mask causes the child to touch his face more frequently.
- Try to find the right size of mask for the child's face and be sure to adjust for a secure fit. The regular adult-sized face mask may be too large for a small child. N95 masks are not recommended for children and should be reserved for healthcare workers at increased risk of exposure to COVID-19.
- Children older than 2 years old may use a face shield together with a face mask. Ensure that the use of a face shield does not pose a risk of suffocation for the child. Neonates and children less than 2 years old

should NOT use a face shield. Face shields must be thoroughly disinfected using alcohol or detergent solution then air-dried after every use.

- The child and all household members should practice hand hygiene (handwashing or use of hand disinfection) following contact with the child suspected or confirmed to have COVID-19.
- Teach the child to cover his/her mouth and nose during coughing or sneezing using tissue, inner part of the elbow or sleeves, followed by hand hygiene.

Caregiver

- Ideally, assign one person of good health, non-elderly, and with no underlying comorbidities and immunocompromising conditions, to avoid undue risk to the caregiver.
- Caregivers should wear a surgical mask that covers their nose and mouth when in the same room as the patient. DO NOT touch or handle masks during use. Once wet or dirty with secretions, remove the mask WITHOUT touching the front and replace immediately with a dry mask. DO NOT reuse masks. Cloth masks do not provide adequate protection in this setting and should NOT be used.
- Caregiver should use disposable gloves when handling oral or respiratory secretions, stool or urine. Wash and disinfect hands after removing gloves.

Hygiene and Sanitation

- Proper hand washing with soap and water for at least 20 seconds should be performed in these situations:
  - Before and after contact with the child, especially after handling the child's secretions
  - Before and after preparing the child's food / feeding the child
  - After assisting the child in using the toilet or diaper-changing, and after bathing the child
  - If hands are visibly dirty
- Use disposable paper towels or clean cloth towels (with frequent replacements) to dry hands.
- Avoid direct contact with the child's secretions and stool.
- The toilet should be flushed with the lid down to prevent droplet splatter and aerosol clouds.
- Clean and disinfect surfaces frequently touched in the room as well as toilet surfaces using regular household soap or detergent. Ensure cleaning agents are properly labeled and stored beyond the child's reach, to prevent accidental ingestion/poisoning.

Laundry and Disposal of Soiled Linen and Diapers

- Waste generated during home care (including diapers, tissue/wipes, etc.) should be placed into a waste bin with a lid in the child's room. The trash bag must be tightly sealed before disposal.
- Do not shake dirty laundry; this minimizes the possibility of dispersing the virus through the air.
- Clothes/beddings/pillows/stuffed toys used by the child must be washed separately.
- Machine washing with warm water and laundry detergent is recommended. If machine washing is not possible, soiled linen can be soaked in hot water and soap in a large drum using a stick to stir and being careful to avoid splashing. The drum should then be emptied, and the linens soaked in 0.05% chlorine for approximately 30 minutes. The laundry should then be rinsed with clean water. If still dirty, soiled linen may be washed thoroughly using regular laundry soap/household detergent and warm water, then allowed to dry under the sun.
- If stools are on surfaces of linen or towels, the stool should be carefully removed with paper towels and immediately safely disposed of in a toilet or latrine. Then the soiled linen or towels should be treated as soiled linens.
- Wear disposable gloves and face masks when handling soiled items. Place all used disposable gloves, face masks, and other contaminated items in a lined container before disposing of them with other household waste.
- Wash hands with soap and water (or use an alcohol-based hand sanitizer) immediately after handling these items. Soap and water should be used preferentially if hands are visibly dirty.

Home Therapies

- Specific medications against COVID-19 are still under investigation. Studies are still currently being evaluated, consolidated, and reviewed to ensure that recommendations are evidence-based.
- Antipyretics such as paracetamol may be given to make the febrile child more comfortable. The use of ibuprofen has not been shown to be associated with worse clinical outcomes compared to paracetamol in one study of adult patients with COVID-19. However,

more studies are needed to ascertain the safety of ibuprofen in children with COVID-19.

- The child may be prescribed empiric antibiotic treatment according to his or her physician's clinical judgment. Antibiotics should be used rationally based on existing national guidelines for PCAP and respiratory tract infections.
- Home nebulization should be avoided unless the child's physician decides that it is indicated, because the risk of infection transmission via droplet nuclei or aerosols may increase during nebulizer treatments. Use a metered-dose inhaler if necessary.
- While getting essential vitamins and minerals such as Vitamin D3 and Zinc from supplements may help bolster the immune system, emphasis must be made on providing a balanced diet and proper nutrition, as well as adequate hydration. There is currently no evidence showing supplements provide direct benefits for children with COVID-19.
- Steam inhalation, or the practice of inhalation of water vapor by leaning over a bowl of boiling water, has been shown to be ineffective in treating and preventing COVID-19. In addition, it has been found to be associated with scald burns.

Emotional and Mental Support

- If the child can comprehend, parents are encouraged to talk to the child about their condition in a way they can understand, giving reassurance that they are being observed closely at home with the supervision of their doctor.
- Limit the family's exposure to news coverage, including social media. Children may misinterpret what they see and hear, and thus can be frightened about something they do not understand.
- Continue with the child's regular routine while under quarantine at home and allow time for learning activities and simple play if the child feels well enough for it. Observe limits in screen time as recommended for the child's age.

Monitoring

- The caregiver should be instructed to record the child's symptoms using the symptom monitoring form (Appendix B), and should notify the healthcare provider if the child's symptoms worsen or if one of the child's contacts develops symptoms. It may be necessary to bring the child to the nearest health care facility for proper assessment if symptoms worsen or if no improvement is seen in 2-3 days at home.

II. PATIENTS WITH MODERATE, SEVERE OR CRITICAL SYMPTOMS

All patients with moderate, severe or critical symptoms should be admitted, would be assumed as having COVID-19 and should be tested for such (see "Diagnostics" below). Alternatively, if the facility is not equipped to handle COVID-19 patients, coordination with a COVID-19 referral center must be done.

A. Inpatient Management

1. The child should be admitted in the hospital and placed in an isolation room or in a dedicated COVID-19 ward/floor, as soon as possible.
2. A dedicated healthcare worker should be in full Personal Protective Equipment (cap, N95 mask, goggles, face shield, full impermeable gown, gloves, and shoe covers) when handling the patient. Proper donning and doffing of PPEs and infection control measures should be observed at all times.
3. Specimen collection must be performed by a knowledgeable medical worker. Ensure that assistance is available as the child may be uncooperative during the procedure. Collect a nasopharyngeal swab (NPS) and / or an oropharyngeal swab (OPS), and if possible, a lower respiratory tract specimen. Samples must be sent to the Research Institute for Tropical Medicine (RITM) or to a DOH-accredited laboratory through the proper channels. Case investigation forms (CIF) must be accurately filled out for proper documentation.
4. The WHO recommends standard, contact, and droplet precautions with eye and face protection, with addition of airborne precautions as needed during aerosol-generating procedures.

B. Diagnostics

1. **Molecular-based assays**

Nucleic acid amplification testing (NAAT) using the **reverse transcriptase polymerase chain reaction (RT-PCR)** is the preferred method for diagnosing SARS-CoV-2 infection. Appropriate specimens include

samples collected from the upper (pharyngeal swabs, nasal swabs, nasopharyngeal secretions) and/or lower airways (sputum, airway secretions, bronchoalveolar lavage fluid). The Department of Health advices the collection of both nasopharyngeal and oropharyngeal specimens. For patients for whom it is clinically indicated (e.g. those receiving invasive mechanical ventilation), a lower respiratory tract aspirate or bronchoalveolar lavage sample should be collected and tested as a lower respiratory tract specimen.

Recent US CDC guidelines include saliva as an option for molecular testing, after studies demonstrated similar viral loads for this compared with nasal and throat swab samples (Byrne et al., 2020). This allows the specimen to be collected by the person being tested, either at home or at a testing site under supervision, and therefore conserves personal protective equipment.

Among the upper respiratory tract specimens, nasopharyngeal and nasal swabs have the highest sensitivity. In a study by Wang et al. of 1,078 specimens collected from 205 adult patients with confirmed COVID-19 infection, RT-PCR positivity was highest in bronchoalveolar lavage specimens (93%), followed by sputum (72%), nasal swab (63%), pharyngeal swab (32%), feces (29%) and blood (1%). None of the urine specimens tested positive.

A similar study by Yuan et al. of 212 children comparing the viral load in throat and anal swab has shown that 78 of 212 patients were confirmed with SARS-CoV-2 infection according to the positive results obtained from either throat or anal swabs. Of the 78 patients, 17 were positive on anal swabs, 37 were positive on throat swabs, and 24 were positive on both. The RT-PCR positivity rate was 78.2% for throat swabs vs 52.6% for anal swabs.

SARS-CoV-2 preferentially proliferates in type II alveolar cells (AT2) and peak of viral shedding appears 3 to 5 days after the onset of disease. Median duration of viral RNA detection was 20 days and the longest observed duration of viral shedding was 37 days in survivors. Appropriate respiratory specimens should be collected as soon as possible once a suspect COVID-19 case is identified, regardless of the time of symptom onset. A positive test for SARS-CoV-2 confirms the diagnosis of COVID-19. If initial testing is negative but the suspicion for COVID-19 remains, resampling and testing from multiple respiratory tract sites is recommended. Results of RT-PCR assays may be affected by the adequacy of sample, collection, handling and transport of specimen, and timing of sample collection in relation to symptom onset. Kucirka et al. reported that on day 1 from exposure, the sensitivity of RT-PCR is 0%. Before symptom onset (on the average, day 4 from exposure), the sensitivity is at 33%. On the day of symptom onset (typically day 5 from exposure), the sensitivity is at 62%. This further increases to 80% on the 3rd day of symptoms (or average of day 8 from exposure). Sensitivity decreases to 34% on day 21 of exposure. The sensitivity is highest 3 days after symptom onset on average, or 8 days after exposure.

The timing of RT-PCR testing in infants born to COVID-19 positive mothers is discussed in the Philippine Obstetrical and Gynecological Society (POGS)-Philippine Pediatric Society (PPS) Care of Suspect/Confirmed COVID-19 Newborns Interim Guidelines (Version 4.0, September 25, 2020).

2. Antigen Tests

Antigen tests detect the presence of viral proteins (antigens) expressed by the COVID-19 virus in a sample, usually obtained through nasal or nasopharyngeal swabs. After collection, the sample is placed into an extraction buffer or reagent, and the extract is allowed to interact with antibodies that are either (1) embedded into a lateral flow immunochromatographic test device (rapid antigen test); or (2) processed through a laboratory-based automated assay machine.

The main advantages offered by antigen tests are relatively lower costs and faster turnaround times. Although both antigen and RT-PCR tests perform best at points in time when

viral load is highest, antigen tests are usually less sensitive. In contrast, the specificity of antigen tests are generally as high as the RT-PCR.

Several antigen tests are registered locally with the Philippine FDA and have undergone validation by the RITM. The Health Technology Assessment Council (HTAC), which provides guidance to DOH and PhilHealth on technologies to be funded by the government, recommends a minimum sensitivity of 80% and specificity of 97% for rapid antigen test kits.

HTAC further recommends that rapid antigen tests should be used only for symptomatic COVID-19 patients, close contacts and those with history of exposure, in outbreaks and in areas without access to RT-PCR confirmatory testing. For symptomatic cases, the test should be done within 5-7 days of symptom onset; close contacts of positive individuals may be tested 4-11 days after exposure.

In situations where the pre-test probability is moderate to high (for example, symptomatics or asymptomatic close contacts), positive results are generally interpreted as true positives, while negative results should be confirmed by RT-PCR. In contrast, for asymptomatics without known exposure, a positive antigen test should be confirmed by RT-PCR, while a negative test is usually taken as a valid result.

Based on DOH guidance, a positive antigen test result cannot be used as a basis for reporting a case, and still needs to be confirmed with RT-PCR.

3. Serologic Tests

Specific antibodies (IgM and IgG) are produced after SARS-CoV-2 infection and can be detected by a variety of methods from the blood, e.g. lateral flow immunochromatographic assay (LFIA), enzyme linked immunosorbent assay (ELISA), chemiluminescence immunoassay (CLIA), etc. Determining unique viral protein targets to reduce cross-reactivity to other coronaviruses is a challenge and can affect test sensitivity and specificity.

According to a Cochrane systematic review by Deeks et al., pooled results for IgG, IgM, IgA, total antibodies and IgG/IgM all showed low sensitivity during the first week from onset of symptoms (less than 30.1%), rising in the second week, and reaching their highest values in the third week. The combination of IgG/IgM had a sensitivity of 30.1% at day 1 to day 7 from the time of exposure, 72.2% at 8 to 14 days, 91.4% at 15 to 21 days, and 96% at 21 to 35 days. There are insufficient studies to estimate sensitivity of tests beyond 35 days post-symptom onset.

To date, serologic testing is not recommended as a stand-alone test for diagnosing COVID-19, and must always be done in conjunction with RT-PCR testing. Rapid point-of-care LFIAs are not recommended due to their low sensitivity and high false negative rates. The laboratory-based immunoassays CLIA and ELISA are the preferred tests for antibody determination, and this is best done on the third week onwards from the onset of symptoms. It should also be noted that at present, it is still unknown whether antibodies persist following infection and whether the presence of antibodies confers protective immunity against future infection.

