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 World Health Organization has declared coronavirus disease 2019 (COVID-19) to be a global pandemic. As the total number of reported cases increase, it is prudent to assume that the number of pediatric cases will also rise. Most of the cases are in adults, with higher risk of severe infection reported in older patients and those with chronic medical conditions. Although only a small number of cases are in children, there is a need to be able to evaluate and manage these cases in an expedient manner so as to ensure favorable outcomes, particularly in those with comorbidities, such as malnutrition, chronic heart, lung or kidney disease, HIV, immunodeficiency or malignancy. There is also limited data on the disease course and potential for adverse outcomes in neonates and young infants, who may be more vulnerable to the infection (Y Dong et al., 2020).

The purpose of this rapid advice is 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.

This rapid advice is divided into two parts: Part 1 will mainly focus on proper triaging of children and Part 2 will largely focus on basic concepts of management.

Part 1 SCREENING AND ASSESSMENT

According to the Centers for Disease Control and Prevention, data for human infection with coronaviruses suggest that the incubation period may range for 2-14 days but is estimated at 4 days (Guan et al., 2020). This will be the time frame considered for exposure in this report.

I. SYMPTOMS AND/OR EXPOSURE HISTORY

A. Investigate whether the child has had any acute respiratory infection symptoms within 14 days, for which no other plausible alternative etiology can be considered.
    1. Symptoms of acute respiratory infection in children include:
        a. Fever defined as an axillary temperature of 38°C and above
        b. Cough
        c. Sore throat
        d. Difficulty of breathing (fast breathing, chest indrawing, noisy breathing in a calm child)

    2. Other symptoms may also be present which warrant close observation of the child, such as:
        a. Rhinorrhea
        b. Diarrhea
        c. Vomiting
        d. Abdominal pain
        e. Fatigue
        f. Headache
        g. Rashes
        h. Myalgia

B. Assess the child's travel history or history of close contact:
        a. Evaluate if the child has been in close contact with sick individuals, whether from home or during travel, who are proven COVID-19 patients or highly suspected of COVID-19. *Close contact* is defined by the WHO as a person who is involved in any of the following from 2 days before and up to 14 days after the onset of symptoms in the confirmed or probable case:
        b. Having face-to-face contact with a COVID-19 patient within 1 meter and for >15 minutes;
        c. Providing direct care for patients with COVID-19 disease without using proper personal protective equipment;
        d. Staying in the same close environment as a COVID-19 patient (including sharing a workplace, classroom or household or being at the same gathering) for any amount of time;
        e. Travelling in close proximity with (that is, within 1 m separation from) a COVID-19 patient in any kind of conveyance; and
        f. Other situations, as indicated by local risk assessments

    Take note of any history of recent travel within the last 14 days to areas with localized transmission or local communities under enhanced 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.

    Note: Exposure to a possible COVID-19 case (formerly patient under monitoring or PUM) is not considered close contact.

C. 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. If laboratory tests such as a complete blood count and/ or chest imaging are available, check if results are compatible with a consideration of COVID-19 (see below, section on Other Laboratory Tests).

E. If either exposure evaluation, clinical features or laboratory tests is positive, the symptomatic child is considered a **suspect COVID-19 case** (formerly Patient Under Investigation or PUI).

F. If none of the features described above is present, the child is considered to have 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 Intervention" guidelines as described in Part 2.

II. CLASSIFICATION CRITERIA

After the child is assessed to be a **suspect COVID-19 case** (formerly Patient Under Investigation or PUI)*:*

A. Classify as **suspect COVID-19 case with Severe/Critical symptoms** if they fulfill the criteria stated below. Criteria for **Severe/Critical** symptoms are as follows:

1. Any child with cough or difficulty of breathing PLUS at least ONE of the following:
    a. Central cyanosis or SpO2 <90%
    b. Severe respiratory distress (e.g. grunting, very severe chest indrawing)
    c. Signs of pneumonia with a general danger sign: inability to breastfeed or drink, lethargy/movement only when stimulated, unconsciousness, or convulsions
    d. Other signs: chest indrawing, fast breathing (in breaths/min):
        <2 months: RR ≥60 breaths per minute
        2-11 months: RR ≥50 breaths per minute
        1-5 years: RR ≥40 breaths per minute
2. Any child with suspected or proven infection and ≥2 SIRS criteria, of which one must be abnormal temperature or white blood cell count (sepsis)
3. Any child presenting with septic shock, defined as hypotension (SBP <5th centile or >2SD below normal for age) or at least 2 of the following:
    a. Altered mental state
    b. Tachycardia (HR > 160 bpm in infants or > 150 bpm in children) or bradycardia (HR <90 bpm in infants or <70 bpm in children)
    c. Prolonged capillary refill (>2 sec) or warm vasodilation with bounding pulses
    d. Tachypnea
    e. Mottled skin or petechial or purpuric rash
    f. Increased lactate

g. Oliguria
h. Hyperthermia or hypothermia

Note:
"Difficulty of breathing" is intended to capture dyspnea or air hunger AND NOT nasal congestion or other upper airway obstruction.

B. Classify as **suspect COVID-19 case with Non-severe symptoms** if they do not fulfill the criteria for suspect case with Severe/Critical symptoms.

Patients with Non-severe symptoms may range from **Mild** to **Moderate** symptoms. Children with **Mild** symptoms are patients with uncomplicated upper respiratory tract viral infection, may have non-specific symptoms such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, or headache. Rarely, patients may also present with diarrhea, nausea and vomiting. Patients with **Moderate** symptoms include frequent fever and cough (mostly dry which may become productive), or wheezing but no obvious shortness of breath. Some may be asymptomatic but with imaging findings, which are considered subclinical (Dong et al., 2020).

C. Classify as **probable COVID-19 case** if the suspect case fulfills any one of the following listed below:
   a. Suspect case for whom testing for COVID-19 is inconclusive
   b. Suspect who underwent testing for COVID 19 but not conducted in a national or subnational reference laboratory or officially accredited laboratory for COVID-19 confirmatory testing
   c. Suspect case for whom testing could not be performed for any reason

D. Classify as **confirmed COVID-19 case** if positive for SARS-CoV-2 on a nucleic acid detection test such as reverse transcriptase polymerase chain reaction (RT-PCR) regardless of symptoms.

The table below compares the previous and current surveillance definitions utilized by the Department of Health (See Appendix A Case Definitions for Surveillance for more details).

