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 the wealth of scientific and clinical knowledge on COVID-19 in children.

This rapid advice has been updated from the previous version (version 2, released 12 April 2020) as new knowledge on pediatric COVID-19 has become available in recent literature. It aims to provide guidance to 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 three parts: part 1 discusses basic concepts on COVID-19 in children, including local epidemiology, disease transmission, risk factors, clinical manifestations, and classification of severity; part 2 mainly focuses on proper screening and triaging of children; and part 3 largely focuses on basic concepts of management.

PART 1. COVID-19 IN CHILDREN

I. LOCAL EPIDEMIOLOGY AND BURDEN OF ILLNESS IN CHILDREN

As of 16 August 2020, the Department of Health has recorded 10,873 confirmed COVID-19 cases aged 19 years and below, of whom 51.6% were males. Majority of cases were between 15-19 years old, comprising 40.7% of total cases, followed by the 10-14 years age group at 23.2%, 0-4 years age group at 20%, and 5-9 years age group at 16.1%.

A total of 64 deaths were recorded among confirmed cases 19 years and below, giving a case fatality rate of 0.6%. Among the deaths, 48.4% were seen in the 0-4 years old age group, followed by the 15-19 age group with 29.7% of total deaths.

II. INCUBATION PERIOD

The incubation period of the SARS-CoV-2 virus is on average 5-6 days, but can last up to 14 days. 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. 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 beyond this period. Asymptomatic infection has been described in literature, with a wide range of reported incidence ranging from 1% to 78% depending on the population studied. How asymptomatic infection drives transmission is a subject that has yet to be elucidated.

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 also occur in certain situations where viral particles are aerosolized through aerosol-generating procedures such as non-invasive positive pressure ventilation (NIPPV, BiPAP and CPAP), endotracheal intubation and extubation, cardiopulmonary resuscitation (CPR), open suctioning of airway secretions, high frequency oscillatory ventilation, tracheostomy, chest physiotherapy, nebulizer treatment, sputum induction, nasogastric tube placement and bronchoscopy.

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, despite prior claims that vertical transmission does not occur. Evidence of placental infection with SARS-CoV-2 was seen in a mother infected with COVID-19, with the neonate also testing positive for COVID-19 on nasopharyngeal and rectal swab RT-PCR. A systematic review on vertical transmission of COVID-19 also concluded that vertical transmission of infection cannot be excluded in several of the reported cases. 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. Evidence has also shown that children with COVID-19 are capable of transmitting the disease to adults and to other children. Yet despite these findings, the exact role of children in the extent of disease transmission has yet to be clearly determined and would need to be further investigated.

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%)

V. CLINICAL MANIFESTATIONS OF COVID-19 IN CHILDREN

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. CLASSIFICATION OF SEVERITY OF COVID-19 IN CHILDREN

The following classification of severity of COVID-19 in children is adopted from Dong et al.:

Table 2. Classification of severity of COVID-19 in children

Classification	Description
Asymptomatic infection	A child with a positive 2019-nCoV nucleic acid test, without any clinical symptoms and signs, and normal chest imaging.
Mild infection	A child with symptoms of acute upper respiratory tract infection, including fever, fatigue, myalgia, cough, sore throat, runny nose, and sneezing. Physical examination shows congestion of the pharynx and no auscultatory abnormalities. Some cases may have no fever, or have only digestive symptoms such as nausea, vomiting, abdominal pain and diarrhea.
Moderate infection	A child with frequent fever and cough, mostly dry cough followed by productive cough, with or without wheezing, but no shortness of breath. Physical examination shows

	abnormal auscultatory findings and no hypoxemia. Chest x-ray findings reveal pneumonia. Some cases may have no clinical signs and symptoms, but chest CT scan shows lung lesions, which are subclinical.
Severe infection	A child with early respiratory symptoms such as fever and cough, may be accompanied by gastrointestinal symptoms such as diarrhea. The disease progresses after around 1 week, and dyspnea occurs, with central cyanosis. Oxygen saturation is less than 92%, accompanied by other manifestations of hypoxia.
Critical condition	Children who quickly progress to acute respiratory distress syndrome (ARDS) or respiratory failure, and may also have shock, encephalopathy, myocardial injury or heart failure, coagulation dysfunction, and acute kidney injury. Organ dysfunction can be life-threatening.

In the same 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.