4. Ancillary Laboratory Tests

Preliminary laboratory tests are listed below. The possible results seen in patients with COVID-19 are based on recently published studies. Other tests may be ordered depending on the child's presentation and upon the physician's discretion.

a. Complete blood count (CBC)

In the systematic review by Hoang et al., the results of complete blood counts seen among children with COVID-19 are as follows:

Table 6. Complete blood count picture in children with COVID-19

Parameter	Mean
Leukocytes (normal range: 4.0-12.0 x 10^3/uL)	7.1 x 10^3/uL
Neutrophils (normal range: 54-62%)	44.4%
Lymphocytes (normal range: 25-33%)	39.9%
Hemoglobin (normal range: 11.5-14.5 g/dL)	12.9 g/dL
Platelets (normal range: 150-450 x 10^3/uL)	272.5 x 10^3/uL

The WBC count is generally normal, however, lymphopenia has been frequently reported, with a median absolute lymphocyte count (ALC) of 1,201 cells/uL (normal ALC 1,500-3,000 cells/uL).

Platelet count may be normal. However, thrombocytopenia has been reported in several case reports of COVID-19 patients presenting with fever, initially assessed to have dengue fever based on positive serology. The presentation of fever and thrombocytopenia is important to recognize in the local setting where dengue fever is common.

b. Inflammatory markers

Among the inflammatory markers investigated, procalcitonin, D-dimer and interleukin-6 were found to be elevated. Increased procalcitonin levels may be seen in patients with severe COVID-19 without bacterial co-infection; however, a rapid rise or significantly elevated procalcitonin may also indicate secondary bacterial infection

Table 7. Inflammatory markers in children with COVID-19

Parameter	Mean
C-reactive protein (CRP) (male normal range: 0.6-7.9 mg/L) (female normal range: 0.5-10 mg/L)	9.4 mg/L
Procalcitonin (normal value: ≤ 0.15 ng/mL)	0.25 ng/mL
Erythrocyte sedimentation rate (ESR) (normal range: 0-20 mm/h)	14.1 mm/h
D-dimer (normal value: < 0.4 mg/L)	0.7 mg/L
Lactate dehydrogenase (normal range: 150-500 U/L)	276.6 U/L
Fibrinogen (normal range: 220-440 mg/dL)	224.2 mg/dL
Interleukin-6 (normal value: ≤ 1.8 pg/mL)	26.1 pg/mL
Ferritin (normal range: 10-60 ng/mL)	51.6 ng/mL
Creatine kinase Normal range for age: children: **50-458 U/L depending on age, refer to Harriet Lane 22nd Edition.** adult normal range: 5-130 U/L	197.9 U/L

c. Arterial Blood Gas (ABG) or pulse oximetry

Obtaining an arterial blood gas analysis or performing pulse oximetry can be done to assess the severity of hypoxemia in patients with pneumonia. An oxygen saturation at room air of <

95% may indicate pneumonia; a value < 90% may indicate severe pneumonia.

d. Other tests to determine alternative etiology or secondary infection

Whenever possible, it is advised to determine an alternative etiology for the patient's symptoms. However, co-infections with COVID-19 have been documented, and tests that are positive for other bacterial or viral pathogens do not rule out COVID-19.

Consider the following diagnostic tests, depending on the patient's presenting signs and symptoms:

- **Bacterial and fungal cultures** (blood, stool, urine and other appropriate specimens) to test for bacterial or fungal infection, ideally collected before start of antimicrobial or antifungal therapy
- **Dengue NS1 and dengue serologic tests (IgM, IgG)** must be requested for patients who present with symptoms of dengue. Take note, however, that symptoms of dengue and COVID-19 overlap, and that there have been reported cases of confirmed COVID-19 patients with false positive dengue NS1 and serology
- Rapid antigen detection tests for specific bacterial or viral pathogens
- Multiplex respiratory or gastrointestinal panel tests

5. Imaging studies

a. **Chest x-ray**

Chest x-ray is the recommended first line imaging modality in children suspected to have COVID-19 presenting with respiratory symptoms. However, this modality has limited sensitivity and specificity, hence, a negative chest x-ray does not exclude pulmonary involvement in patients with laboratory-confirmed COVID-19, nor does it indicate absence of infection in cases of suspected COVID-19 not yet confirmed by RT-PCR.

Table 8. Chest x-ray findings in children with COVID-19

Classification	Chest x-ray findings	Suggested reporting language
Typical findings of pediatric COVID-19	Bilateral distribution peripheral and/or subpleural ground glass opacities and/or consolidation	Imaging findings are commonly seen with COVID-19 pneumonia in children. Differential diagnosis also includes other viral or atypical pneumonia.
Indeterminate findings of pediatric COVID-19	Unilateral peripheral or peripheral and central ground glass opacities and/or consolidation, bilateral peribronchial thickening and/or peribronchial opacities, or multifocal or diffuse ground glass opacities and/or consolidation without specific distribution	Imaging findings can be seen with COVID-19 pneumonia in children. However, they are nonspecific and differential diagnosis includes both infectious and non-infectious etiologies.
Atypical findings of pediatric COVID-19	Unilateral segmental or lobar consolidation, central unilateral or bilateral ground glass opacities and/or consolidation, single round consolidation i.e., round pneumonia with or without air bronchogram, pleural effusion, or lymphadenopathy	Imaging findings are atypical or uncommonly reported in cases of COVID-19 pneumonia in children. Recommend consideration of alternative diagnosis.
Negative for pediatric COVID-19	No CXR findings suggestive of pneumonia	No CXR findings present to suggest pneumonia (Note: CXR has limited sensitivity for COVID-19, especially in early stages)

b. **Chest CT scan**

Chest CT scan is not recommended as the initial diagnostic test in pediatric patients suspected to have COVID-19. Chest CT scan findings of COVID-19 in the pediatric population are not pathognomonic but may be suggestive of the diagnosis in the appropriate clinical setting. It may be considered in patients with a worsening clinical course who are not responding appropriately to therapy, or to further investigate a specific pulmonary condition.

Table 9. Chest CT scan findings in children with COVID-19

Classification	Chest CT scan findings	Suggested reporting language
Typical findings of pediatric COVID-19	Bilateral, peripheral and/or subpleural ground glass opacities and/or consolidation in lower lobe predominant pattern	Imaging findings are commonly seen with COVID-19 pneumonia in children. Differential diagnosis also includes other viral or atypical pneumonia, hypersensitive pneumonitis, and eosinophilic lung disease. In addition, fungal infection in immunocompromised children when "halo" sign is present.
Indeterminate findings of pediatric COVID-19	Unilateral peripheral or peripheral and central ground glass opacities and/or consolidation, bilateral peribronchial thickening and/or peribronchial opacities, multifocal or diffuse ground glass opacities and/or consolidation without specific distribution, or the "crazy paving" sign	Imaging findings can be seen with COVID-19 pneumonia in children. However, non-specific and differential diagnosis includes infectious and non-infectious etiologies.
Atypical findings of pediatric COVID-19	Unilateral segmental or lobar consolidation, central unilateral or bilateral ground glass opacities and/or consolidation, discrete small nodules, lung cavitation, pleural effusion, or lymphadenopathy	Imaging findings are atypical or uncommonly reported in cases of COVID-19 pneumonia in children. Recommend consideration of alternative diagnosis.
Negative for pediatric COVID-19	No chest CT findings suggestive of pneumonia in children	No CT findings present to suggest pneumonia (Note: CT may be negative in the early stages of COVID-19).

5. Chest ultrasound

Chest ultrasound has been used as an alternative to chest x-ray and chest CT scan in the diagnosis of pneumonia in COVID-19 patients due to its ease of use at point-of-care, absence of radiation exposure, and lower cost than CT scan. Chest CT scans performed in COVID-19 patients have been shown to have a strong correlation with chest ultrasound.

The following are ultrasonographic features seen in COVID-19 pneumonia:

- Thickening of the pleural line with pleural line irregularity
- B lines in a variety of patterns including focal, multi-focal, and confluent
- Consolidations in a variety of patterns including mutifocal small, non-translobar, and translobar with occasional mobile air bronchograms
- Appearance of A lines during recovery phase
- Pleural effusions are uncommon

C. Pharmacologic Interventions for Children with Severe and Critical COVID-19

Since the SARS-CoV-2 is a newly detected virus and COVID-19 cases were only diagnosed in January 2020, there is limited data on the treatment and prevention of this illness in children, and many of the clinical trials are still ongoing. There have been numerous observational research, randomized controlled trials, and even systematic reviews for specific treatments for COVID-19 in adults. Ethically, new drugs are tested first in adults before testing them in children unless there is an important reason to do so, such as if the disease is only seen in children. For this review, data from children were collected when available, and adult research results were heavily relied upon.

The Committee has divided the therapies according to when they should be used according to the severity of illness, as seen in Figure 4 below. Those recommended for use should be used routinely for that category, and experimental options should only be used in the context of a clinical trial or for compassionate use as specified.

The use of experimental drugs should be discussed with the child's parents or legal guardian, carefully explaining the potential clinical benefits and potential adverse reactions of these investigational drugs. The clinician should obtain a signed informed consent form (see Appendix D for sample informed consent form).

Figure 4. Therapies for COVID-19 according to Severity

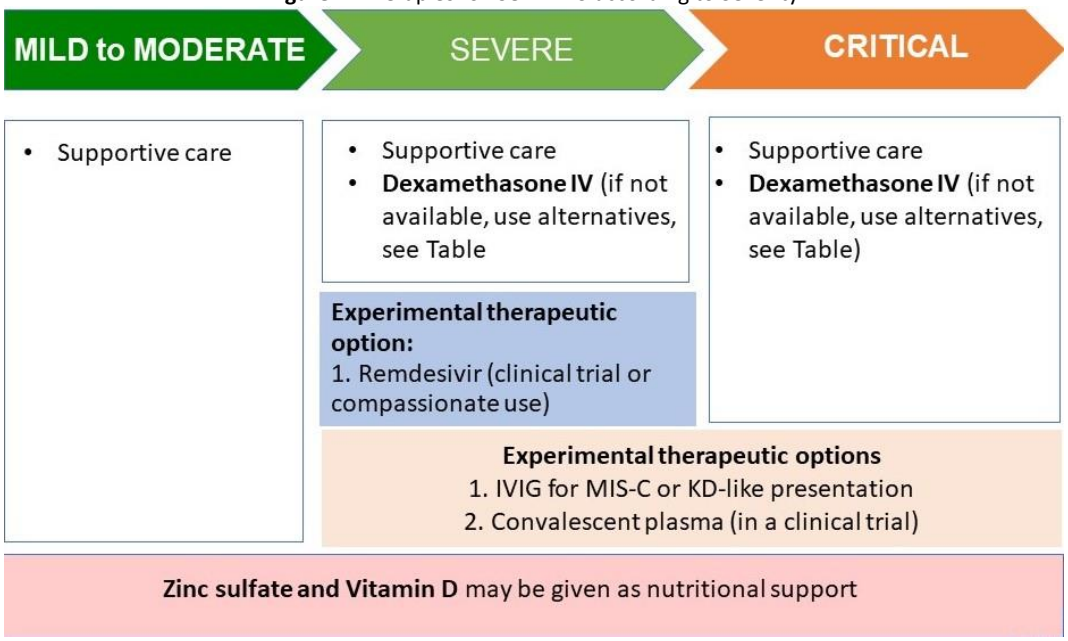


Table 10. Recommended therapy for severe and critical COVID-19

DRUG and Indication	Dosing Regimen/ Duration	Contraindications	Adverse Effects
CORTICOSTEROIDS (CS) for severe & critical COVID-19	**Dexamethasone**: 0.15 mg/kg IV once daily (max. dose: 6mg) Up to 10 days or until discharge *Alternative CS if IV dexamethasone is not available:* 1. **Methylprednisolone**: 0.8 mg/kg IV once daily (max dose: 32mg) OR 2. **Hydrocortisone**: <1 month: 0.5 mg/kg IV every 12 hrs for 7 days followed by 0.5 mg/kg IV once daily for 3 days ≥1 month: 1.3 mg/kg IV every 8 hrs (max dose 50mg; max total daily dose 150mg) *Alternative oral CS:* **Dexamethasone** PO: 0.15mg/kg PO OD (max. dose: 6mg) OR **Prednisolone**: 1 mg/kg orally once daily (max dose: 40mg)	• Systemic fungal infection • Systemic infection, unless specific anti-infective therapy is employed • Hypersensitivity to the active ingredient or any other component	• Adrenal suppression • Immunosuppression (reactivation of latent infections, secondary infections) • Hyperglycemia • Psychiatric disturbances • Increased blood pressure • Peripheral edema • Myopathy (particularly if used with neuromuscular blocking agents) • Hypernatremia • Avascular necrosis • Adrenal insufficiency