Old Classification	New Classification
Neither PUI nor PUM	Non-COVID case
PUM	Possible case (with exposure/contact, but no symptoms)
PUI – mild, severe and critical who has not been tested and for testing	Suspect
PUI – mild, severe and critical with inconclusive, inadequate or no available testing	Probable
COVID-19 positive	Confirmed

Part 2 CLINICAL MANAGEMENT

Since there is no specific antiviral yet proven to be effective for COVID -19, management remains focused on providing best supportive care, management of co-existing conditions

and treatment of possible bacterial co-infections. Table 1 classifies pediatric patients suspected or confirmed to have COVID infection and harmonizes COVID -19 disease classification with PCAP classification; this can serve as a guide for clinical management.

I. PATIENTS WITH NON-SEVERE 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.

A. Home Intervention

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.
- The child and household members should wear a surgical face mask when in the same room or when interacting inside the home as much as possible. 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.

- 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. N-95 masks are not recommended for children and should be reserved for healthcare workers at increased risk of exposure to COVID-19.
- 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.
- Caregiver should use disposable gloves when handling oral or respiratory secretions, feces 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 excreta are on surfaces of linen or towels, the excreta 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. Data on ibuprofen use is equivocal at this time.
- 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.

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 (see Annex for sample monitoring form), 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.

B. Discontinuation of Home Isolation for Patients with Suspected, Probable or Confirmed COVID-19

1. Patients for whom no PCR test was done

Based on recommendations from the US CDC, persons who have symptoms of COVID-19 but were not tested for SARS-CoV-2 and were advised to care for themselves at home may discontinue home isolation when the following conditions are met:

a. At least 3 days (72 hours) have passed since recovery, defined as resolution of fever without the use of fever reducing medications and improvement in respiratory symptoms (e.g. cough, shortness of breath); AND
b. At least 7 days have passed since symptoms first appeared

The World Health Organization simplifies its discharge criteria with the advice to complete home quarantine for 14 days after resolution of symptoms.

2. Patients with PCR-confirmed COVID-19

Based on US CDC guidelines, persons with PCR-positive test result for COVID-19 who have symptoms and were directed to care for themselves at home may discontinue home isolation under the following conditions:

a. Resolution of fever without the use of fever-reducing medications, AND
b. Improvement in respiratory symptoms (e.g., cough, shortness of breath),

AND, If with access to repeat testing:

Negative results of an approved molecular assay for COVID-19 from at least two consecutive nasopharyngeal / oropharyngeal swab specimens collected ≥24 hours apart.

Where repeat testing is not possible, WHO recommends that confirmed patients remain isolated for an additional two weeks after symptoms resolve.

II. PATIENTS WITH SEVERE/CRITICAL SYMPTOMS

All patients with *severe/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. Inpatient Management

1. The child, should be admitted in the hospital and placed in an isolation room, or to 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 designated 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.

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 (Huang C et al 2020; Zhou F et al 2020). 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 SARSCoV-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 (WHO Interim Guidance Mar 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. immunochromatography, ELISA, chemiluminescence immunoassay, etc. As these tests are still in the early stages of development, determining unique viral protein targets to reduce cross-reactivity to other coronaviruses is a challenge and can affect test sensitivity and specificity.

Likewise, the antibody response to the virus is still being characterized. Based on limited studies, IgM is detectable 5-10 days after symptom onset, with < 40% patients being positive in the first 7 days of illness. IgG is said to be detectable 21 days after symptom onset. Thus, these tests also have limited utility for early detection of disease. Furthermore, it is not known how long IgM or IgG antibodies to SARS-CoV-2 will remain in the body after infection and if they confer long lasting immunity against subsequent infection.

Currently there are several Philippine FDA-registered IgM/ IgG antibody rapid diagnostic tests. Based on DOH guidelines (see Appendix F), these tests are to be used for specific patient categories, and in conjunction with RT-PCR tests**.**

3. Other Laboratory Tests

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

- **Complete blood count** - White blood cell counts may vary, but leukopenia, leukocytosis, and lymphopenia have been reported, although lymphopenia appears most common (Lu et al., 2020). Platelet count may be normal (Tang et al., 2020). However, throbocytopenia has been noted in a case report of two COVID+ adult patients presenting with fever, initially assessed to have dengue fever based on positive serology (Yan et al 2020). The presentation of fever and thrombocytopenia can be important to recognize in the local setting where dengue fever is common.
- **Imaging studies**
  - **Chest x-ray** findings may show unilateral or bilateral patchy infiltrates, multiple small patchy shadows and interstitial changes, remarkable in the lung periphery, with severe cases developing to bilateral multiple ground-glass opacity, infiltrating shadows, and pulmonary consolidation, with infrequent pleural effusion (Cai et al., 2020; Chen et al., 2020).
  - **Chest CT scans** show typical viral pneumonia patterns (Liu et al., 2020) with ground-glass opacification with or without consolidative abnormalities.
  - **Chest ultrasound** has been used as an alternative to chest CT scan due to its ease of use at point-of-care, absence of

radiation exposure, and lower cost. Experience in adults have shown the following findings: thickening of the pleural line with pleural line irregularity, B lines in a variety of patterns including focal, multifocal, and confluent, and consolidation (Peng et al., 2020).

- **CRP and Procalcitonin** - patients with COVID-19 may have normal or elevated procalcitonin and CRP; a rapid rise or significantly elevated procalcitonin may indicate secondary bacterial infection, but may also be seen in severe COVID-19 without bacterial co-infection (Xia et al. 2020).
- **Arterial Blood Gas (ABG) or pulse oximetry** – to assess the severity of pneumonia; oxygen saturation at room air <95% measured by pulse oximetry may indicate pneumonia and if <90% may indicate severe pneumonia

b. **Other tests to determine alternative etiology or secondary infection.** Whenever possible, it is advised to determine an alternative etiology of acute respiratory infection or diarrhea using appropriate diagnostics, which may include the following:

- Bacterial and Fungal Cultures (blood, and/or stool, urine and other appropriate specimens) – to test for bacteria or fungi, ideally collected before antimicrobial or antifungal therapy
- Rapid antigen detection tests for specific bacterial or viral pathogens
- Multiplex respiratory or gastrointestinal panel tests

Co-infections have been documented, however, and tests that are positive for other bacterial or viral pathogens do not rule out COVID-19.

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

Since the SARS-COV2 is a newly detected virus and COVID-19 cases were only diagnosed in January 2020, there is very scarce data on the treatment and prevention of this disease in adults, more so in children. Currently, only investigational drugs are being recommended for adults and clinical trials are still underway. Ethically, new drugs are tested first in adults prior to 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 is less severe in children and has lower mortality rates compared to adults. Mild cases were seen in 50.9%, moderate cases in 38.8%, severe and critical cases in 5.2% and asymptomatic cases in 4.4%. Thus, research in adults should be prioritized, before those in children. This is also the reason for recommending these experimental agents **ONLY** in severe/critical cases because majority of children have mild disease or are asymptomatic. Prophylaxis in children is also not recommended at this time for the same reason.