In contrast to adult patients with COVID-19, most children and adolescents present with mild to moderate symptoms; only a small percentage of patients develop severe and critical manifestations. 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.

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;
   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: 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 any of the following: exposure evaluation, clinical evaluation or ancillary laboratory tests (particularly imaging procedures) is positive, **the diagnosis of COVID-19 should be considered** (Figure 1).

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 (07 August 2020)

Category	Criteria
SUSPECT CASE **(two suspected case definitions A or B)**	**A.** A person who meets the <u>clinical</u> **AND** <u>epidemiological</u> criteria: <u>Clinical criteria</u>: 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, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status. **AND** <u>Epidemiological criteria</u>: 1. Residing or working in an area with high risk of transmission of the virus: for example, closed residential settings and 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 health setting, including within health facilities and within households, 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 who requires hospitalization).
PROBABLE CASE	**A.** A patient who meets clinical criteria above AND is a contact of a probable or confirmed case, or epidemiologically linked to a cluster of cases which has had at least one confirmed case identified within that cluster. **B.** A suspected case (described above) with chest imaging showing findings suggestive of COVID-19 disease* * 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 **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 who was a contact of a probable or confirmed case or epidemiologically linked to a cluster which has had at least one confirmed case identified within that cluster.
CONFIRMED CASE	A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Source: World Health Organization. Public health surveillance for COVID-19. Interim guidance. 07 August 2020. Accessed at https://www.who.int/publications/i/item/who-2019-nCoV-surveillanceguidance-2020.7.

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 WHO Clinical Management of COVID-19 (27 May 2020), which have recently been adopted by the Department of Health.

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
Other complications that have been described in COVID-19 patients include acute, life-threatening conditions such as: acute pulmonary embolism, acute coronary syndrome, acute stroke and delirium. Clinical suspicion for these complications should be heightened when caring for COVID-19 patients, and appropriate diagnostic and treatment protocols available.		

Table Notes:
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.

The SOFA score ranges from 0 to 24 and includes points related to six organ systems: respiratory (hypoxemia defined by low PaO_2/FiO_2); coagulation (low platelets); liver (high bilirubin); cardiovascular (hypotension); central nervous system (low level of consciousness defined by Glasgow Coma Scale); and renal (low urine output or high creatinine). Sepsis is defined by an increase in the sepsis-related SOFA score of ≥ 2 points. Assume the baseline score is 0 if data are not available.

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. Clinical Management of COVID-19. Interim Guidance. 27 May 2020. Accessed at https://www.who.int/publications/i/item/clinical-management-of-covid-19.

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 try to separate themselves from other people in the household.
- 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.
- 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 as much as possible.
- Children younger than 2 years old should 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.
- Try to find the right size of mask for your child's face and be sure to adjust it 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 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 C, 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.
- 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, referral to a COVID-19 referral center must be done.

A. In-patient 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 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.

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) guidelines on the clinical approach to the management of

COVID-19 in pregnancy and the newborn (revised May 7, 2020).

2. **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.

A systematic review by Bastos et al. compared the diagnostic accuracy of different methods of serological tests (ELISA, LFIA, and CLIA). The pooled sensitivity of ELISA was 84.3%, of LFIA was 66%, and of CLIA was 97.8% However, the study also reported a high or unclear risk of bias in 98% of the studies, and results were not stratified by the timing of sample collection in relation to symptom onset in 67% of the studies.

At present, it is still unknown whether antibodies persist following infection and whether the presence of antibodies confers protective immunity against future infection.

To date, serologic testing is not recommended as a standalone test for diagnosing COVID-19, and must be done always in conjunction with RT-PCR testing. Rapid point-of-care LFIAs are not recommended due to its 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.

Currently, there are several Philippine FDA-registered IgM/IgG antibody tests. The DOH has released guidelines on the use of these serologic tests (see DOH Department Memorandum 2020-0151, Interim Guidelines on Expanded Testing for COVID-19, released 31 March 2020). However, it must be emphasized that these tests are not recommended for use in diagnosing acutely ill patients nor for screening of patients. Their use should be limited mainly for seroprevalence studies in identified populations or areas, and not as standalone tests for the diagnosis of COVID-19.