Table 11. Experimental therapies for severe and critical COVID-19 in children

DRUG and Indication	Dosing Regimen/ Duration	Contraindications	Adverse Effects
REMDESIVIR Hospitalized and requires supplemental oxygen (but does not require oxygen delivery through a high flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO)	For hospitalized adult and pediatric patients (aged ≥ 12 years and weighing ≥40 kg): Remdesivir 200 mg IV over 30– 120 min on D1, 100 mg IV on Day 2 to Day 5 (3.5 kg to <40 kg): Remdesivir 5 mg/kg IV over 30– 120 min on Day 1, followed by 2.5 mg/kg once daily on Day 2 to Day 5 Duration: 5 up to 10 days	• eGFR is <30 mL/min • ALT levels increase to > 5 times the upper limit of normal (ULN)	• Nausea • ALT and AST elevations • Hypersensitivity • Increases in prothrombin time • Drug vehicle is SBECD (sulfobutylether-beta-cyclodextrin), which has been associated with renal toxicity. SBECD accumulation may occur in patients with moderate or severe renal impairment.
INTRAVENOUS IMMUNOGLOBULIN (IVIG) MIS-C and Kawasaki disease-like presentation	1-2 g/kg over 8-12 hours* *Assess cardiac function and fluid status before giving IVIG; should only be administered when cardiac function is restored.	• History of anaphylaxis to human Ig • IgA deficient patients with antibodies against IgA and a history of hypersensitivity	• Hypersensitivity reaction, including anaphylaxis • Infusion reactions: headache, chills, myalgia, wheezing, tachycardia, lower back pain, nausea, hypotension • Renal failure • Thromboembolism • Aseptic meningitis syndrome • Hemolysis • Transfusion-related acute lung injury • Transmission of infectious pathogens
CONVALESCENT PLASMA Consider in a clinical trial	8-10ml/kg, with a maximum of 600ml, as slow infusion over 1-4 hours	• Previous reactions to plasma infusion • With IgA deficiency • Pregnant or breastfeeding If with previously repeated transfusions	• Fever • Hypersensitivity reaction • Circulatory overload • Transfusion-related acute lung injury

Table 12. Nutritional support

Vitamin/ Mineral	Dosing Regimen/Duration	Adverse Reactions
Zinc sulfate	2 months - <5 years: 15mg elemental Zn BID ≥ 5 years: 20mg elemental Zn BID Formulation: 27.5mg/mL (equivalent to 10mg elemental Zn) 55mg/5mL (equivalent to 20mg elemental Zn)	• Allergic reaction • Nausea • Abdominal pain • Decreased copper absorption
Vitamin D3 (Cholecalciferol)	< 2 years: 1,000 IU/day ≥ 2 years: 2,000 IU/day Formulation: 800IU, 1000IU, 2000IU softgel capsule	• Hypercalcemia

See Appendix C for the rationale for pharmacologic recommendations.

***Disclaimer*:** Recommendations were made based on the best available evidence. As the knowledge on this disease is still evolving, these recommendations may change as more evidence becomes available.

III. DISCHARGE FROM ISOLATION AND DISCONTINUATION OF TRANSMISSION-BASED PRECAUTIONS

The WHO COVID-19 Clinical Management Living Guidance (25 January 2021) and the Department of Health Omnibus Interim Guidelines for COVID-19 (October 2020) recommend the following guidelines for discharge from isolation and discontinuation of transmission-based precautions:

1. Discharge criteria for suspect, probable, and confirmed COVID-19 cases shall no longer entail repeat testing.
2. Symptomatic patients with confirmed or probable COVID-19 can be discharged from isolation and discontinue transmission-based precautions once the following criteria are fulfilled:
   - For symptomatic patients with mild symptoms: 10 days after symptom onset, inclusive of 3 days of being clinically recovered and asymptomatic
   - For symptomatic patients with moderate, severe or critical symptoms: 21 days from the onset of illness, inclusive of 3 days of being clinically recovered and asymptomatic
3. For asymptomatic immunocompetent cases who test positive on RT-PCR and remained asymptomatic: 10 days after positive test for SARS-CoV-2.
4. Close contacts who remain asymptomatic for at least 14 days from date of exposure can discontinue their quarantine without the need of any test.

Ultimately, clinical judgement and suspicion of SARS-CoV-2 infection determine whether to continue or discontinue empiric transmission-based precautions.

For symptomatic patients discharged to home prior to completion of the prescribed quarantine and isolation period, the decision to send the patient home should be made in consultation with the patient's healthcare team and local health authorities. It should include considerations of the home's suitability for and patient's ability to adhere to the isolation recommendations.

After discharge, ensure that the following considerations are kept in mind:

- See section on *Home Interventions* (above) for advise on infection control, hygiene and monitoring in the home setting.
- Follow-up in 2 to 4 weeks after discharge.
- Once fully recovered, ensure that the child's immunizations are up to date. Consult the child's healthcare provider for proper scheduling.

PART 4. COVID-19 PREVENTION AND CONTROL

I. PREVENTION OF COVID-19 IN CHILDREN

In the Philippines and globally, COVID-19 in the pediatric age group is less common compared with adults. Children are least affected with an incidence of <10% while the most vulnerable still belong mostly

to the older age group. Nonetheless, the pediatric age group remains to be a vulnerable population. Studies have shown that asymptomatic children, like adults, can efficiently transmit infection as well. Children with COVID-19 commonly have mild symptoms but some children can get severe manifestations requiring hospitalization with some cases resulting to death.

Prevention of SARS-CoV-2 infection in children is similar to that in adults. Face protection with masks and face shields, physical distancing, and hand hygiene still constitute the primary methods of infection prevention with considerations placed in terms of children's ability to adhere to these recommendations. Adherence to all these minimum heath standards set by authorities as well as other comprehensive approaches in the community is important in preventing infection.

Staying at home as a form of physical distancing has been recommended for the prevention of COVID-19 infection in children. There are however, instances when going outside is necessary and may prove to be beneficial for children. Should parents or other adult caregivers decide to bring their children outside of their homes, the following recommendations aim to decrease the risk of infection and transmission of SARS-CoV-2.

A. Face protection

1. Children (2 years of age or older) and their accompanying adults shall wear masks when outside their homes and when around people who live outside of their household. Ensure that masks are worn correctly, consistently, and safely. Masks of a proper size should be used to fully cover the nose, mouth, and chin. Three-layer cloth masks or surgical masks may be used; masks with valves or other configurations are not recommended.
2. Children younger than 2 years old shall not wear masks due to risk of suffocation. A mask is also not recommended in the following situations: if the child has difficulty breathing when wearing it, if the child has a cognitive or respiratory impairment giving them a difficult time tolerating the mask, if the mask is a possible choking or strangulation hazard, and if wearing a mask causes the child to touch their face more frequently.
3. Face shields shall also be worn correctly and consistently. Face shields should cover the entire face, wrap around the sides of the face, and extend to below the chin. Caution should be taken while wearing one to avoid injuries that could break it and harm the eyes or face.
4. In cases where children cannot tolerate masks, face shields may be considered an alternative to masks but it should be noted that they do not provide the equivalent protection from infection and transmission of the virus as compared to masks.
5. Children should be frequently reminded not to touch the face coverings. Perform hand hygiene before and after wearing the mask and face shield.

B. Physical Distancing

1. Physical distancing, sometimes referred to as social distancing, means keeping a safe space between a person and other people who are not from the same household to reduce the spread of the virus. When in public, physical distancing of at least 1 meter from people who are not your household members shall be maintained. Avoid people who are sick and coughing.
2. If possible, avoid interactions with people outside of your household contacts. If unavoidable, a thirty-minute interaction or less shall be done.
3. Outside trips shall be planned well so that the necessary preparations are made. Visit establishments that are compliant to health standards set by the health authorities. Avoid peak hours and crowded areas where it may be difficult to stay at least 1 meter away from others who are not from your household. Know and follow the guidance from local public health authorities of the places that you intend to visit.
4. Choose outdoor facilities or establishments with good ventilation.

5. Avoid activities where close contact cannot be avoided (i.e. playground activities, sports, videoke sessions, etc.)
6. When using public transportation, keep at least 1 meter away from other passengers or transit operators.

C. Personal Hygiene and Handwashing

1. Wash hands frequently and thoroughly with soap and water for at least 20 seconds or use a hand sanitizer with at least 60% alcohol content. Avoid alcohol-based hand sanitizers that are not approved by the Food and Drug Administration (FDA). Children should be supervised to ensure they are doing handwashing correctly.
2. Avoid touching surfaces if possible; wash hands afterwards.
3. Pack soap for handwashing, hand sanitizer with at least 60% alcohol, disinfecting wipes, tissues, extra masks and face shields, and a resealable bag to store the mask while not in use (e.g. while eating or drinking). Consider also packing your own utensils should you decide to eat outside.
4. Encourage toilet use before leaving the home and try to minimize using public toilets. Should the need to use a public restroom arise, maintain a distance of at least 1 meter from others, keep masks on, and wash hands with soap and water immediately after.
5. Observe proper cough etiquette when coughing or sneezing.
6. Once back at home, ensure proper mask disposal and handwashing with soap and water for at least 20 seconds or use a hand sanitizer with at least 60% alcohol content. For older children, encourage taking a shower upon reaching home; for younger ones, sponge bath may be done by parents.

Children and other family members who are sick should stay at home. Children who are immunocompromised, with medical conditions that make them vulnerable to COVID-19, and those who cannot properly abide with the minimum health standards should stay at home.

Children and adolescents shall be supervised by their parents or other adult caregivers in settings outside the home to ensure that they are compliant with minimum health standards for the prevention of SARS-CoV-2 infection and transmission. Ensure that standards are consistently followed by both adults and children once outside the home, including when using public transportation. Adults shall communicate to the child or adolescent the importance of compliance to these standards.

Observe for the development of COVID-19 symptoms among household members who have gone outside the home. Should a household member develop symptoms, isolate and call your doctor or local healthcare providers for advice.

While a vaccine against COVID-19 awaits availability in the country; there are no medications recommended to prevent infection and transmission.

II. COVID-19 VACCINATION

The COVID-19 pandemic is a global public health problem that has caused fear, panic, substantial economic losses and social disruption worldwide. Currently, no drug treatments have been able to clearly demonstrate significant clinical benefits for all population groups; results from the studies are contradictory and inconclusive. Furthermore, it is not known until when COVID-19 will remain as a worldwide pandemic. It is also not known if immunity is acquired after symptomatic or asymptomatic SARS-CoV-2 infection and how long it might last. The development of a safe and effective COVID-19 vaccine is therefore considered crucial to reduce transmission of SARS-CoV-2, contain the current outbreak and help prevent future outbreaks. Vaccines will be necessary for the development of both individual protection and population-level herd immunity.

The World Health Organization and regulatory authorities have defined criteria for the ideal vaccine against the SARS-CoV-2 (WHO, 2020). The vaccine should be able to induce protection in all high-risk individuals and exhibit a good safety profile across multiple population groups. It should be able to rapidly induce protective immunity after just 1 or 2 doses and result in long-lasting protection for at least

1 year, with yearly booster doses if necessary. A vaccine efficacy of 70% or more is ideal. However, the World Health Organization has acknowledged that a 50% vaccine efficacy rate will probably already have a substantial beneficial impact. Vaccination should not result in higher risk of severe disease or development of antibody-enhanced disease. Due to exigency, the vaccine should be quickly mass-produced, thermostable and easily administered to allow usage in resource-limited areas, and should be safe to be co-administered with other routine vaccines (WHO, 2020; Poland et al., 2020).

A. Vaccine Virus Targets

Two important targets for vaccine development are the protrusions from the surface known as the surface spike or S-protein and the nucleocapsid protein encasing the RNA genetic material. Antibodies may be directed at both the spike protein and the nucleocapsid proteins. However, the spike protein appears to be the major target for neutralizing antibodies and the predominant antigenic target for SARS-CoV-2 vaccine development. Development of neutralizing antibodies to the spike protein blocks binding of the virus to the ACE2 receptor of target cells and prevents uptake and viral entry. Vaccines that will stimulate both neutralizing antibodies against the spike proteins and the development of T and B cell memory are crucial for the clearance of SARS-CoV-2 infection and long-term protection (Pandey et al., 2020; Calina et al., 2020).

B. Vaccine Technology Platforms

As soon as China announced that a novel coronavirus had been identified as the cause of the Wuhan outbreak and published the genetic sequence of SARS-CoV-2, research and development activities for a vaccine against the disease proceeded quickly. A striking feature of the vaccine development landscape for COVID-19 is the range of technology platforms being evaluated. Several standard platforms, such as inactivated, live-attenuated, and protein subunit vaccines which have been used in licensed products, are being pursued. In addition, novel or next generation approaches are also being investigated with the hope of identifying a safe and effective SARS-CoV-2 vaccine that can be used in the near future. This includes DNA- and RNA-based strategies, and replicating and nonreplicating viral vector strategies. Some of these innovative vaccine technology platforms are being developed based on knowledge from similar products using the same platform technology created during the MERS, SARS and EBOLA outbreaks (Pandey et al., 2020; Calina et al., 2020). It is conceivable that some vaccine platforms may be better suited to specific population subtypes (such as the elderly, children, pregnant women or immunocompromised patients).