DRUG	DOSING REGIMEN	DURATION	CONTRAINDICATIONS
Hydroxychloroquine* 200 mg tablet	5 mg/kg/day BID (Max: 400mg/dose) Day 1 6-8 y/o 1 tab BID 9-11 y/o 1 ½ tab BID ≥ 12 y/o 2 tabs BID Days 2 - 5 6-8 y/o ½ tab BID 9-11y/o ½ to 1 tab BID ≥ 12 y/o 1 tab BID If the patient cannot swallow the tablet, crush and dissolve in a small amount of water, milk or juice to be given with meals.	5 days May be extended to 10 days depending on clinical status	- <6 years of age - Hypersensitivity to 4-aminoquinolines - Presence of retinal or visual field changes - Epilepsy - Porphyria - Psoriasis
OR			
Chloroquine* 250 mg tablet (equivalent to 150mg of Chloroquine base)	10mg(base)/kg/day BID (Max: 500mg phosphate or 300 mg base/dose) 0-11months ½ tab BID 1-3 y/o 1 tab BID 4-6 y/o 1 ½ tab BID 7-11 y/o 2 tabs BID 12-15 y/o 3 tabs BID ≥ 16 y/o 4 tabs BID If the patient cannot swallow the tablet, crush and dissolve in a small amount of water, juice, milk, or chocolate syrup to be given with meals.	5 days May be extended to 10 days depending on clinical status	- Hypersensitivity to 4-aminoquinolines - Presence of retinal or visual field changes - Epilepsy - Porphyria - Psoriasis
PLUS			

Azithromycin 200 mg / 5mL susp 500 mg tablet 500 mg vial	10 mg/kg QD (Max: 500 mg / day)	5 days	- Hypersensitivity to any macrolide - History of cholestatic Jaundice or hepatic dysfunction associated w/ prior use
AND			
Vitamin D3 (Cholecalciferol) 800 IU, 1000 IU, 2000 IU softgel cap	<2 years: 1,000 IU/day >2 years: 2,000 IU/day	5 days	
AND			
Zinc sulfate 27.5 mg/mL (equivalent to 10mg elemental Zn); 55mg / 5mL (equivalent to 20mg elemental Zn)	2 months - <5 years: 15mg elemental Zn BID 5 years and older: 20mg elemental Zn BID	7 days, then give regular RDA dose	

* There is a lack of high-quality evidence to conclude that chloroquine or hydroxy-chloroquine is effective and safe for the treatment of COVID-19. This is an off-label use, thus, close monitoring by health authorities and hospital administration is required and informed consent from the parent or legal guardian must be sought before initiation of treatment (see Appendix E).

Other antiviral therapy:

1) **Lopinavir/Ritonavir**
   - Not recommended to be used in children with severe COVID-19

2) **Ribavirin**
   - Not recommended to treat severe pediatric COVID-19, but may be used for coinfection with Respiratory syncytial virus (RSV)

3) **Oseltamivir**
   - Not recommended to treat severe pediatric COVID-19, but may be used for coinfection with Influenza virus

Adjunctive therapy:

1) **Corticosteroids**
   - Should not be routinely used to treat patients with COVID-19-associated pneumonia or ARDS
   - Corticosteroids may be given in the following cases:
     - Critically ill patients with a hyperinflammatory state or a clinical picture compatible with secondary hemophagocytic lymphohistiocytosis (HLH)
     - Septic shock if adequate fluid resuscitation and vasopressor therapy are not able to restore hemodynamic stability

- In the aforementioned situations, a low-dose corticosteroid (equivalent to methylprednisolone 1-2 mg/kg/day) given over a short course (3-5 days) may be used.

2) Intravenous Immunoglobulin (IVIG)

- IVIG can be used in severe/critical cases of COVID-19 when indicated as an immunomodulator, but its efficacy for COVID-19 in children needs further evaluation
- Recommended dose: 1 g/kg/day for 2 days or 400 mg/kg/day for 5 days

See Appendix C Monographs from the Philippine National Formulary 2019 for more information on hydroxychloroquine and chloroquine, and Appendix D 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.

D. Discharge Considerations

1. Children can be discharged from a health care facility once the following criteria are met:
    a. Body temperature is back to normal for more than three (3) days
    b. Respiratory symptoms have already improved
    c. Pulmonary imaging shows resolution of inflammation
    d. Although a negative nucleic acid test from respiratory tract samples is desirable, when the availability of tests is limited, patients may be discharged once clinically improved. Home isolation should be continued for 14 days after the resolution of symptoms (see part B. Discontinuation of Home Isolation for Patients with Suspected, Probable or Confirmed COVID-19). A repeat test can be done 14 days after discharge, to decrease the likelihood of a PCR test returning positive due to non-viable virus.