3. **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 complete blood count picture seen in children with COVID-19 is 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: 6 months to 2 years (male) 50–292 U/L 6 months to 2 years (female) 38–260 U/L 3–5 years (male) 59–296 U/L 3–5 years (female) 42–227 U/L 6–8 years (male) 54–275 U/L 6–8 years (female) 50–231 U/L 9–11 years (male) 55–324 U/L 9–11 years (female) 52–256 U/L 12–14 years (male) 63–407 U/L 12–14 years (female) 45–257 U/L 15–17 years (male) 68–914 U/L 15–17 years (female) 45–458 U/L 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 perfoming 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

4. 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	Imaging findings are atypical or uncommonly reported in cases of COVID-19 pneumonia in children. Recommend consideration of alternative diagnosis.

	lymphadenopathy	
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).

c. **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. Experimental Therapeutic Interventions for Severe Suspected, Probable or Confirmed COVID-19 in Children

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 adults and children, and many of the clinical trials are still ongoing. 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. Based on observational data in 2,143 children from China, COVID-19 disease is less severe in children compared to adults and has lower mortality rates. Asymptomatic cases were 4.4%, mild cases were seen in 50.9%, moderate cases in 38.8% while severe and critical cases totaled 5.2%. Thus, research in adults should be prioritized before those in children. Antiviral agents are recommended ONLY in severe cases because the majority of children are either asymptomatic or experience mild disease only. Prophylaxis in children is also not recommended at the moment because of this.

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

Table 10. Experimental Therapeutic Interventions for Severe Suspected, Probable or Confirmed COVID-19 in Children

DRUG	INDICATION	DOSING REGIMEN / DURATION	ADVERSE EFFECTS
ANTIVIRAL			
Remdesivir (for clinical trial or compassionate use only, informed consent from the parent or legal guardian must be sought	Treatment of COVID-19 in hospitalized patients • With SpO_2 < 94% on ambient air or those who require supplemental oxygen • On mechanical ventilator or ECMO (extracorporeal membrane oxygenation)	**3.5 kg to < 40kg:** LD of 5mg/kg on day 1 followed by 2.5mg/kg once daily from day 2 onwards via IV infusion over 30-120 minutes **40 kg and higher:** Adult dose: LD of 200mg on day 1, 100mg from day 2	• Transient elevations in AST or ALT after multiple days of therapy • Mild reversible PT prolongation without INR change or hepatic effects • Drug vehicle is SBECD (sulfobutylether beta-cyclodextrin sodium),

before initiation of treatment)		onwards via IV infusion over 30-120 minutes **Duration:** • 5 days for those not on mechanical ventilation or ECMO and clinically improving • 10 days for those on mechanical ventilation, on ECMO and not clinically improving Formulation: 100mg/vial	which has been associated with renal toxicity • GI symptoms (e.g., nausea and vomiting) **Drug Interaction**: • Coadministration of Remdesivir and Chloroquine or Hydroxychloroquine sulfate is not recommended based on in vitro data showed an antagonistic effect
ADJUNCTIVE TREATMENT			
Dexamethasone	Severe COVID-19 • On mechanical ventilation • ARDS • Shock/cardiac dysfunction • With substantially elevated LDH, D-dimer, IL-6, IL-2R, CRP, and/or ferritin	0.15 mg/kg PO or IV once daily (max. dose: 6mg) Up to 10 days or until discharge Formulation: 4mg/mL, 2mL ampoule	• Adrenal suppression • Immunosuppression (activation of latent infections, secondary infections) • Hyperglycemia • Psychiatric disturbances • Increased blood pressure • Peripheral edema • Myopathy (particularly if used with neuromuscular blocking agents) • Delayed viral clearance (as shown in past outbreaks of SARS and MERS)
Tocilizumab (for clinical trial or compassionate use only, informed consent from the parent or legal guardian must be sought before initiation of treatment)	May be considered in the following: • Severe/critical COVID-19 pneumonia with hyperinflammation or cytokine storm • Rapid worsening of respiratory gas exchange • Age 2 years old and above • No other viral/fungal infection, TB, bacterial sepsis, hepatitis B	8 mg/kg/dose IV, given as 1-hour infusion Additional dose may be given 12 hours after the first if clinical status worsens or with no improvement Maximum dose: 800 mg/dose	• Increased serum cholesterol • Increased ALT and AST • Hypertension • Skin rash • Diarrhea • Leukopenia, neutropenia, thrombocytopenia • Headache • Upper respiratory tract infection, nasopharyngitis

Intravenous immunoglobulin (IVIG)	Multisystem Inflammatory Syndrome in Children (MIS-C)	1-2 g/kg over 8-12 hours	• 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

See Appendix C for the rationale for 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 World Health Organization has presented an updated recommendation reflecting recent findings that persistently positive RT-PCR tests do not necessarily indicate infectiousness (WHO criteria for releasing COVID-19 patients from isolation, 17 Jun 2020). These updates are reflected in the current DOH recommendations which employ a combination of time- and symptom-based strategies, stating that repeat RT-PCR testing is no longer a prerequisite for discontinuation of quarantine, isolation or transmission-based precautions.