The different vaccine platforms vary in their potential safety and immunogenicity, speed and cost of manufacturing, and other features important for meeting global demand (Pandey et al., 2020; Calina et al., 2020). Leading in COVID-19 vaccine development are messenger RNA (mRNA) vaccines. RNA-based vaccines introduce mRNA fragments that encode for specific viral proteins, such as the viral spike proteins that are produced by the host cells. Since there are no RNA vaccines approved for human use at this time, COVID-19 vaccines would be the first RNA vaccines to be developed using this platform.

Major vaccine technology platforms, their main strengths and weaknesses, and the list of vaccine candidates utilizing the platform are briefly described in Table 13. These vaccines are at different stages in their testing.

Table 13. Major vaccine technology platforms with their main strengths and weaknesses

Vaccine platform	Mechanism	Strengths	Weaknesses	Developers (Phase)
Inactivated vaccines	Produced by growing SARS-CoV-2 in cell culture then chemically inactivating the virus; contain killed whole or small parts of viruses which cannot cause disease	Relatively safe, even for immunocompromised; immune responses to a SARS-CoV-2 inactivated vaccine would target not only the spike protein but also other components of the virus	Do not always create a strong or long-lasting immune response; require repeated and/or booster doses; require adjuvants, i.e. aluminium salts, to create a strong or long-lasting immune response; require biosafety level 3 facility for production; increased cost of vaccine production since inactivated live virus require stabilization of the structure in the dry form, separate supply of the solvent, and cold-chain transportation	• Sinovac Research and Development, Inc (Phase 3) • Sinopharm-Wuhan Institute of Biological Products (Phase 3) • Sinopharm-Beijing Institute of Biological Products (Phase 3) • Bharat Biotech International Limited (Phase 3)
Protein subunit vaccines	Consist of a single protein molecule that assembles (or "coassembles") with other protein molecules to form a protein complex; contain only essential components or certain antigenic determinants of pathogenic microorganisms that best stimulate the immune system; obtained either starting from conventional cultivation processes, or by recombinant DNA technology	Wide experience and existing large-scale production capacity using this platform; antigen determinants included in the vaccine increase the efficiency of the immune response, and the presence of a small number of pathogens safely generate an immune response and reduce the risk of side effects	Antigens are weak immunogens so conjugation with a protein molecule or addition of an adjuvant may be necessary to induce adequate long-term immunity; adjuvants are frequently associated with local reactions to the vaccination site	• Novavax (Phase 3) • Anhui Zhifei Longcom Biopharmaceutical - Institute of Microbiology, Chinese Academy of Sciences (Phase 3) • Clover Biopharmaceuticals Inc./GSK/Dynavax (Phase 1)
Viral-vectored (nonreplicating) vaccines	Use inactivated or killed viral vector such as the adenovirus that has been genetically engineered to not replicate in vivo and to express proteins of SARS-CoV-2 recognized	Genetically engineered virus vector cannot cause disease but produces coronavirus proteins to safely generate an immune response	Requires large variation of purification methods and reliable confirmation of purity and activity of the viral vector; pre-existing immunity to the vector can attenuate	• AstraZeneca-University of Oxford (Phase 3) • Janssen Pharmaceutical (Phase 3) • Gamaleya Research Institute-

	by the immune system to elicit an immune response; use of viral vectors that are uncommon in humans, i.e. vectors derived from animal viruses (chimpanzee adenovirus), may be used to ensure no attenuation of pre-existing immunity to the vector		immunogenicity of the vaccine	Health Ministry of the Russian Federation (Phase 3) • CanSino Biologics,Inc-Beijing Institute of Biotechnology (Phase 3)
RNA vaccines	Viral messenger ribonucleic acid (mRNA) fragments encode specific viral proteins of SARS-CoV-2 spike protein; once introduced in the body, viral spike proteins produced by the host cells generate an immune response; mRNA in the vaccine is degraded quickly by normal cellular processes and do not interact with or integrate into the recipient's DNA	Induce strong immune response similar to natural infection, stimulate both humoral and cellular immunity; potential for stable, rapid, large-scale production of RNA vaccines because production is completely in vitro and do not require culture or fermentation procedures; safer than inactivated or protein-based vaccines because they are free from risk of protein contamination or the injected virus to become active	Naked RNA are unstable and difficult to deliver into cell; requires highly efficient carriers such as lipid nanoparticles (LNP) to stabilize and pack the mRNA into an injectable form; must be maintained at very low temperatures, complicating storage	• Pfizer -BioNTech-Fosun Pharma (Phase 2/3) • Moderna-NIAID (Phase 3)

As of December 29,2020, 232 vaccines are in development, 60 are now in human clinical trials and at least 172 preclinical vaccines are under investigation in animals (WHO, 2020). The current development of COVID-19 vaccines now involve partnerships between big pharmaceutical companies and smaller biotechnology companies as well as university-led partnerships.

As early as July 2020, four vaccines in China (developed by Sinopharm in partnership with 2 academic institutions, Sinovac Biotek, and CanSino Biologics) and two in Russia (developed by the Gamaleya Research Institute and the Vektor Institute) were given early or limited approval for use for essential workers (such as healthcare workers and soldiers in the military) without waiting for the results of phase 3 trials. One of the vaccines developed in China (Sinopharm- Beijing Institute of Biological Products) has also been recently approved for general use in China on December 30, 2020.

Recently, two mRNA vaccines have been given emergency use authorization (EUA). The Pfizer-BioNTech COVID-19 vaccine has been authorized for use in the United States, the United Kingdom and Canada, while the Moderna COVID-19 vaccine has been authorized for use in the United States. On December 30, 2020, the United Kingdom authorized the AstraZeneca-Oxford University COVID-19 chimpanzee adenovirus-vectored vaccine for general use. On January 2, 2021, the World Health Organization granted emergency validation to the Pfizer-BioNTech COVID-19 vaccine

which will allow countries worldwide prompt approval of its importation and distribution.

The following section will focus on the three COVID-19 vaccines that have recently received emergency use authorization in the United States and the United Kingdom.

1. **Pfizer-BioNTech (BNT162b2)**

The RNA vaccine (BNT162b2) developed by the German company BioNTech in collaboration with Pfizer and Fosun Pharma is an mRNA vaccine delivered in a lipid nanoparticle to express a full-length spike protein. It is given intramuscularly in two doses 21 days apart. Results from a large placebo-controlled phase 2/3 clinical trial showed the vaccine to have vaccine efficacy of 95% (95% CI, 90.3-97.6) in preventing symptomatic COVID-19 at or after day 7 following the second dose (Polack et al., 2020). Among adults ≥ 65 years who had other medical comorbidities or obesity, vaccine efficacy was 91.7% (95% CI, 44.2-99.8). Vaccine efficacy following a single dose is estimated to be 52% (95% CI, 29.5-68.4) but the actual magnitude and duration of protection from a single dose is unknown because most participants received the second dose three weeks after the first.

Local and systemic adverse effects were dose-dependent and relatively common after the second dose; most were of mild or moderate severity (i.e., did not prevent daily activities). Among participants younger than 55 years, fever was the most common adverse effect reported (16%), followed by severe fatigue, headache, and chills reported in less than 5% of cases (Walsh et al., 2020). Adverse events were slightly lower among older participants. Serious adverse events were reported: shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia. After the vaccine was administered to individuals in the UK outside a clinical trial, 2 health workers, both of whom had a history of anaphylaxis, developed symptoms consistent with anaphylaxis (Polack et al., 2020). It is not clear to which component of the vaccine the participants may have reacted. Following this observation, individuals with a history of anaphylaxis to a vaccine, medicine or food should not receive the Pfizer-BioNTech vaccine. Rare cases of Bell's palsy were also noted in four vaccine recipients. Although the rate did not exceed that in the general population (15 to 30 cases per 100,000 people per year), with similar findings with another mRNA vaccine, ongoing monitoring for possible vaccine-associated Bell's palsy is warranted.

BNT162b2 has been authorized for use in the United States, United Kingdom, and Canada (US FDA, 2020).

2. **Moderna (mRNA-1273)**

The mRNA vaccine developed by the US company Moderna (mRNA-1273) was one of the first vaccines for SARS-CoV-2 to be produced; it was developed and administered to humans within two months of publication of the SARS-CoV-2 genomic sequence. The vaccine utilizes mRNA delivered in a lipid nanoparticle to express a full-length spike protein. It is given intramuscularly in two doses 28 days apart. Preliminary analysis of phase 3 results that enrolled around 30,000 study participants aged 18 years and older showed that mRNA-1273 had 94.1% vaccine efficacy (95% CI, 89.3-96.8) in preventing symptomatic COVID-19 at or after 14 days following the second dose (Widge et al., 2020). Among adults ≥ 65 years of age, vaccine efficacy was 86.4% (95% CI, 61.4-95.5). Among approximately 2,000 participants who only received a single dose of vaccine or placebo, vaccine efficacy following a single dose was 80.2% (95% CI, 55.2-92.5); however, duration of protection from a single dose remains uncertain. A preliminary analysis also suggested a reduction in asymptomatic infections between dose 1 and 2.

Local and systemic adverse effects were dose-dependent and relatively common after the second dose; most were of mild or moderate severity (i.e., did not prevent daily activities or require pain relievers) (Widge et al., 2020). The most common adverse effects among participants younger than 65 years were fever (17%) followed by severe fatigue, headache, myalgias, and arthralgias in 5-10% of cases. Adverse effects were less frequent among older individuals and in individuals with evidence of prior SARS-CoV-2 infection. There were 3 cases of Bell's palsy that were considered potentially related to vaccination. Although the rate did not exceed that in the general population (15 to 30 cases per 100,000

people per year), ongoing monitoring for possible vaccine-associated Bell's palsy is warranted (Widge et al., 2020). Based on interim results of the phase 3 trials, the Moderna mRNA-1273 has been authorized for emergency use in the United States (US FDA, 2020).

3. **AstraZeneca-Oxford Unviersity (ChAdOx1 nCoV-19)**

The British-Swedish company AstraZeneca, in partnership with the University of Oxford and the Serum Institute of India developed a COVID-19 vaccine based on the nonreplicating chimpanzee adenovirus (ChAdOx1) vaccine platform that expresses the spike protein. It is given intramuscularly in two doses given 28 days apart. Pooled interim analysis of four clinical trials from the U.K., Brazil, and South Africa reported vaccine efficacy of 70.4% (95% CI, 54.8-80.6) in preventing symptomatic COVID-19 at or after 14 days following the second dose (Ramasamy et al., 2020). A subgroup of participants inadvertently received a lower vaccine dose for the first of the two vaccine doses, and the vaccine efficacy in this subgroup was 90.0% (95% CI, 28.0-78.2) compared to 62.1% (95% CI, 41-75.7) among those who received full-dose vaccine. Reasons for this difference are uncertain, although the overlapping confidence intervals indicate that the difference is not statistically significant. Differences in the control administered (meningococcal vaccine for both doses at some study sites versus meningococcal vaccine for one dose and saline for another dose at other sites) and in the interval between administration of the two vaccine doses further contribute to uncertainty about the findings.

In earlier-phase trials, fatigue, headache, and fever were relatively common after vaccine receipt and were severe in up to 8% of recipients (Keech et al., 2020). In the phase 3 trial, there were two cases of transverse myelitis in ChAdOx1 nCoV-19 vaccine recipients. One was thought to be possibly related to vaccination and was described as an idiopathic, short-segment spinal cord demyelination; the other was in a participant with previously unrecognized multiple sclerosis and thought to be unrelated to the vaccine (Ramasamy et al., 2020).

Table 14 summarizes interim results from phase 3 trials of the front-runners in the COVID-19 vaccine development. Results may change after final analysis from phase 3 trials.

Table 14. Vaccine efficacy from phase 3 trials of COVID-19 vaccines

Vaccine Developer (Vaccine)	Vaccine platform	Dose	Phase 3 sample size (N)	Age	Vaccine efficacy (VE)*	Adverse effects (AEs)
Pfizer-BioNTech (BNT162b2)	mRNA	2 doses (30 µg per dose) 21 days apart The vaccine must be shipped and stored at ultra-cold temperatures (-70°C)	43,538	≥ 16 years	95% (95% CI, 90.3-97.6)[a]	Local and systemic AEs were dose-dependent and relatively common after the second dose; fever, severe fatigue, headache, chills were serious AEs reported; shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia; 2 BNT162b2 recipients died (one from arteriosclerosis, one from cardiac arrest), both unrelated to the vaccine.