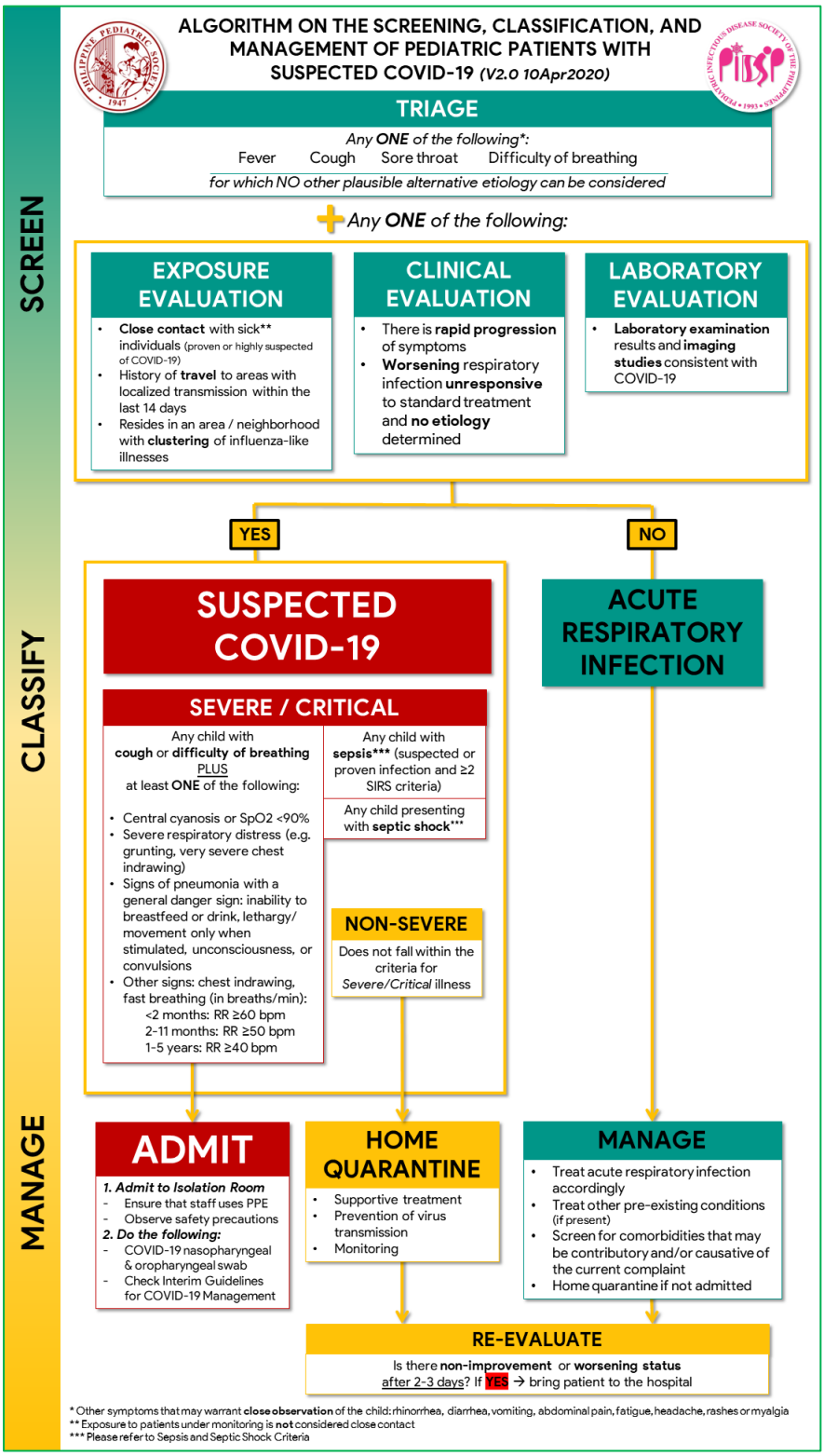
2. After discharge, ensure that the following considerations are kept in mind:

    a. Monitor health status in isolation for 14 days. See *Home Intervention* Section.
    b. Follow-up in 2 to 4 weeks after discharge.
    c. Once fully recovered, ensure that the child's immunizations are up to date. Consult the child's healthcare provider for proper scheduling.

Table 1. Classification of pediatric patients suspected or confirmed to have COVID infection based on severity of signs and symptoms

Classification	Signs and Symptoms	Management
NON-SEVERE	Non-specific symptoms such as fever, cough, sore throat, rhinorrea, diarrhea, vomiting, abdominal pain, fatigue, headache, myalgia	• Home isolation in single room • Maintain adequate hydration • Manage other symptoms as appropriate
SEVERE	Child with non-severe pneumonia has: • cough or difficulty breathing • fast breathing (in breaths/min): <2 months, ≥60 2–11 months, ≥50 1–5 years, ≥40 and no signs of severe pneumonia	• Admit to a designated isolation room • Manage as pediatric community-acquired • pneumonia (pCAP) A/ B • Manage other symptoms as appropriate
	Child with cough or difficulty in breathing, plus at least one of the following: • central cyanosis or SpO2 <90% • severe respiratory distress (e.g. grunting, chest indrawing) • signs of pneumonia with a general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions Other signs of pneumonia may be present: chest indrawing, fast breathing (in breaths/min): <2 months, ≥60 2–11 months, ≥50 1–5 years, ≥40	• Admit to a designated isolation room • Manage as pediatric community-acquired • pneumonia (pCAP) C • Manage other symptoms as appropriate
	Sepsis: suspected or proven infection and ≥2 SIRS criteria, of which one must be abnormal temperature or white blood cell count	
CRITICAL	Septic shock: any hypotension (SBP <5th centile or >2 SD below normal for age) or 2-3 of the following: • altered mental state • Tachycardia (HR > 160 bpm in infants or > 150 bpm in children) or bradycardia (HR <90 bpm in infants or <70 bpm in children) • prolonged capillary refill (>2 sec) or warm vasodilation with bounding pulses • tachypnea • mottled skin or petechial or purpuric rash • increased lactate • oliguria • hyperthermia or hypothermia	• Admit to a designated isolation room • Manage as pediatric community-acquired • pneumonia (pCAP) D • Manage other symptoms as appropriate
	New or worsening respiratory symptoms within one week of known clinical insult	Management will depend on classification of ARDS

Figure 1. **Algorithm on the screening, classification and management of pediatric patients with suspected COVID-19 (Version 2, as of 10 April 2020)**



Appendix A. Case Definitions for Surveillance

Source: World Health Organization. Global surveillance for COVID-19 caused by human infection with COVID-19 virus. Interim Guidance. 20 March 2020

Suspect case

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset;
OR
B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset;
OR
C. A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case

A. A suspect case for whom testing for the COVID-19 virus is inconclusive;
OR
B. A suspect case for whom testing could not be performed for any reason.

Confirmed case

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

Contact

A contact is a person who 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:

- Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;
- Direct physical contact with a probable or confirmed case;
- Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment; OR
- 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 was taken* which led to confirmation.

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

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

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

Pediatrician: (contact details / email address)