A. **Symptomatic patients with confirmed or probable COVID-19** can be discharged from isolation and discontinue transmission-based precautions once the following criteria are fulfilled:
   1. The Clinically recovered based on evaluation by a physician
   2. Absence of COVID-19 symptoms for at least 3 days
   3. Has completed 14 days of isolation, counting from onset of illness

B. **Asymptomatic patients with confirmed or probable COVID-19** can be discharged from isolation and discontinue transmission-based precautions once the following criteria are fulfilled:
   1. Clinically recovered based on evaluation by a physician
   2. Remained symptom-free for 14 days
   3. Has completed 14 days of isolation, counting from date of positive test

C. For patients **suspected of having COVID-19**, CDC recommends that discontinuation of isolation and empiric transmission-based precautions in COVID-19 suspects can be made upon receipt of at least one negative SARS-CoV-2 RT-PCR test performed by a certified laboratory testing facility. If a higher level of clinical suspicion for COVID-19 exists, consider maintaining isolation and transmission-based precautions and

performing a second SARS-CoV-2 RT-PCR. If a COVID-19 suspect case is never tested, the decision to discontinue isolation and transmission-based precautions can be made based upon using the strategy described above for symptomatic confirmed or probable cases.

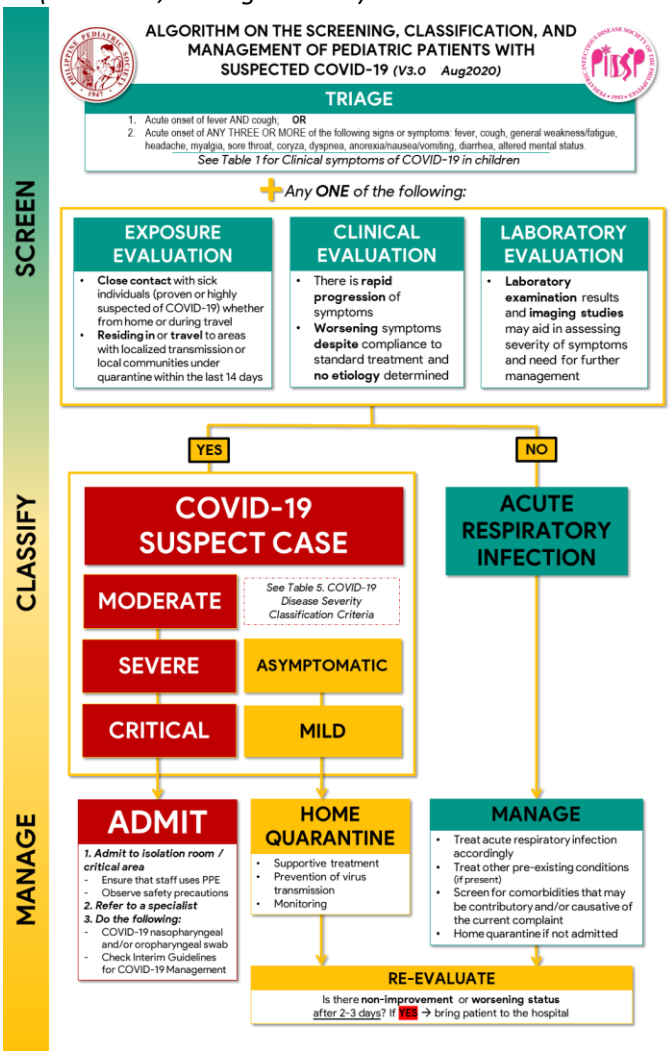
Ultimately, clinical judgement and suspicion of SARS-CoV-2 infection determine whether to continue or discontinue empiric transmission-based precautions.

For symptomatic patients discharged to home prior to completion of the 14 day 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.