						Outside of the clinical trial, anaphylaxis (2 cases) and Bell's palsy (4 cases) were reported
Moderna (mRNA-1273)	mRNA	2 doses (100 µg per dose) 28 days apart mRNA-1273 must be shipped and stored at 35.6-46.4°F (2-8°C)	30,000	≥ 18 years	94.1% (p <0.0001)[b]	Local and systemic AEs were dose-dependent and relatively common after the second dose; fever severe fatigue, headache, myalgias, and arthralgias were the most common AEs among participants < 65 years; AEs were less frequent among older individuals and in individuals with evidence of prior SARS-CoV-2 infection; 3 cases of Bell's palsy considered potentially related to vaccination
AstraZeneca (AZD1222)	nonreplicating chimpanzee adenovirus (ChAdOx1) encoding spike protein	2 doses 21 days apart 5×10^{10} viral particles (standard dose; SD/SD cohort); a subset in the UK trial received a half dose 2.2×10^{10} viral particles as their first dose (low dose) and a standard dose as their second dose (LD/SD cohort) Store refrigerated between 2-8°C for up to 30 days prior to first use; unpunctured vials may be stored between 8-25°C for up to 12 hours	23,848 (UK & Brazil)	18-55 years old	70.4% (95% CI, 54.8-80.6)[c] VE among those who received full standard dose vaccine (SD/SD) was 62.1% (95% CI, 41-75.7); VE in those who received a low dose as their first dose of vaccine (LD/SD) was higher at 90.0% (95% CI, 67.4–97.0)	Fatigue, headache, and fever were common AEs; two cases of transverse myelitis in ChAdOx1 nCoV-19 vaccine recipients, one was thought to be possibly related to vaccination and was described as an idiopathic, short-segment spinal cord demyelination; the other was in a participant with previously unrecognized multiple sclerosis and thought to be unrelated to the vaccine; a potentially vaccine-related serious AE was reported 2 days after vaccination in South Africa in an individual who recorded fever higher than 40°C, but recovered 2 days later

*Vaccine efficacy (VE) – protection against symptomatic COVID-19 disease

[a] Polack FP et al. N Engl J Med. 2020

[b] Widge AT et al.. N Engl J Med. 2020; Moderna 2020

[c] Ramasamy MN et al. Lancet. 2020

C. Recommendations on use of the mRNA COVID-19 vaccines

1. Indications for use

As initial vaccine supplies are limited, the Advisory Committee on Immunization Practices (ACIP) has recommended that these be allocated to health care personnel and long-term care facility residents followed by adults 75 years or older and frontline essential workers.

The choice between the two mRNA vaccines (Pfizer-BioNTech COVID-19 vaccine and Moderna COVID-19 vaccine) is based on availability. They are similar in composition and have been shown to have similar efficacy and safety profiles based on interim results from their respective phase 3 trials.

The differences in age ranges included in the indications reflect the different age ranges included in the phase 3 trials:

- Pfizer-BioNTech COVID-19 vaccine (BNT162b2) is indicated for individuals aged 16 years and older. Children and adolescents younger than 16 years of age are not authorized to receive the Pfizer-BioNTech COVID-19 vaccine at this time.
- Moderna COVID-19 vaccine (mRNA-1273) is indicated for individuals aged 18 years and older. Children and adolescents younger than 18 years of age are not authorized to receive the Moderna COVID-19 vaccine at this time.

Individuals with a history of SARS-CoV-2 infection should still receive one of these vaccines, if indicated; pre-vaccination serologic screening is not recommended (ACIP, 2020).

For individuals with recent, documented SARS-CoV-2 infection, it is recommended to delay vaccination for 90 days from the time of infection to allow others to receive the vaccine sooner, as the risk of reinfection appears extremely low during this interval. The ACIP also suggests that individuals who received monoclonal or convalescent plasma therapy for COVID-19 should delay vaccination for 90 days from the time of receipt (CDC, 2020).

Safety of these vaccines has not yet been established in children or pregnant individuals. However, pregnancy is not a contraindication to vaccine receipt. The decision to vaccinate individuals 16 years and older who are pregnant or breastfeeding should be made on a case-by-case basis, taking into account the individual's preferences, risk of COVID-19, and the unknown fetal effects of the vaccines.

The reported lower severity of COVID-19 in children and lack of studies in children are reasons that none of the vaccines have been approved for use in children. However, the risk of the multisystem inflammatory syndrome in children (MIS-C) following acute infection, the risk of severe disease in children with underlying medical conditions, and the general desire to prevent COVID-19 in children remain compelling reasons for vaccine studies in children. Studies are underway in older children and are planned in younger children.

Eligible individuals with an immunocompromising condition can also receive COVID-19 mRNA vaccines. Although the immunogenicity and efficacy of the vaccines are uncertain in these populations, the potential for severe COVID-19 in this population likely outweighs the uncertainties.

2. Dose and administration

Pfizer-BioNTech COVID-19 vaccine (BNT162b2) is administered in two intramuscular doses of 0.3 mL each, given 21 days apart. If more than 21 days have elapsed after the first dose, the second dose can be given as soon as feasible without repeating the series.

Moderna COVID-19 vaccine (mRNA 1273) is administered in two intramuscular doses of 0.5 mL each, given 28 days apart. If more than 28 days have elapsed after the

first dose, the second dose can be given as soon as feasible without repeating the series.

Each vaccine series should be completed with the same vaccine initially used; there are no data to support the efficacy and safety of using one of the vaccines for the first dose and the other for the second. Other non-COVID-19 vaccines should not be administered within 14 days of COVID-19 vaccine administration; there are no data regarding safety and efficacy when these vaccines are co-administered with other vaccines.

There is no role for post-vaccination testing for COVID-19 unless clinically indicated.

3. Contraindications and precautions

Pfizer-BioNTech COVID-19 vaccine (BNT162b2) and Moderna COVID-19 vaccine (mRNA 1273) are each contraindicated in individuals with a history of severe allergic reaction to any component of that specific vaccine. Because of rare reports of anaphylactoid reactions following administration, the ACIP lists history of severe allergic reaction to any vaccine or injectable therapy as a precaution (but not contraindication) to vaccination (CDC, 2020).

All individuals should be monitored for immediate vaccine reactions following receipt; individuals with history of anaphylaxis should be monitored for 30 minutes and others for 15 minutes. Vaccines should be administered in settings where immediate allergic reactions, should they occur, can be appropriately managed.

4. Patient counseling

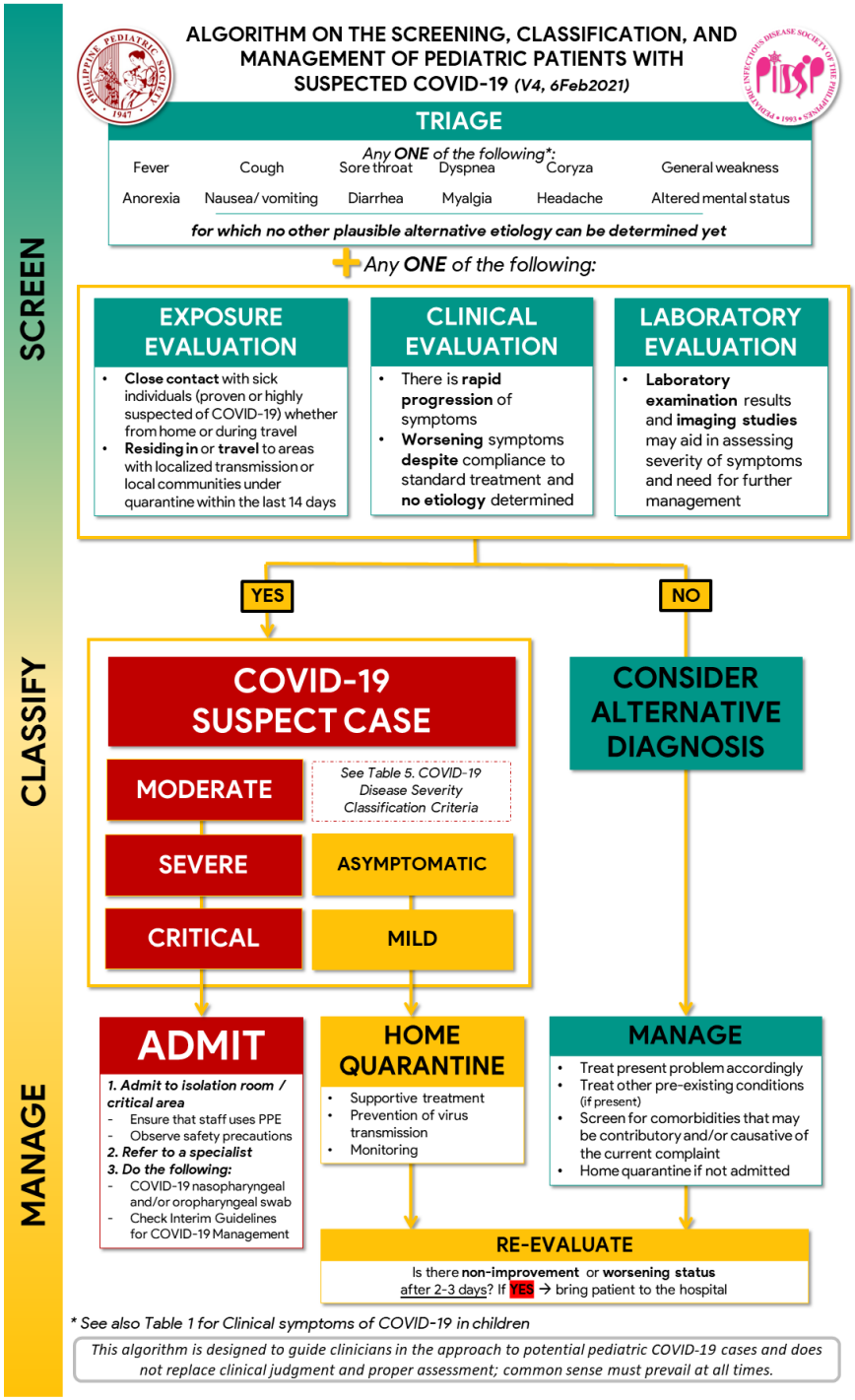
Vaccine recipients should be advised that side effects are common and include local and systemic reactions, including pain at the injection site, fever, fatigue, and headache. Patients should also be advised regarding reports of rare adverse effects such as anaphylaxis and Bell's palsy.

In addition to standard counseling about vaccine information, vaccine providers are required to inform potential recipients that each COVID-19 mRNA vaccine is available under EUA and is not a licensed vaccine.

SARS-CoV-2 infection might still occur despite vaccination. Given the currently limited information on how much the mRNA COVID-19 vaccines may reduce transmission in the general population and how long protection lasts, vaccinated persons should be reminded to continue other personal preventive measures to reduce SARS-CoV-2 transmission. This includes physical distancing, personal hygiene, use of protective equipment, following quarantine guidance after an exposure to someone with COVID-19, and following any applicable workplace or school guidance.

Various vaccines may become available in different countries and may have different dosing schedules. Different countries may also have specific allocation priorities for distributing the initial vaccine supplies. Clinicians should refer to local guidelines for additional details.

Algorithm on the screening, classification and management of pediatric patients with suspected COVID-19 (Version 4, 06 February 2021)



Note: The algorithm intends to capture as many cases as possible by expanding the criteria set by the WHO, i.e., the WHO definition states “Acute onset of fever AND cough OR ANY THREE OR MORE” vis-a-vis this interim guideline’s “ANY ONE OF THE FOLLOWING”.

Appendix A. Case Definitions for Surveillance

Source: World Health Organization. Public health surveillance for COVID-19. Interim guidance. 16 December 2020. Accessed at *https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2*

SUSPECT CASE

A. A person who meets the clinical **AND** epidemiological criteria:

Clinical criteria:

1. Acute onset of fever AND cough;

OR

2. Acute onset of **ANY THREE OR MORE** of the following signs or symptoms: fever, cough, general weakness/fatigue[1], headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting[1], diarrhea, altered mental status.

AND

Epidemiological criteria:

1. Residing or working in an **area with high risk of transmission of the virus**: closed residential settings, humanitarian settings such as camp and camp-like settings for displaced persons, anytime within the 14 days prior to symptom onset;

OR

2. Residing or travel to an area with community transmission anytime within the 14 days prior to symptom onset;

OR

3. Working in **any health care setting**, including within health facilities and within the community, anytime within the 14 days prior to symptom onset.

B. A patient with **severe acute respiratory illness** (SARI: acute respiratory infection with history of fever or measured fever of ≥ 38°C; and cough; with onset within the last 10 days; and requires hospitalization).