Appendix C. Monographs from the Philippine National Formulary 2019

HYDROXYCHLOROQUINE

Oral: 200 mg tablet (as sulfate)
NOTE: Hydroxychloroquine sulfate 200 mg is equivalent to 155 mg hydroxychloroquine base and 250 mg chloroquine phosphate.
Indications: Management of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA)
Contraindications: Pre-existing maculopathy of the eye; retinal or visual field changes attributable to 4aminoquinolines; long-term use in children
Dose:
Rheumatoid arthritis, *by mouth*, ADULT, initially 400 to 600mg daily taken with food or milk; increase dose gradually until optimum response level is reached; usually after 4–12 weeks dose should be reduced by ½ to a maintenance dose of 200 to 400 mg daily in 1–2 divided doses (maximum daily dose, 6.5 mg/kg or 400 mg, whichever is lower); CHILD, up to 6.5 mg/kg daily or 400 mg, whichever is lower. Lupus erythematosus, *by mouth*, ADULT, 400 mg 1–2 times daily for several weeks to months depending on response; 200–400 mg daily in 1 to 2 divided doses for prolonged maintenance therapy (maximum daily dose, 6.5 mg/kg or 400 mg, whichever is lower).
Dose Adjustment:
Renal and Hepatic Impairment:
Dose adjustment may be necessary.
Precautions:
WARNING: Should be prescribed only by physicians familiar with its use. May cause dizziness and blurred vision.
Cardiovascular effects e.g. rare cardiomyopathy in long term use; hematologic effect e.g. agranulocytosis, aplastic anemia, and thrombocytopenia;
Neuromuscular effects e.g. myopathy, neuromyopathy, and progressive weakness;
Ophthalmic effects e.g. loss of visual acuity, macular pigmentary changes, and loss of foveal reflex; G6PD deficiency; Hepatic impairment;
Porphyria and psoriasis;
Pediatric (use caution due to increased sensitivity to aminoquinolones).
Pregnancy (may decrease the incidence of cardiac malformations associated with neonatal lupus);
Lactation (excreted into breast milk).
SKILLED TASKS. May impair ability to perform skilled tasks,
such as operating machinery or driving.
Adverse Drug Reactions:
Common: Ataxia, dizziness, emotional disturbance, headache, irritability, lassitude, nerve deafness, nervousness, nightmares, psychosis, seizure, suicidal tendencies, vertigo, alopecia, bleaching of hair, bullous rash, dyschromia, exacerbation of psoriasis, pruritus, urticaria, exacerbation of porphyria, weight loss,
anorexia, diarrhea, nausea, stomach cramps, vomiting, agranulocytosis, anemia, aplastic anemia, hemolysis, leukopenia, thrombocytopenia, hepatic insufficiency, angioedema, myopathy, accommodation disturbance, corneal changes, decreased visual acuity, epithelial keratopathy, macular degeneration, macular edema, maculopathy, nystagmus, optic disk disorder (pallor/atrophy), retinal pigment changes, retinal vascular disease, retinitis pigmentosa, retinopathy, scotoma, vision color changes, visual field defect, tinnitus, bronchospasm, respiratory failure (myopathy related)

Less Common: Hypoglycemia (potentially fatal), keratopathy
Rare: Cardiomyopathy
Drug Interactions:
Avoid concomitant use with:
Increases risk of adverse or toxic effects of the following drugs:
Artemether, Dapsone (*hemolytic reactions*),
Lumefantrine, Mefloquine (*convulsions*; *QTcprolongation*)[if concomitant use cannot be avoided, delay administration of mefloquine until at least 12
hours after the last dose of hydrochloroquine]
Administration: Administer with food or milk.
Pregnancy Category: Not classified
ATC Code: Not available

CHLOROQUINE

Oral: 250 mg tablet (as phosphate or diphosphate) (150 mg base)
Inj.: 50 mg/mL (as phosphate or diphosphate), 20 mL vial (IM, IV) An aminoquinoline antimalarial, found effective in extra intestinal amoebiasis
Indication: Treatment of extraintestinal amoebiasis
Contraindications: Presence of retinal or visual field changes either attributable to 4aminoquinoline compounds or any other etiology; patients with epilepsy
Dose:
Extraintestinal amoebiasis, *by mouth*, ADULT, 1 g (600 mg base) on day 1, followed by 500 mg (300 mg base) after 6 hours, 24 hours, and 48 hours following the first dose, may
be combined with an intestinal amebicide.
Hepatic amoebiasis, *by mouth,* ADULT, 600 mg (as base) daily for 2 days, then 300 mg daily for 2 or 3 weeks given with emetine or dehydroemetine; CHILD, up to 3 mg/kg daily (maximum daily dose, 300 mg).
Dose Adjustment:
Renal Impairment:
For mild-to-moderate renal impairment, dose reduction is warranted.
For severe impairment, the patient should be referred to a specialist.
Precautions:
G6PD deficiency; Psoriasis may be worsened. Porphyria cutanea tarda
Epilepsy; May aggravate myasthenia gravis; neurological disorders. QT interval
Renal impairment; hepatic impairment (avoid concurrent therapy with hepatotoxic drugs); severe GI disorders.
Pregnancy (in the first trimester of pregnancy, quinine in combination with clindamycin for 7 days is the treatment
of choice – this combination can be used throughout pregnancy; in acute malaria and third trimester: benefit of prophylaxis and treatment outweighs risk).
NOTE: If clindamycin is not available, then quinine should be given as monotherapy.
Breastfeeding (at doses used for malaria prophylaxis; amount in milk is probably too small to be harmful, and inadequate for reliable protection against malaria in the breastfed infant; avoid breastfeeding when used for rheumatic disease).
NOTE: If the patient continues to deteriorate after chloroquine medication – suspect resistance and administer quinine IV as an emergency measure.

Adverse Drug Reactions:
Common: GI disturbances, itch, lack of appetite, pruritus, skin eruptions, weight loss
Less Common: Anxiety, confusion, dizziness, drowsiness, headache, hypotension, irreversible retinopathy, paresthesia, personality changes, psychotic episodes, reversible corneal opacities, sleep disorders, vertigo, visual disturbances
Rare: Hypersensitivity reactions, pancytopenia, porphyria, prolonged QT interval, psoriasis, neuromyopathy, seizure, rash, Steven-Johnsons Syndrome, thrombocytopenia, tinnitus, toxic epidermal necrolysis, CV collapse (potentially fatal); convulsions (potentially fatal); coma (potentially fatal)
Drug Interactions:
NOTE: Chloroquine has a long half-life; consequently, the potential for drug interactions may persist for weeks after it has been stopped.
Monitor closely with: Reduces the absorption of Chloroquine: Antacids (e.g. Aluminum or Magnesium Hydroxide)
Avoid concomitant use with:
Increases risk of adverse or toxic effects of the following drugs:
Artemether + Lumefantrine (*potentially hazardous interactions*), Drugs which prolong QT Interval (*arrhythmia*; *prolonged QT interval*), Other Antimalarials e.g. Mefloquine (*arrhythmia*; *prolonged QT interval*)
Administration: To avoid nausea and vomiting, tablets should be administered after meals.
NOTE: If part or all of a dose is vomited, re-administer the same amount.
Pregnancy Category: C
ATC Code: P01BA01

Appendix D. Rationale for Recommendations of the Experimental Therapeutic Interventions for Severe PUI and Confirmed COVID-19 in Children

Since the SARS-COV2 is a newly detected virus and COVID-19 cases were only diagnosed in January 2020, there is very scarce data on the treatment and prevention of this illness in adults, more so in children. At the moment, only investigational drugs are being recommended for adults and clinical trials are still underway. Ethically, new drugs are tested first in adults prior to 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 2143 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. This is also the reason for recommending the antiviral agents 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.

1. **Recommendation: Hydroxychloroquine or chloroquine may be used to treat pediatric patients with severe COVID-19 disease**.
   Informed consent must be obtained prior to prescribing hydroxychloroquine or chloroquine pediatric COVID-19 patients.