Figure 1. Algorithm on the screening, classification and management of pediatric patients with suspected COVID-19 (Version 3, 20 August 2020)



Appendix A. Case Definitions for Surveillance

Source: World Health Organization. Public health surveillance for COVID-19. Interim guidance. 07 August 2020. Accessed at https://www.who.int/publications/i/item/who-2019-nCoV-surveillanceguidance-2020.7

SUSPECT CASE
(two suspected case definitions A or B)

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, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status.

AND

Epidemiological criteria:

1. Residing or working in an area with high risk of transmission of the virus: for example, closed residential settings and 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 health setting, including within health facilities and within households, 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 who requires hospitalization).

PROBABLE CASE

A. A patient who meets clinical criteria above AND is a contact of a probable or confirmed case, or epidemiologically linked to a cluster of cases which has had at least one confirmed case identified within that cluster.

B. A suspected case (described above) with chest imaging showing findings suggestive of COVID-19 disease*

* 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.

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 who was a contact of a probable or confirmed case or epidemiologically linked to a cluster which has had at least one confirmed case identified within that cluster.

CONFIRMED CASE

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

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;
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: 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 Recommendations of the Experimental Therapeutic Interventions for Severe Suspected, Probable or Confirmed COVID-19 in Children

Drugs with Anti-SARS-COV-2 Activity

1. Remdesivir

Remdesivir is an intravenous (IV) investigational nucleotide prodrug of an adenosine analog. It has demonstrated in vitro activity against severe acute respiratory syndrome coronavirus 2 (SARS-COV-2, and in vitro and in vivo activity (based on animal studies) against SARS-CoV and the Middle East Respiratory Syndrome (MERS-CoV). Remdesivir binds to the viral RNA dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription.

The first published report concerning Remdesivir compassionate use described clinical improvement in 36 of 53 hospitalized patients (68%) with severe COVID-19. On May 1, 2020, the US FDA issued EUA (Emergency use Authorization) of Remdesivir to allow emergency use of the agent for severe COVID-19 (confirmed or suspected) in hospitalized adults and children.

EUA of Remdesivir was based on the preliminary data analysis of the Adaptive COVID-19 Treatment trial (ACTT) last April 29, 2020. The analysis included 1,063 hospitalized patients with advanced COVID-19 and lung involvement, showing that patients who received Remdesivir recovered faster than similar patients who received placebo (31% faster recovery time vs. placebo ($P<0.001$). The median time to recovery was 11 days in patients treated with Remdesivir compared with 15 days in the placebo group. This effect was not observed in patients with mild to moderate disease: time to recovery was 5 days for both the Remdesivir group and the placebo group. For patients with severe disease who constitute approximately 90% of the study population, time to recovery was 12 days in the Remdesivir group and 18 days in the placebo group. However, there was no difference seen in time to recovery in patients who started Remdesivir when they were already on mechanical ventilation or ECMO.

The safety and effectiveness of Remdesivir for COVID-19 treatment have not been fully evaluated in pediatric patients. It is available through a PhilFDA Drug Emergency Use (DEU) Authorization for adults and children and through a compassionate use program for patients aged <18 years with COVID-19.

Recommendation: Remdesivir may be used to treat pediatric patients with severe COVID-19 disease in a clinical trial setting or for compassionate use. Informed consent must be obtained prior to prescribing Remdesivir for pediatric COVID-19 patients.

2. Hydroxychloroquine/Chloroquine

Hydroxychloroquine and chloroquine are antimalarial drugs which 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-COV-2 by inhibiting receptor binding and membrane fusion. Hydroxychloroquine was found to be 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. An article by Gao 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. No details were provided on the patients, but 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 compared to controls and more efficient viral reduction when azithromycin was added. A small trial in patients with mild COVID-19 disease was recently published, which showed patients on hydroxychloroquine had a shorter time to recovery for fever and cough as well as a higher proportion of improved pneumonia compared to those in the control group. Azithromycin was added as it showed higher viral clearance in the French study.