C. Asymptomatic person not meeting epidemiologic criteria with a **positive SARS-CoV-2 Antigen-RDT[2]**

PROBABLE CASE

A. A patient who meets **clinical criteria** above **AND** is a **contact of a probable or confirmed case**, or linked to a **COVID-19 cluster[3]**

B. A **suspect case with chest imaging** showing findings suggestive of COVID-19 disease[4]

C. A person with recent onset of **anosmia** (loss of smell) or **ageusia** (loss of taste) in the absence of any other identified cause

D. **Death**, not otherwise explained, in an adult with **respiratory distress** preceding death AND **was a contact of a probable or confirmed case** or linked to a **COVID-19 cluster[3]**

CONFIRMED CASE

A. A person with a positive **Nucleic Acid Amplification Test (NAAT)**

B. A person with a **positive SARS-CoV-2 Antigen-RDT AND** meeting either the **probable case definition or suspect criteria A OR B**

C. An **asymptomatic person with a positive SARS-CoV-2 Antigen-RDT** who is a **contact of a probable or confirmed case**

[1] Signs separated with slash (/) are to be counted as one sign

[2] NAAT is required for confirmation (see diagnostic testing for SARS-CoV-2)

[3] A group of symptomatic individuals linked by time, geographic location and common exposures, containing at least one NAAT-confirmed case or at least two epidemiologically linked, symptomatic (meeting clinical criteria of Suspect case definition A or B)

persons with positive AgRDTs (based on ≥97% specificity of test and desired >99.9% probability of at least one positive result being a true positive)

[4] Typical chest imaging findings suggestive of COVID-19 include the following:

- **Chest radiography**: hazy opacities, often rounded in morphology, with peripheral and lower lung distribution
- **Chest CT**: multiple bilateral ground glass opacities, often rounded in morphology, with peripheral and lower lung distribution
- **Lung ultrasound**: thickened pleural lines, B lines (multifocal, discrete, or confluent), consolidative patterns with or without air bronchograms

Definitions:

1. Close Contact

Contact is defined by the WHO as a person who has experienced any one of the following exposures **during the 2 days before and the 14 days after the onset** of symptoms of a probable or confirmed case:

a. Face-to-face contact with a probable or confirmed case within 1 meter and for **at least 15 minutes** (see *note* below);
b. Direct physical contact with a probable or confirmed case;
c. Direct care for a patient with probable or confirmed COVID-19 disease without using recommended personal protective equipment; OR
d. Other situations as indicated by local risk assessments

Note: The **Centers for Disease Control and Prevention (CDC)** recently released a revised definition of ***close contact*** (21 October 2020), which sets exposure for a **cumulative total of 15 minutes** or more over a 24-hour period. Factors to consider when defining close contact include (i) proximity; (ii) duration of exposure; (iii) symptomaticity of individuals involved; (iv) likelihood of generation of respiratory aerosols; and (v) other environmental factors.

For confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample that led to confirmation was taken.

2. Influenza-like Illness (ILI)

A condition with sudden onset (within 3 days of presentation and fever should be measured at the time of presentation) of fever ≥ 38°C and cough or sore throat in the absence of other diagnoses

3. Severe Acute Respiratory Infection (SARI)

An acute respiratory infection with onset during the previous 7 days requiring overnight hospitalization. A SARI case must meet the ILI definition AND any one of the following: (a) shortness of breath or difficulty of breathing; (b) severe pneumonia of unknown etiology, acute respiratory distress, or severe respiratory disease possibly due to novel respiratory pathogens (such as COVID-19).

Appendix B. Sample Symptom Monitoring Form

(Adapted from WHO and CDC recommendations by the "PH COVID-19 Health Care Workers' Chat Group" Team in collaboration with PSPHP, and Foundation of Family Medicine Educators)

Name: _____

Quarantine period: _____ to _____

Instructions: Monitor the child twice a day (AM and PM). Put a check (✓) if symptoms are present. For fever, write down the exact temperature of the child.

Week ___	Date _____		Date _____		Date _____		Date _____		Date _____		Date _____		Date _____	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
No symptoms														
Fever (write temp)														
Cough														
Sore throat														
Difficulty of breathing														
Runny nose														
Diarrhea														
Vomiting														
Abdominal pain														
Fatigue														
Headache														
Muscle pains														
Other symptoms 1. 2. 3.														
Medicines given 1. 2. 3.														

Important contact numbers to remember:

DOH COVID-19 Hotline: (02) 894-COVID or (02) 894-26843 or 1555

Provincial/City/Municipality COVID-19 Hotline: (contact details)

Hospital Emergency Room: (name of hospital and contact details)

Pediatrician: (contact details / email address)

Appendix C. Rationale for Pharmacologic Interventions

A. Recommended Therapy for Severe and Critical COVID-19

Corticosteroids

Patients with severe COVID-19 can develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. It has been hypothesized that the anti-inflammatory effects of corticosteroids might prevent or mitigate these complications.

The safety and efficacy of dexamethasone or other corticosteroids as treatment modalities for COVID-19 have not been sufficiently evaluated in the pediatric population. However, data extrapolated mostly from the Randomised Evaluation of COVID-19 therapy (RECOVERY) trial and the meta-analysis by WHO, which have mostly involved adult subjects, have shown benefits in survival for severely & critically ill patients.

In a meta-analysis of 1703 patients (median age 60 years, interquartile range 52-68 years) studying the effect of corticosteroid use on all-cause mortality at 28 days, the summary OR reported was 0.66 (95% CI, 0.53-0.82; p<0.001) based on a fixed-effect meta-analysis, with no safety concerns. The fixed-effect OR for the association with mortality was 0.64 (95% CI, 0.50-0.82; p<0.001) for dexamethasone compared to placebo; OR of 0.69 (95% CI 0.43-1.12; p=0.13) for hydrocortisone; and an OR of 0.91 (95% CI, 0.29-2.87; p=0.87) for methylprednisolone.

In a review done by the living WHO guideline on drugs for COVID-19, they reviewed evidence from 8 RCTs (N=7184) regarding corticosteroid use in the treatment of severe COVID-19. There was an 8.7% reduction of 28-day mortality in the critically ill and a 6.7% reduction in the severely ill. Systemic corticosteroids reduced the risk of 28-day mortality in critically ill patients (moderate certainty evidence; relative risk 0.80, 95% CI 0.70-0.91), with an absolute effect estimate of 87 fewer deaths per 1000 patients (95% CI, 124 fewer to 41 fewer). In patients with severe COVID-19, systemic corticosteroids can also reduce death risk (moderate certainty evidence; relative risk 0.80, 95% CI 0.70-0.92); absolute efficacy estimate of 67 fewer deaths per 1000 patients (95% CI 100 fewer to 27 fewer). In contrast, low certainty evidence suggested an increase in 28-day mortality of 3.9% in the non-severely ill.

Corticosteroid use for 7-10 days was not significantly associated with an increased risk of adverse events, such as gastrointestinal bleeding, super-infections, neuromuscular weakness, neuropsychiatric effects, and stroke and myocardial infarction. There was, however, an increased risk of hyperglycemia (RR1.16, 95% CI 1.08 – 1.25) and hypernatremia (RR 1.64, 95% CI 1.32 – 2.03).

Systemic corticosteroids may be administered by both the intravenous (IV) and oral routes. However, critically ill patients may not absorb any nutrients or medications due to intestinal dysfunction or poor perfusion. Hence, IV corticosteroids are generally preferred over oral if intestinal dysfunction is suspected, or the patient can still take medications per orem.

Recommendation: **Corticosteroids are recommended to be given for severe & critical COVID-19 in children. Corticosteroids are NOT recommended for asymptomatic and non-severe COVID-19 in children.**

B. Experimental Therapies for Severe and Critical Covid-19 in Children

1. Remdesivir

Remdesivir is a novel monophosphoramidate adenosine analog prodrug which is metabolized to an active triphosphate form that inhibits viral RNA synthesis. It has in vitro and in vivo broad antiviral activity against several viruses, including coronaviruses, and inhibits all human and animal coronaviruses, including SARS COV-2. Remdesivir is currently the only drug approved by the US Food and Drug Administration for the treatment of COVID-19.

On 5 November 2020, the final report of ACTT-1(Adaptive COVID-19 Treatment Trial 1), sponsored by NIH (National Institutes of Health), was published. One thousand sixty-two participants were enrolled and received either placebo for 10 days or intravenous (IV) remdesivir at a dose of 200 mg on Day 1 and then 100 mg daily for up to 9 more days. The primary study endpoint was time to clinical recovery. Remdesivir significantly reduced the time to recovery compared to placebo (median time to recovery was 10 days vs. 15 days; recovery rate ratio 1.29; 95% CI, 1.12–1.49; $P < 0.001$). The benefit of Remdesivir for reducing time to recovery was most evident in the subgroup of hospitalized patients who required supplemental oxygenation at study enrollment. In patients who required high-flow oxygen or noninvasive ventilation at study enrollment (ordinal scale 6, n = 193), there was no observed difference in time to recovery between the Remdesivir and placebo groups. Among the patients on mechanical ventilation or ECMO at study enrollment (ordinal scale 7, n = 285), there was no observed difference in time to recovery between the Remdesivir and placebo groups (recovery rate ratio). There was no difference in the median time to recovery between the Remdesivir and placebo groups among patients classified as having mild to moderate disease at enrollment. Mild to moderate disease was defined as SpO_2 >94% on room air and a respiratory rate of <24 breaths/minute without supplemental oxygen**. The conclusion of the ACTT-1 was that Remdesivir reduced the time to clinical recovery in patients with severe COVID-19. The benefit of Remdesivir was most apparent in hospitalized patients who only required supplemental oxygen.** There was no observed benefit of Remdesivir in those on high flow oxygen, non-invasive ventilation, mechanical ventilation, or ECMO, but the study was not powered to detect differences within subgroups. There was no observed benefit of Remdesivir in patients with mild to moderate COVID-19, but the number of participants in these categories was relatively small.

In the latest treatment guidelines of the WHO last December 2020, recommendations were based on 4 trials (ACTT-1, SIMPLE Moderate, Solidarity, and Wang), with 7333 participants. The NMA (network metaanalysis) provided relative estimates of effect for patient-important outcomes. The GDG (guideline development group) panel found a lack of evidence that Remdesivir improved outcomes that matter to patients, such as reduced mortality, need for mechanical ventilation, time to clinical improvement, and others. GRADE evidence summary suggested that Remdesivir has possibly no effect on mortality (odds ratio 0.90, 95% confidence interval [CI] 0.70 - 1.12; absolute effect estimate 10 fewer deaths per 1000 patients, 95% CI from 29 fewer - 11 more deaths per 1000 patients; low certainty evidence); and possibly no effect on the other important outcomes identified by the panel, with similar low to very low certainty of evidence. However, the low certainty evidence for these outcomes, especially mortality, does not prove that remdesivir is ineffective; rather, there is insufficient evidence to confirm that it does improve patient-important outcomes. Subgroup analysis indicated that Remdesivir treatment possibly increased mortality in the critically ill and possibly reduced mortality in the non-severely and severely ill. The panel judged the overall credibility of this subgroup effect to be insufficient to make subgroup recommendations. SIMPLE-MODERATE trial could not be included in the subgroup analysis as it only enrolled patients with non-severe COVID-19. Therefore, **for hospitalized patients with COVID-19 infection, regardless of disease severity, the Solidarity Trial gave a conditional recommendation against administering Remdesivir in addition to usual care.** The panel highlighted that despite the conditional recommendation against Remdesivir, they support further enrolment into RCTs evaluating Remdesivir, primarily to provide higher certainty of the evidence for specific subgroups of patients. None of the included RCTs enrolled children, adolescents (<19y/0), and although older people were included in the trials, their outcomes were not reported separately. Also, there are no pharmacokinetic or safety data on Remdesivir for children. Given this, the applicability of this recommendation to children is currently uncertain. There was no evidence of increased risk of severe adverse events (SAEs) from the trials.

Remdesivir use in children

Remdesivir has been available through compassionate use to children with severe COVID-19 since February 2020. A phase 2/3 trial (CARAVAN) of Remdesivir was initiated in June 2020 to assess safety, tolerability, pharmacokinetics, and efficacy in children with moderate-to-severe COVID-19 (5). Data were presented on compassionate use of

Remdesivir in children at the virtual COVID-19 Conference held July 10-11, 2020. Results showed most of the 77 children with severe COVID-19 improved with Remdesivir. Clinical recovery was observed in 80% of children on ventilators or ECMO and 87% of those not on invasive oxygen support.

A Multicenter Interim Guidance on Use of Antivirals for Children With Coronavirus Disease 2019/Severe Acute Respiratory Syndrome Coronavirus 2 recommended the following guidelines on the use of Remdesivir in children: Remdesivir to be used only in children with positive SARS-CoV-2 viral testing, is suggested for children with severe COVID-19 that requires supplemental oxygen (or an increased requirement from baseline) but without the need for new or increased non-invasive or invasive mechanical ventilation or ECMO and should be considered for all children with critical COVID-19 (new or increased need for noninvasive or invasive mechanical ventilation, hemodynamic instability requiring vasoactive agents, multisystem organ failure, or a rapidly worsening clinical trajectory) unless there are contraindications. The panel recommends a duration of up to 5 days of Remdesivir therapy for children with severe COVID-19. If Remdesivir is used for children with critical COVID-19, the panel suggests a duration of 5–10 days, with durations of up to 10 days considered on a case-by-case basis for children not improving after 5 days of therapy. When available, patients should be enrolled in clinical trials.

***Recommendation*: Remdesivir may be considered in the treatment of pediatric hospitalized patients with severe COVID- 19 disease that requires supplemental oxygen in a clinical trial setting or for compassionate use. Informed consent must be obtained prior to prescribing Remdesivir for pediatric COVID-19 patients. It is not recommended for mild, moderate, and critical COVID-19.**

2. Intravenous Immunoglobulin

In autoimmune diseases, IVIG is used by several mechanisms targeting both soluble and cellular mediators of the inflammatory immune response. This multitude of anti-inflammatory mechanisms and proven safety record of the drug prompted the clinical evaluation of IVIG in managing severe and critically ill COVID-19 patients. It has been hypothesized that earlier administration of IVIG, given between 7-10 days after infection, may help interrupt the cytokine storm and enhance immune function. The evidence of the efficacy of IVIG in both the adult and pediatric population for the treatment of COVID 19 is still limited.