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 to treat autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. In vitro studies have revealed their direct anti-viral activity against SARS-COV2 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. More evidence from ongoing clinical trials is expected soon. Since there is a lack of high-level evidence for use in the pediatric age group, it is recommended that hydroxychloroquine or chloroquine should only be used for children with severe COVID-19 disease. Azithromycin was added as it showed higher viral clearance in the French study. It may also be used for patients wherein a bacterial respiratory infection cannot be ruled out.

2. **Recommendation: Zinc may be given to pediatric patients with severe COVID 19**.

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 (WHO, 2011). In the Philippines, the prevalence of zinc deficiency in the young population is as follows: pre-school children 6 months to < 5 years, 21.6%; school children 6 to 12 years, 30.8%; and adolescents 13 to 19 years, 28.9% (Marcos, 2015). 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 (Awotiwon, 2017). Zinc supplementation has a role in the early cure of pneumonia and it also decreased the total hospital stay of children with severe pneumonia (Shezad, 2015). It reduced the number of days of acute lower respiratory Tract Infection (ALRI) in Thai children, as well as their stay in the hospital. (Reksuppaphol, 2019) 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 (Sakulchit, 2017). 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 (te Velthuis, 2010). Previous *in vitro* study has shown that chloroquine, an antimalarial agent, acts as a zinc ionophore in human ovarian cancer cells (Xue, 2014). Zinc supplement may affect not only COVID-19-related symptoms like diarrhea and lower respiratory tract infection but also on the SARS COV2 virus itself. (Zhang, 2020).

3. **Recommendation: Vitamin D_3 may be given to pediatric patients with severe COVID 19**.

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 (Lei Zhang, 2020). Vitamin D boosts immune defenses and reduces excessive inflammation. Low levels of vitamin D are associated with respiratory tract infections (Bergman, 2013). 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 (Angeles-Agdeppa, 2019). The overall prevalence of combined vitamin D deficiency (<50 umol/L) and insufficiency (51-75 umol/L) was 48.7% among Filipino adults (Angeles-Agdeppa, 2013).
Vitamin D reduces the risk of RTIs through several mechanisms. Vitamin D helps maintain tight junctions, gap junctions, and adherens junctions (Schwalfenberg, 2011). Several studies discussed how viruses disturb junction integrity, increasing infection by the virus and other microorganisms (Kast, 2017) (Chen, 2020) (Rossi, 2020). This action by viruses is an important reason why viral infections progress to pneumonia. Vitamin D enhances cellular natural 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 (Huang, 2020). Vitamin D supplementation may be used as an adjunct to antibiotics for the treatment of acute childhood pneumonia (Rashmi, 2018). 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.

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

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. A systematic review of its use in SARS-CoV and MERS-CoV infections showed the treatment of patients with LPV/r improved outcomes. The review included a retrospective matched cohort study of SARS patients which showed that treatment with LPV/r was associated with an improved clinical outcome, especially when given in the early stage of the disease. Treatment with LPV/r alone or in combination with other antiviral drugs was also shown to improve clinical outcomes in case reports of MERS patients.

A retrospective study of 36 pediatric patients (aged 0–16 years) with confirmed COVID-19 from Zhejiang received interferon-alpha, while 14 patients (39%) received lopinavir-ritonavir syrup twice a day, and six (17%) needed oxygen inhalation. Results showed mean time in the hospital was 14 days and all patients were cured.

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. The study enrolled 199 patients with and an oxygen saturation (Sao2) of 94% or less while they were breathing ambient air. Patients were randomly assigned in a 1:1 ratio to receive either LPV/r twice a day for 14 days, in addition to standard care, or standard care alone. 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). Secondary outcomes, on the other hand, show that 28-day mortality was numerically lower in the treatment group than in the standard-care group but was not significant; there was no significant difference in viral shedding as well as for other outcomes such as duration of oxygen therapy, duration of hospitalization, and time from randomization to death.

5. **Recommendation: Ribavirin is not recommended to treat severe pediatric COVID-19, but may be used for coinfection with Respiratory syncytial virus (RSV).**

Ribavirin is a broad-spectrum nucleoside analog antiviral with activity against many RNA and DNA viruses such as human metapneumoviruses and some coronaviruses. However, in vitro testing showed it has no selective antiviral activity against SARS-COV2. Ribavirin administered intravenously was used combination with interferon-alpha or lopinavir/ritonavir which showed a lower risk of ARDS and death among patients who had SARS-COV1 infection. But ribavirin was not efficacious in several clinical studies on SARS-CoV2. The patients who received ribavirin had a fatal outcome and still had PCR evidence of SARS-COV2 in the lung. The use of ribavirin has also been associated with significant toxicity such as hemolysis and anemia.

6. **Recommendation: Corticosteroids should not be routinely used to treat patients with COVID-19-associated pneumonia or ARDS. Corticosteroids may be given in the following cases:**
    - **Critically ill patients with a hyperinflammatory state or a clinical picture compatible with secondary hemophagocytic lymphohistiocytosis (HLH)**
    - **Septic shock if adequate fluid resuscitation and vasopressor therapy are not able to restore hemodynamic stability.**
    - **In the aforementioned situations, a low-dose corticosteroid (equivalent to methylprednisolone 1-2 mg/kg/day) given over a short course (3-5 days) may be used.**

Controlled clinical trials on the use of corticosteroids in treating COVID-19 pneumonia or other severe acute respiratory infections caused by coronaviruses in children are lacking. A published, but not peer-reviewed, report (pre-print) of 26 adult patients with severe COVID-19 pneumonia demonstrated that the use of methylprednisolone at 1-2 mg/kg/day for 5 to 7 days was associated with shorter duration of supplemental oxygen (8.2 days vs 13.5 days; $p<0.001$) and better radiographic findings. However, since this study was among adults, was retrospective in nature, with the possible risk of confounding, the evidence is insufficient to formulate definite recommendations. Indirect evidence was therefore used from studies on corticosteroids in other respiratory viral infections and pediatric ARDS.

A randomized controlled trial of dexamethasone for bronchiolitis in the pediatric population showed no significant difference in clinical outcomes (rate of admission and improvement in rapid assessment change score) between the dexamethasone group and the placebo group. A meta-analysis in adults with influenza pneumonia showed higher mortality, a longer length of ICU stay, and higher rates of secondary infection in the corticosteroid group compared to placebo. In another systematic review, corticosteroid use in SARS patients did not show a survival benefit and may cause harm (delayed viral clearance, psychosis, diabetes, avascular necrosis, and osteoporosis).