Unfortunately, subsequent trials did not show any benefit (time to temperature normalization, duration of hospitalization, and mortality) in the use of hydroxychloroquine in hospitalized patients with COVID 19. The RECOVERY Trial is an open-label, adaptive design RCT conducted in the UK to test a range of drugs, including hydroxychloroquine, for treating patients hospitalized with COVID-19. On June 5, 2020, the chief investigators of the RECOVERY TRIAL in the UK announced the discontinuation of the hydroxychloroquine arm due to a lack of benefit. There was no significant difference between the 1,542 patients who received hydroxychloroquine compared with3,132 patients who received standard of care alone, for the 28-day mortality (25.7% vs. 23.5%, hazard ratio 1.11, 95% CI 0.98–1.26) along with no difference between hospitalization duration. On June 17, 2020, the World Health Organization decided to stop the hydroxychloroquine arm based on new data from the SOLIDARITY and RECOVERY trials and other evidence that showed no benefit for patients with COVID-19. In some trials, increased incidence of gastrointestinal adverse effects was noted, while observational trials reported a higher incidence in ventricular arrhythmias and prolongation of QTc intervals in adults given hydroxychloroquine.

Several ongoing trials in adults, as well as six trials using hydroxychloroquine or chloroquine in children, are continuing. Results from these trials shall determine the role of these aminoquinolines in the management of COVID-19.

Recommendation: Hydroxychloroquine and chloroquine are not recommended to be routinely given to children with COVID-19.

3. Lopinavir/Ritonavir

Lopinavir/ritonavir is a protease inhibitor licensed for use in combination 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 as well. However, recent studies have shown no benefit in patients for which 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 study compared 1596 patients randomized to LPV/r with 3376 patients randomized to usual care alone. There was no significant difference in the primary endpoint of 28-day mortality (22.1% LPV/r vs. 21.3% usual care (relative risk 1.04 [95% CI 0.91-1.18]) and the results were consistent in the different subgroups of patients. There was also no evidence of beneficial effects on the risk of progression to mechanical ventilation or length of hospital stay. The SOLIDARITY Trial spearheaded by the WHO has also released a statement stating that it has discontinued the trial's hydroxychloroquine and LPV/r arms. The recommendation was based on SOLIDARITY trial interim results and from a review of the evidence from all trials presented at the 1-2 July WHO Summit on COVID-19 research and innovation, which showed LPV/r produce little or no reduction in the mortality of hospitalized COVID-19 patients when compared to standard of care.

Recommendation: Lopinavir/Ritonavir is not recommended to treat children with COVID-19.

Adjunctive Therapy for Suspected and Confirmed COVID-19

1. Dexamethasone

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 from adult studies have shown benefits in survival for severely ill patients.

Preliminary results from the Randomised Evaluation of COVID-19 therapy (RECOVERY) trial in the UK, showed initial findings that dexamethasone reduced the risk of 28-day mortality by 35% in patients on ventilator support (RR 0.65, 95%CI 0.48-0.88, p=0.0003) and by 20% in patients receiving oxygen support (RR 0.80, 95%CI 0.67-0.96, p=0.0021) compared with those receiving usual care. There was no added benefit in patients not requiring respiratory support (RR=1.22, 95%CI 0.86-1.75, p=0.14). The pediatric arm of the RECOVERY trial and other studies in children are ongoing.

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. However, the benefits from corticosteroids should be balanced with its possible adverse effects such as delayed viral clearance, as seen in the SARS and MERS outbreaks, worsening of clinical outcomes, including secondary bacterial infection and mortality.

In a meta-analysis of 1 small cohort study and 7 RCTs for non-COVID-19, ARDS showed a reduction in mortality (RR 0.72, 95%CI=0.55 to 0.93). In patients with severe COVID-19 without ARDS, there was very low-quality evidence of an increase in mortality with corticosteroid use (HR 2.30, 95%CI=1.00 to 5.29). Observational data from SARS and MERS studies showed very low-quality evidence of a small or no reduction in mortality, as well as a delay in viral clearance.

Recommendation: Dexamethasone may be given for severe COVID-19 in children, specifically those on mechanical ventilation, acute respiratory distress syndrome (ARDS), shock/cardiac dysfunction, substantially elevated LDH, D-dimer, IL-6, IL-2R, CRP, and or/ferritin).

2. Tocilizumab

Tocilizumab is a recombinant humanized anti-IL6 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. 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.

In a prospective, open-label study that enrolled 63 adult patients, all of the patients received antiretroviral protease inhibitors (lopinavir/ritonavir 45/63 patients, darunavir/cobicistat 18/63 patient) and either tocilizumab IV (8 mg/kg) or tocilizumab SQ (324 mg); within 24 hours after this initial dose, a second dose was administered to 52 of the 63 patients. Following administration of tocilizumab, fever resolved except for one patient, and CRP, ferritin, and D-dimer levels declined. The ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) improved. Tocilizumab administration within 6 days from admission in the hospital was associated with an increased likelihood of survival (HR 2.2 95%CI 1.3–6.7, p<0.05). No moderate or severe adverse events were reported. The overall mortality rate was 11% (7 of 63 patients). No details were provided regarding the rate of secondary infections after tocilizumab use.