IVIG has been reported in a few cohort studies of adult COVID-19 patients and even less in pediatric patients. There are no randomized controlled trials or efficacy data available. However, IVIG has been widely used in children for the treatment of several conditions, including Kawasaki disease, for which it has generally been shown to be safe.

Reports from the US, Italy, and the UK have demonstrated the use of IVIG in pediatric patients with COVID-19 and multisystem inflammatory syndrome in children (MIS-C), especially those with a Kawasaki disease-like presentation. Most of these patients received high-dose IVIG, and the majority of these patients improved and had recovery of cardiac function.

It has been hypothesized that earlier administration of IVIG, given between 7-10 days after infection, may help interrupt the cytokine storm and enhance immune function. However, more data are needed to support this theory. In a recent pre-print release, a retrospective study of 58 adult cases of severe or critical COVID-19 in Wuhan, China, compared the outcomes of patients given IVIG $\leq$48 h of admission and those started >48 h of admission. There was a statistically significant difference in 28-day mortality between the $\leq$48 h group (23.3%) and in the >48 h group (57.1%) (p=0.009). There was also a significantly shorter length of hospital stay in the $\leq$48 h group (11.50 $\pm$ 1.030) than in the >48 h group (16.96 $\pm$ 1.620 days) (p=0.0055), a shorter length of ICU stay (9.533 $\pm$ 1.089 vs 13.50 $\pm$ 1.632, p=0.0453), and a lower proportion of patients needing mechanical ventilation (6.67% vs 32.14%, p=0.016) in the $\leq$48 h group.

Another multicenter cohort study that included 325 adult critical patients with COVID-19 showed no difference in the 28-day and 60-day mortality with IVIG in the overall cohort. However, in the subgroup analysis, IVIG was associated with a significant reduction in the 28-day mortality in patients with critical COVID-19. Earlier administration (admission ≤7 days) with a high dose (>15 g/d) exhibited a significant reduction of 60-day mortality in these critical patients. However, these patients received numerous other treatments, which limit the interpretation of findings. These studies support earlier administration of IVIG.

There is a lack of evidence on the benefits of IVIG in children with COVID 19. However, it is universally used for multisystem inflammatory syndrome by pediatricians globally and Kawasaki-like disease after COVID-19.

Recommendation: **IVIG should not be routinely given for pediatric COVID-19. However, it can be given for patients presenting with a multisystem inflammatory syndrome, especially those with a Kawasaki disease-like presentation.**

3. Convalescent Plasma

Blood plasma from donors who have recovered from COVID-19 may contain antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that may help suppress the virus and modify the inflammatory response. Neutralizing antibodies are thought to be the main active component. These block the virus's entry into a cell by binding to the virus and regulating the immune system to mediate the phagocytosis of immune cells and remove the virus.

The 2nd living update of a Cochrane systematic review included 19 studies (2 randomized controlled trials, 8 controlled non-randomized studies of interventions, and 9 non-controlled non-randomized studies of interventions) 38,160 participants of whom 36,081 received convalescent plasma. The 2 RCTs were both stopped early, with 189 participants, of whom 95 received convalescent plasma. Control groups received standard care at the time of treatment without convalescent plasma. The result of the review is uncertain whether convalescent plasma decreases all-cause mortality at hospital discharge (risk ratio (RR) 0.55, 95% confidence interval (CI) 0.22 to 1.34; 1 RCT, 86 participants; low-certainty evidence). It is also uncertain whether convalescent plasma decreases mortality (time to event) (hazard ratio (HR) 0.64, 95% CI 0.33 to 1.25; 2 RCTs, 189 participants; low-certainty evidence). Convalescent plasma may result in little to no difference in improvement of clinical symptoms (i.e., need for respiratory support) at seven days (RR 0.98, 95% CI 0.30 to 3.19; 1 RCT, 103 participants; low-certainty evidence). Convalescent plasma may increase improvement of clinical symptoms at up to 15 days (RR 1.34, 95% CI 0.85 to 2.11; 2 RCTs, 189 participants; low-certainty evidence), and at up to 30 days (RR 1.13, 95% CI 0.88 to 1.43; 2 studies, 188 participants; low-certainty evidence). No studies reported on the quality of life.

A systematic review on the use of convalescent plasma for pediatric patients with COVID-19 was published. Eight studies were case reports of children treated with convalescent plasma therapy (14 children, age range, 9 weeks to 18 years); 5 children had a chronic disease during the hospital stay, 5 received drugs (e.g., remdesivir) in addition to convalescent plasma therapy. No convalescent plasma therapy-related adverse events were reported in 5 studies, and 3 made no mention of adverse events. Seven studies concluded that convalescent plasma therapy could be a useful therapeutic option; one study made no claims. Only 3 of the 13 retrieved trials underway were planned exclusively for children. They found insufficient clinical information on the safety and efficacy of convalescent plasma therapy in children. Nevertheless, the positive outcomes of the few case reports published to date suggest that convalescent plasma therapy may be of potential benefit.

A recent randomized, double-blind, placebo-controlled trial of convalescent plasma with high IgG titers against SARS-CoV-2 in older adult patients within 72 hours after the onset of mild Covid-19 symptoms was published. The primary endpoint was severe respiratory disease, defined as a respiratory rate of 30 breaths per minute or more, oxygen saturation of less than 93% while the patient was breathing ambient air, or both. The trial was stopped early at 76% of its projected sample size because cases of Covid-19 in the trial region decreased considerably. A total of 160 patients

underwent randomization. In the intention-to-treat population, severe respiratory disease developed in 13 of 80 patients (16%) who received convalescent plasma and 25 of 80 patients (31%) who received placebo (relative risk, 0.52; 95% confidence interval [CI], 0.29 to 0.94; P = 0.03), with a relative risk reduction of 48%. A modified intention-to-treat analysis that excluded 6 patients who had a primary end-point event before infusion of convalescent plasma or placebo showed a larger effect size (relative risk, 0.40; 95% CI, 0.20 to 0.81). No solicited adverse events were observed. Early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of COVID-19.

Another open-label, parallel-arm, phase II, multicenter, randomized controlled (not included in the Cochrane review) investigated the effectiveness of using convalescent plasma to treat moderate Covid-19 in adults. Four hundred sixty-four patients admitted with confirmed moderate covid-19, 235 were assigned to convalescent plasma with best standard of care (intervention arm) and 229 to best standard of care only (control arm). Participants in the intervention arm received two doses of 200 mL convalescent plasma, transfused 24 hours apart. The presence and levels of neutralizing antibodies were not measured prior; stored samples were assayed at the end of the study. Progression to severe disease or all-cause mortality at 28 days after enrolment occurred in 44 (19%) participants in the intervention arm and 41 (18%) in the control arm (risk difference 0.008 (95% confidence interval −0.062 to 0.078); risk ratio 1.04, 95% confidence interval 0.71 to 1.54). Convalescent plasma was not associated with a reduction in progression to severe covid-19 or all-cause mortality. This trial is replicable and approximates convalescent plasma use in real-life settings with limited laboratory capacity. A prior measurement of neutralizing antibody titers in donors and participants might further clarify the role of convalescent plasma in the management of COVID-19.

The appropriate volume for transfusion has not yet been determined. Based on previous pandemics and expert opinion, a volume from 200 to 600 ml (to 8 to 10 ml/kg, with a maximum of 600 ml) once per day and up to three consecutive days has been suggested. This scheme can be repeated once. Higher volumes could be contraindicated due to the risk of transfusion-associated circulatory overload. Pediatric dosing is confined to clinical trials, which typically dose based on body weight.

There is currently limited evidence of convalescent plasma as a therapeutic intervention in COVID-19 in adults and pediatric patients. However, clinical trials of COVID-19 convalescent plasma in both groups are ongoing.

***Recommendation*: There are insufficient data for convalescent plasma to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19 in children. It may be used in children with severe or critical COVID 19 only in a clinical trial setting.**

C. Treatments which are No Longer Recommended

1. Hydroxychloroquine/Chloroquine

Hydroxychloroquine and chloroquine are antimalarial drugs that were used widely in endemic areas before the era of resistance. These drugs are also used for their immunomodulatory effects of treating autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. In vitro studies have revealed their direct antiviral activity against SARS-COV2 by inhibiting receptor binding and membrane fusion. Hydroxychloroquine was more potent than chloroquine in antiviral action with an EC50 of 0.72 µM versus 5.47µM for chloroquine. In addition, their strong immunomodulatory effects are hoped to prevent the cytokine storm seen in COVID-19 patients. Gao's article announced preliminary findings from clinical trials in China involving 100 patients showing that chloroquine prevented exacerbations of pneumonia, promoted virus-free conversion, and shortened the disease course. This prompted the inclusion of chloroquine in the Chinese National Health Commission Guidelines on Diagnosis, Treatment and Prevention of Pneumonia caused by COVID-19. Researchers in France published preliminary results

of a non-randomized study using hydroxychloroquine in 20 patients showed a higher reduction of viral carriage on the 6th day than controls, and more efficient viral reduction azithromycin was added.

Since then, numerous clinical trials have been performed using either hydroxychloroquine or chloroquine. The WHO published The Therapeutics and COVID-19 Living Guideline, a global collaboration, a living, systematic review, and network analysis. The recommendation for hydroxychloroquine was derived from a network meta-analysis of pooled data from 30 trials with 10,921 participants with COVID-19. It was found that HCQ and CQ probably do not reduce mortality or mechanical ventilation. It may even increase the risk for death and mechanical ventilation. Absolute effects difference between the standard of care for mortality was 10 more per 1000 (CI 95% 5 fewer -28 more). Other outcomes such as time to symptom resolution, hospital admission, and mechanical ventilation duration are uncertain.

Adverse effects such as diarrhea, nausea, and vomiting were increased in patients given HCQ. However, it was uncertain whether HCQ increases cardiac toxicity and arrhythmias.
It was also stated that the WHO Guideline Development Group felt that future studies would probably not identify any subgroup which would benefit from the use of HCQ or CQ.

***Recommendation*: Hydroxychloroquine and chloroquine are not recommended for the treatment of children with COVID-19.**

2. Lopinavir/Ritonavir

Lopinavir/ritonavir is a protease inhibitor licensed for use combined with other antiretroviral drugs for the treatment of HIV-1 in adults, adolescents, and children above the age of 2 weeks. It was previously used in the treatment of SARS-CoV and MERS-CoV infections; this was the initial basis for its use against SARS-CoV-2. However, recent studies have shown no benefit in patients for whom this drug was used to treat COVID-19.

A randomized, controlled, open-label trial that evaluated LPV/r in addition to standard care in hospitalized adults with confirmed SARS-CoV-2 infection showed no benefit with LPV/r treatment beyond standard care. Results showed treatment with LPV/r was not associated with a difference from standard care in the time to clinical improvement (hazard ratio for clinical improvement, 1.24; 95%CI 0.90 to 1.72).

The RECOVERY Trial, which included LPV/r among the drugs evaluated against COVID-19, also showed no benefits for patients given this treatment. The trial randomly allocated 1616 patients to receive LPV/r and 3424 patients to receive usual care with 28-day mortality as the primary outcome being evaluated. Overall, 374 (23%) patients allocated to LPV/r and 767 (22%) patients allocated to usual care died within 28 days (rate ratio 1·03, 95% CI 0·91–1·17; p=0·60). No significant difference between treatment and control group was also seen for secondary outcomes of risk of 1) time until discharge alive from the hospital, 2) discharge alive from the hospital within 28 days, and 3) progression to mechanical ventilation.

The SOLIDARITY Trial spearheaded by the WHO has also shown that LPV/r produces little or no reduction in hospitalized COVID-19 patients' mortality compared to standard of care. A total of 11,330 patients from around the world were entered in the trial evaluating repurposed anti-viral drugs, including remdesivir, hydroxychloroquine, interferon beta-1a, and LPV/r. Notably, a total of 1411 patients were assigned to receive LPV/r. Death occurred in 148 of 1399 patients receiving LPV/r and 146 of 1372 receiving its control (rate ratio, 1.00; 95% CI, 0.79 to 1.25; P=0.97). No drug definitely reduced mortality, overall or in any subgroup, or reduced initiation of ventilation or hospitalization duration. A meta-analysis was also done (combining the SOLIDARITY and

RECOVERY trials and the data from Cao et al.). It showed that for LPV/r, the joint rate ratio for death was 1.01 (95% CI, 0.91 to 1.13).

The WHO living guidelines on Therapeutics and COVID-19 recommend against administering LPV/r for treatment of COVID-19 patients with any disease severity and any duration of symptoms. This recommendation was based on a meta-analysis of 7 trials with 7429 participants; notably, the included studies did not enroll patients under 19 years old. Data analysis showed that LPV/r probably has no effect on mortality (odds ratio 1.0, CI 95% [0.82–1.2]), does not reduce mechanical ventilation (odds ratio 1.16, CI 95% [0.98–1.36]), and may have no effect on the duration of hospitalization; the effect on viral clearance and time to clinical improvement is very uncertain; treatment may increase the risk of diarrhea and nausea/vomiting while the effect of LPV/r on acute kidney injury is uncertain. Although some uncertainty remains, the guidelines also state that further research is unlikely to uncover a subgroup of patients that benefit from LPV/r on the most important outcomes (mortality, mechanical ventilation) given the consistent results in trials.