For ARDS in children, a single randomized controlled trial in a small population (N=35) showed higher PaO_2/FiO_2 ratios in the steroid group on days 8, and fewer patients required supplemental oxygen at PICU transfer. However, there was no significant difference in length of ICU stay, length of hospital stay, ventilator-free days, or hospital mortality. According to the Pediatric Acute Lung Injury Consensus Conference Group, corticosteroids cannot be recommended as routine therapy in pediatric ARDS due to lack of evidence.

However, recent studies from China have shown that severe COVID-19 is associated with a hyperinflammatory state, with elevated cytokine levels reminiscent of a secondary HLH. Corticosteroids and other immunosuppressive agents can be used in patients with a high likelihood of HLH.

7. **Recommendation: Intravenous Immunoglobulin (IVIG)**

- **IVIG can be used in severe cases of COVID-19 when indicated as an immunomodulator, but its efficacy for COVID-19 in children needs further evaluation**
- **Recommended dose: 1 g/kg/day for 2 days or 400 mg/kg/day for 5 days**

The use of intravenous immunoglobulin (IVIG) has been reported in a few descriptive studies of adult COVID-19 patients, and even less in pediatric patients. There are no randomized controlled trials or efficacy data available.

In a pediatric report of 10 cases of COVID-19 in Guangzhou China, 1 patient was given IVIG at 300 mg/kg/day for 3 days, with good clinical outcome. In another report on 8 severe COVID-19 pediatric patients, 4 were given IVIG together with virazole, oseltamivir, and interferon. Out of the 4, 2 were discharged, while 2 remained in the ICU during the time of publication. In other larger case series of pediatric patients, most cases were mild and none were given IVIG. In adult studies that reported the use of IVIG, treatment was mostly multimodal, therefore, are not conclusive on the effects of IVIG alone. Furthermore, a trial on antibody-based therapies (immune plasma, hyperimmune globulin, monoclonal antibody) in seasonal influenza did not demonstrate a benefit in clinical outcomes.

For severe COVID-19 patients, similar to SARS, IVIG is primarily used as an immunomodulator to inhibit the production of proinflammatory cytokines and increase the production of anti-inflammatory mediators. It has been hypothesized that IVIG at 0.3 – 0.5 g/kg/day given for 5 days, would be best given early, between 7-10 days after infection, to interrupt the cytokine storm and enhance immune function. However, clinical trials are needed to support this theory. A randomized controlled clinical trial of IVIG in patients with severe COVID-19 is underway (NCT 04261426).

Appendix E. 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]***

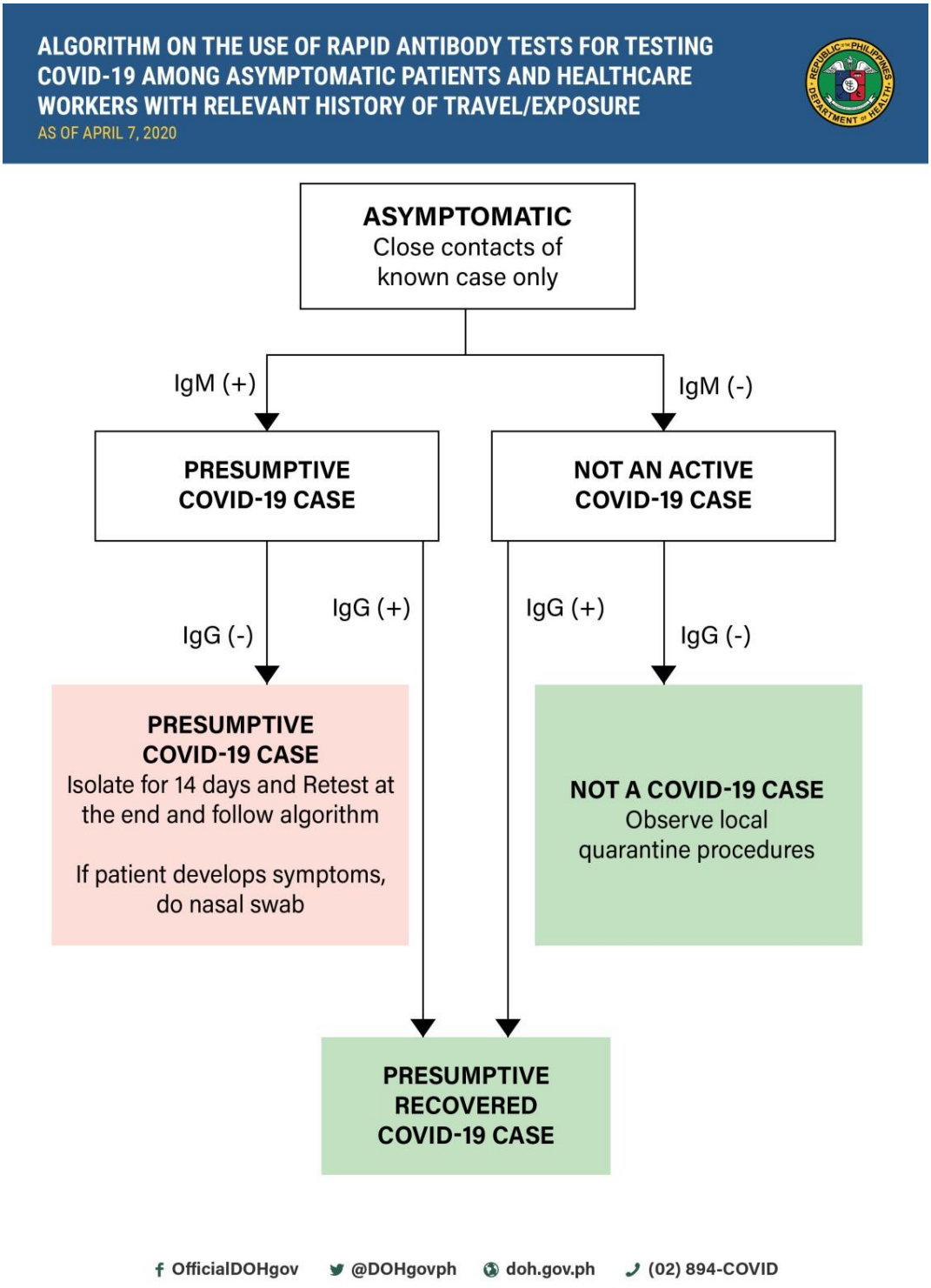
This treatment is subject to oversight by this hospital's Institutional Ethics/ Review Board/ Committee. If you have questions about your rights or any unresolved question, concerns, or complaints, talk to them at _____ ***[Insert contact information]***.