Similar results were noted in a retrospective cohort study of 21 hospitalized patients with severe or critical COVID -19 pneumonia who received tocilizumab plus standard of care, body temperatures of all patients returned to normal after

one day. Peripheral oxygen saturation, inflammatory markers, and chest computed tomography (CT) scan showed improvement. Serious adverse events were not noted, and there were no deaths reported.

In another retrospective cohort study, 544 patients (tocilizumab n=179, standard of care n=365), tocilizumab treatment was also associated with a reduced risk of invasive mechanical ventilation or death compared with standard care group however higher cases of new infections (24 (13%) of 179 patients treated with tocilizumab, versus 14 (4%) of 365 patients treated with standard of care alone) such as bacterial, viral, invasive fungal infections, and tuberculosis, hepatitis B and herpes simplex 1 reactivation.

Cases of anaphylaxis, severe allergic reactions, severe liver damage and hepatic failure, and intestinal perforation have been reported after long term tocilizumab administration in patients without COVID-19.

While the results of some studies were promising, there were no studies done in children, and the results of several ongoing clinical trials should be awaited prior to its routine clinical application.

Recommendation: Tocilizumab should not be routinely used for patients with severe pneumonia due to COVID-19 in patients with cytokine storm or hyperinflammation except in a clinical trial setting or for compassionate use. Informed consent must be obtained prior to prescribing tocilizumab for pediatric COVID-19 patients.

3. Intravenous Immunoglobulin

IVIGs are sterile, purified IgG products manufactured from pooled human plasma and usually contain more than 95% unmodified IgG, which has intact Fc-dependent effector functions and only trace amounts of immunoglobulin A or immunoglobulin M. The evidence of the efficacy of IVIG in both the adult and pediatric population is still limited.

The use of 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.

In another multicenter cohort study that included 325 critical adult patients with COVID-19, it 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 $\leq$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.

Recommendation: IVIG should not be routinely given for pediatric COVID-19. However, it can be given to patients presenting with multisystem inflammatory syndrome.

Supportive Treatment

1. Zinc

Zinc is an important micronutrient supporting 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. 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 deficient children are at increased risk of restricted growth, and developing diarrheal diseases, as well as respiratory tract infections such as acute lower respiratory tract infections. Zinc supplement given to zinc-deficient children could reduce measles-related morbidity and mortality caused by lower respiratory tract infections. Zinc supplementation has a role in the early cure of pneumonia, and it also decreased the total hospital stay of children with severe pneumonia. It reduced the number of days of acute lower respiratory Tract Infection (ALRI) in Thai children, as well as their stay in the hospital. Zinc supplementation has been shown to reduce the duration and limit the complications of diarrhea in children by increasing intestinal fluid absorption, supporting mucosal integrity, and enhancing immune response. Increasing the concentration of intracellular zinc with zinc-ionophores like pyrithione can efficiently impair the replication of a variety of RNA viruses. In addition, the combination of zinc and pyrithione at low concentrations inhibits the replication of SARS-coronavirus. Previous *in vitro* study has shown that chloroquine, an antimalarial agent, acts as a zinc ionophore in human ovarian cancer cells. Zinc supplement may affect not only COVID-19-related symptoms like diarrhea and lower respiratory tract infection but also on the SARS-CoV-2 virus itself.

Recommendation: Zinc may be given as supportive treatment in pediatric patients with severe COVID-19.

2. Vitamin D

Vitamin D is not only a nutrient but also a hormone, which can be synthesized in our body with the help of sunlight. In addition to its role in maintaining bone integrity, it also stimulates the maturation of many cells, including immune cells. Vitamin D boosts immune defenses and reduces excessive inflammation. Low levels of vitamin D are associated with respiratory tract infections. Children with acute pneumonia may be vitamin D deficient. 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 umol/L) and insufficiency (51-75 umol/L) was 48.7% among Filipino adults.

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 induction of antimicrobial peptides, including human cathelicidin and defensins, and by reducing 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 proinflammatory 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 D_3 may be given as supportive treatment to all pediatric patients with severe COVID-19.

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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