3. Tocilizumab

Tocilizumab is a recombinant humanized anti-IL-6 antibody licensed for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and giant cell arteritis. It is also used for the induction of the rapid reversal of cytokine release syndrome (CRS), a form of cytokine storm caused by chimeric antigen T– cell (CART) immunotherapy.[2] Since it can bind to the IL-6 receptor with high affinity, it can prevent IL-6 from binding to its receptor, rendering it incapable of immune damage to target cells and alleviating the inflammatory responses.

High serum concentrations of IL-6 are strongly associated with severe COVID-19 and served as the biologic basis for early off- label use of tocilizumab for COVID-19. Several phase 3 clinical trials have evaluated the safety and efficacy of tocilizumab plus standard of care among hospitalized adults with COVID-19 pneumonia vs. placebo plus standard of care.

The preliminary report of REMAP-CAP (NCT02735707), Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia, showed that critically ill patients with Covid-19 receiving organ support in intensive care, treatment with tocilizumab and sarilumab improved outcome, including survival. Patients were randomized to receive either tocilizumab (8mg/kg) (N=353) or sarilumab (400mg) (N=48) or standard care (control) (N=402). Median organ support-free days were 10 (interquartile range [IQR] -1, 16), 11 (IQR 0, 16) and 0 (IQR -1, 15) for tocilizumab, sarilumab and control. Hospital mortality was 28.0% for tocilizumab, 22.2% for sarilumab and 35.8% for control. There were 9 serious adverse events reported in the tocilizumab group, including 1 secondary bacterial infection, 5 bleeding, 2 cardiac events, and 1 deterioration in vision. There were 11 serious adverse events in the control group, and no serious adverse events were noted in the sarilumab group.

The results of the EMPACTA (Evaluating Minority Patients with Actemra) (NCT04372186) trial also showed positive results. Tocilizumab was given within the first 2 days of ICU admission, and it reduced the likelihood of progression to mechanical ventilation or death, but it did not improve survival. Two hundred forty-nine patients received tocilizumab, and 128 patients received a placebo. The cumulative percentage of patients who had received mechanical ventilation or who had died by day 28 was significantly lower in the tocilizumab group (12.0%; 95% [CI], 8.5 to 16.9) than in the placebo group (19.3%; 95% CI, 13.3 to 27.4). Death from any cause by day 28 occurred in 10.4% of the patients in the tocilizumab group and 8.6% of those in the placebo group (95% CI, –5.2 to 7.8).

The Boston Area COVID-19 Consortium (BACC) Bay Tocilizumab Trial (NCT04356937) aims to prevent the progression of Covid-19 among patients that were not on the mechanical ventilator. 243 COVID-19 patients with hyper inflammation were enrolled in the study; 161 received tocilizumab and 81 received placebo. Compared to

placebo, early administration of tocilizumab did not prevent progression to intubation or death (hazard ratio [HR] 0.83, 95% CI 0.38-1.81, p = 0.64), did not prevent clinical worsening (HR 1.11, 95% CI 0.59-2.10, p = 0.73) and did not reduce duration of supplemental oxygen (HR 0.94, 95% CI 0.67-1.30, p = 0.69). Patients who received tocilizumab had fewer serious infections than patients who received placebo (8.1% vs.17.3%; P=0.03).

The RCT-TCZ-COVID-19 (NCT04346355) is a prospective, open-label, randomized clinical trial of 126 patients with confirmed COVID-19 pneumonia and Pao_2/Fio_2 ratio between 200 and 300 mm Hg and either fever or a CRP ≥10 mg/dL and/or CRP level increased to at least twice from admission. Results showed no difference in rates of clinical worsening within 14 days, 17 of 60 patients (28.3%) in the tocilizumab group and 17 of 63 (27.0%) in the standard care group. No difference were noted in ICU admission rate (10.0% vs 7.9%), or rate of hospital discharge at 14 days (56.7% vs 57.1%) or 30 days (90.0% vs 92.1). The tocilizumab group did not have increased infections compared to the control group.

The effects of different treatments for COVID 19 were compared in a systemic review by Siemieniuk, R. et al. 85 randomized control trials were included (41,669 COVID-19 patients). Data showed that compared with standard of care, tocilizumab does not affect the following (low certainty evidence): mortality (95% CI, RD 5 per 1000 patients, -0.46 to 81), the risk for mechanical ventilation (95% CI, RD -35 per 1000 patients, -80 to 54), adverse events leading to discontinuation (95% CI, RD -8 per 1000 patients, -15 to 300), duration of hospital stay (95% CI, MD -2.5 days, -6.9 to 1.8), length of ICU stay (95% CI, MD -4.5 days, -13.8 to 4.9), time to symptom resolution(95% CI, MD -1.8 days, -5 to 3.4) and ventilator-free days (95% CI, MD 4.7 days, -5 to 3.4). This systematic review will include 4 additional randomized control trials on tocilizumab on its next update.

There is a lack of high-quality evidence evaluating the efficacy and safety of tocilizumab for the management of severe COVID-19. The Infectious Diseases Society of America, CDC, and NIH COVID 19 Treatment Guidelines all recommended that Tocilizumab be given only in the clinical trial context. More data from ongoing clinical trials are needed to establish the role of tocilizumab in the management of such patients. There are no published studies on the use of Tocilizumab in the pediatric population.

D. Nutritional Support

Nutritional interventions should be viewed as an INTEGRAL part of the management of infections.

Recommendations for supportive care for children with coronavirus disease 2019 (COVID-19) are similar to adults. Among the recommendations are bed rest and ensuring adequate calories and hydration. Getting essential vitamins and minerals such as Vitamin D3 and Zinc from supplements may bolster the immune system.

1. Zinc

Zinc is an essential micronutrient supporting the growth and normal function of the immune system. Zinc deficiency results in dysfunction of both humoral and cell-mediated immunity and increases susceptibility to infectious diseases. Children who are living in low-income settings are often undernourished and zinc-deficient. Zinc deficient children are at increased risk of restricted growth, developing diarrheal diseases, and respiratory tract infections such as acute lower respiratory tract infections. In the Philippines, the prevalence of zinc deficiency in the young population is as follows: pre-school children six months to < 5 years, 21.6%; school children 6 to 12 years, 30.8%; and adolescents 13 to 19 years, 28.9%.

Zinc supplementation has a role in the early cure of pneumonia, and it also decreased the total hospital stay of children with severe pneumonia. Zinc supplements given to zinc-deficient children could reduce measles-related morbidity and mortality caused by lower respiratory tract infections. A systematic review has demonstrated that

zinc supplementation was significantly associated with reducing pneumonia rates and recommended supplementing zinc intake in deficient populations.

Zinc supplementation has been shown to reduce the duration and limit diarrhea complications in children by increasing intestinal fluid absorption, supporting mucosal integrity, and enhancing immune response. A meta-analysis found that zinc supplements' beneficial effects have been most clearly demonstrated in south Asia when children were given at least 70 milligrams of zinc per week. Zinc supplement may affect not only COVID-19- related symptoms like diarrhea and lower respiratory tract infection but also the SARS-CoV-2 virus itself.
Zinc is known for its anti-viral, anti-inflammatory, and immunomodulatory activities. It is also well-tolerated/ Based on existing information on its beneficial and harmful effects, it can be concluded that a risk-benefit ratio is in favor of Zinc supplementation in COVID-19. Ongoing clinical trials will further define its role in the management of this disease.

***Recommendation*: Zinc may be given as nutritional support for pediatric COVID-19 patients.**

2. VITAMIN D3

Vitamin D is a nutrient and a hormone that can be synthesized in our body with the help of sunlight. In addition to its role in maintaining bone integrity, it also stimulates many cells' maturation, including immune cells. Vitamin D boosts immune defenses and reduces excessive inflammation. It favors macrophages' ability to mature and prevents macrophages from releasing too many inflammatory cytokines and chemokines.

Low levels of vitamin D are associated with respiratory tract infections, and children with acute pneumonia may be vitamin D deficient. In a meta-analysis, low vitamin D status was independently associated with a higher risk of mortality among pneumonia patients. The mean intake of vitamin D among Filipino school children aged 6-12 years and adolescents aged 13-18 years was far below the Adequate Intake. The overall prevalence of combined vitamin D deficiency (<50 μmol/L) and insufficiency (51–74 μmol/L) among children aged 6–12 years in selected areas in the Philippines was 60.6%. Vitamin D reduces the risk of RTIs through several mechanisms.

Vitamin D helps maintain tight junctions, gap junctions, and adherens junctions. Several studies discussed how viruses disturb junction integrity, increasing infection by the virus and other microorganisms. This action by viruses is an important reason why viral infections progress to pneumonia. Vitamin D enhances natural cellular immunity partly through the induction of antimicrobial peptides, including human cathelicidin and defensins, and reduces the cytokine storm induced by the innate immune system. Cathelicidins exhibit direct antimicrobial activities against Gram-positive and Gram-negative bacteria, fungi, and enveloped viruses like CoVs. The innate immune system generates both pro-inflammatory and anti-inflammatory cytokines in response to viral and bacterial infections, as observed in COVID-19 patients.

Vitamin D supplementation may be used as an adjunct to antibiotics for the treatment of acute childhood pneumonia. Although there is no direct evidence that Vitamin D will help in COVID-19 disease, it is recommended because many children are vitamin D deficient, and enhancing their immunity in respiratory tract infections is deemed beneficial.

***Recommendation*: Vitamin D3 may be given as nutritional support for pediatric COVID-19 patients.**

Appendix D. Informed Consent Template

INFORMED CONSENT FOR OFF-LABEL USE OF MEDICATION/S AND/OR USE OF INVESTIGATIONAL DRUG/S FOR COVID-19

Dr. _____ *[Name of physician]* is offering to treat you, your child (in which case the word "you" will refer to "your child" throughout this document), or the person you represent (in which case the word "you" will refer to the person you are representing) with _____ ***[Name of unapproved drug, device, or biologic]*** because you have been clinically diagnosed with probable or confirmed SARS-CoV2 infection, called COVID-19, and there are no standard acceptable drugs at present.

What you should know about this treatment using COVID-19 investigational drug
This treatment has not been approved by the Food and Drug Administration.
For drugs approved for medical use by the Philippine Food and Drug Administration (FDA), the manufacturers' packaging labels, or inserts, state the condition or conditions for which they may be used. Physicians may opt for off-label drug use when convinced that it is for the patient's best interests, and the patient is well-informed and expresses his/her consent for its use, its composition, contraindications, and side effects.
This treatment is considered experimental.
This treatment is not research and you will not be considered a research subject.
Someone will explain this treatment to you.
You give consent to get this treatment.
Whether or not you get this treatment is up to you.
You can choose not to get this treatment.
You can agree to get this treatment now and later change your mind.
If you do change your mind, contact your doctor right away.
Whatever you decide it will not be held against you.
Feel free to ask all the questions you want before you decide.

How long will this treatment last?
We expect that the experimental treatment will last _____ *[days/until a certain event]*.

What happens if I get this treatment?
[Tell the patient what to expect using lay language and simple terms.]

Is there any way this treatment could be bad for me?
[Describe the risks of the treatment]
This treatment may hurt you in ways that are unknown. These may be a minor inconvenience or may be so severe as to cause death.
If you are or become pregnant, this treatment may hurt your baby or your pregnancy in ways that are unknown. These may be a minor inconvenience or may be so severe as to cause death.

Can this treatment help me?
We cannot promise that this treatment will cure you. The goal of this treatment is to _____. ***[Describe the potential benefits of the treatment]***
What else do I need to know?
Efforts will be made to limit your personal information, including medical records, to people who have a need to review this information. Organizations that may inspect and copy your information include appropriate representatives of the _____***[Name of hospital]***, and the FDA or appropriate government agency.
If you are injured or made sick from taking part in this treatment, medical care will be provided. Generally, this care will be billed to you or your insurance. However, it is possible that your insurance will not pay for the care, because the treatment is experimental or with use of investigational drug. Contact your doctor for more information.

Who can I talk to?
If you have questions, concerns, or complaints, or think the treatment has hurt you, you can talk to your doctor at _____ ***[Insert contact information]***

This treatment is subject to oversight by this hospital's Institutional Ethics/ Review Board/ Committee. If you have questions about your rights or any unresolved question, concerns, or complaints, talk to them at _____ ***[Insert contact information]***.

Your signature documents your permission to take part in this experimental treatment.

Signature of person providing consent (patient, legally authorized representative, parent, or guardian)	Date
Printed name of patient	
Printed name of person providing consent, if patient is unable to consent	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	

*Informed Consent Form replicated from Philippine Society for Microbiology and Infectious Diseases (PSMID) Interim Guidance on the Clinical Management of Adult Patients with Suspected or Confirmed COVID-19 Infection, *Version 3.1, as of July 20, 2020*

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