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	

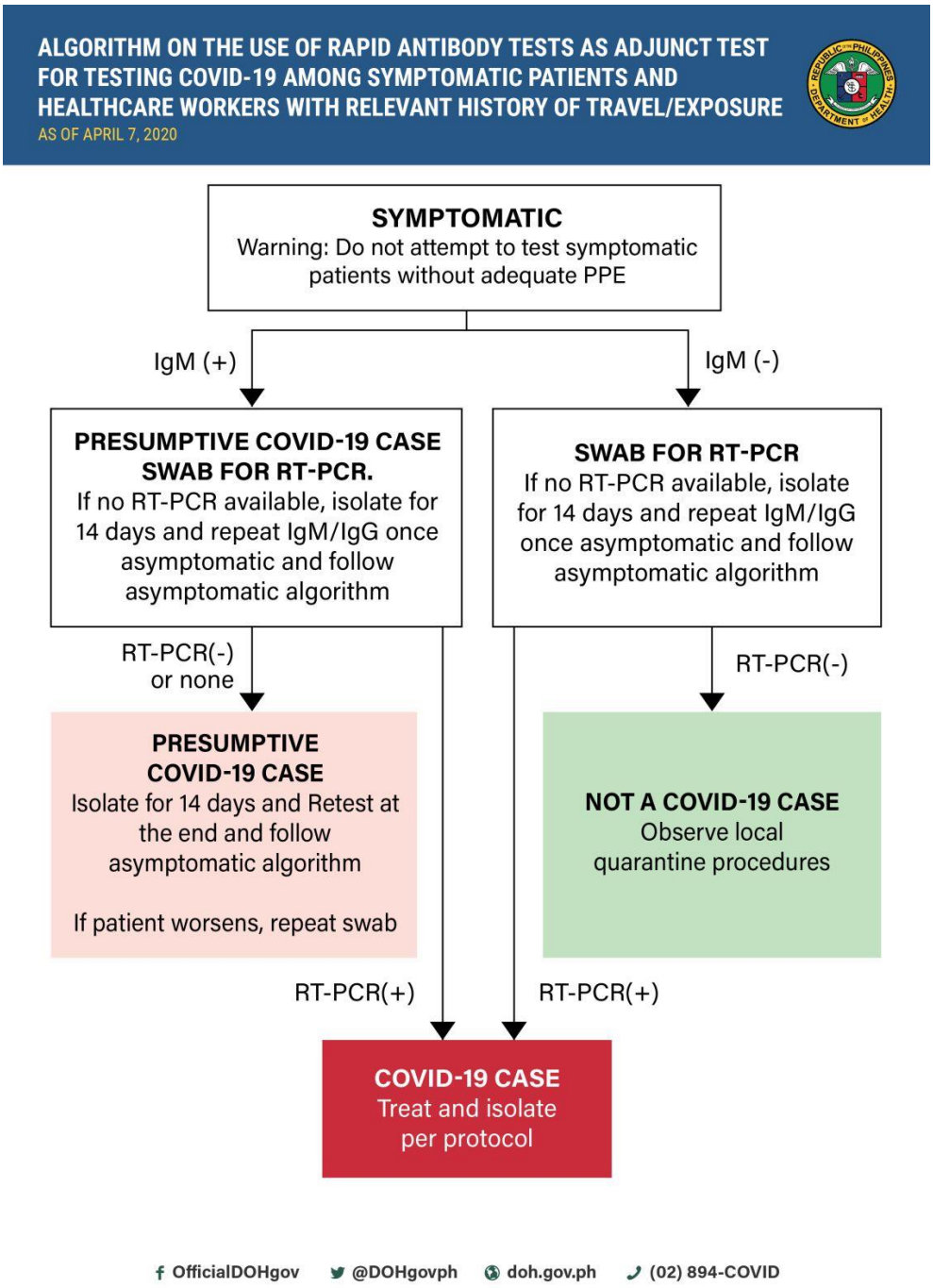
*Informed Consent Form replicated from Philippine Society for Microbiology and Infectious Diseases INTERIM GUIDELINES ON THE CLINICAL MANAGEMENT OF ADULT PATIENTS WITH SUSPECTED OR CONFIRMED COVID-19 INFECTION *Version 2.1, as of 31 March 2020*

Appendix F.1 Algorithm on Use of Rapid Antibody Tests (Asymptomatics)



Source: Department of Health. 2020. Department Memorandum 2020-00151. Interim Guidelines on Expanded Testing for COVID-19.

Appendix F.2 Algorithm on Use of Rapid Antibody Tests (Symptomatics)



Source: Department of Health. 2020. Department Memorandum 2020-00151. Interim Guidelines on Expanded Testing for COVID-19.

QUESTIONS AND ANSWERS ON COVID 19

30 March 2020

EPIDEMIOLOGY	
1. What is COVID-19?	**COVID-19** is the infectious disease caused by the newly discovered coronavirus. The virus causing this disease is the severe acute respiratory syndrome coronavirus 2 or **SARS CoV-2,** a betacoronavirus that is closely linked to the severe acute respiratory syndrome (SARS) virus.
TRANSMISSION	
2. How does COVID-19 spread?	COVID-19 disease can spread from person-to-person through small droplets released from the nose or mouth when a person coughs, sneezes or talks. People get infected when these droplets land directly on the mucosal surfaces of the eyes, nose or mouth or when they breathe in these infectious droplets when in close proximity (distance is less 1 meter or 3 feet away) from an infected person Infectious droplets can also land on objects and surfaces around the person (droplet transmission). People can also get infected when they touch these infected objects or surfaces then touch their eyes, nose or mouth (contact transmission).
3. Who are considered as close contacts?	*Close contact* is defined by the World Health Organization as a person who is involved in any of the following from 2 days before and up to 14 days after the onset of symptoms in the confirmed or probable case: (a) having face-to-face contact with a COVID-19 patient within 1 meter and for >15 minutes; (b) providing direct care for patients with COVID-19 disease without using proper personal protective equipment; (c) staying in the same close environment as a COVID-19 patient (including sharing a workplace, classroom or household or being at the same gathering) for any amount of time; (d) travelling in close proximity with (that is, within 1 m separation from) a COVID-19 patient in any kind of conveyance; and (e) other situations, as indicated by local risk assessments.
4. Can the virus that causes COVID-19 be transmitted through the air?	Studies to date suggest that the virus that causes COVID-19 is mainly transmitted through contact with respiratory droplets rather than through the air and do not appear to linger in the air. Airborne transmission from person-to-person over long distances is unlikely. However, there are still uncertainties regarding transmission of SARS-CoV-2 hence, airborne precautions (N95 mask, eye goggles, gown,cap) are recommended when performing aerosol-

	generating procedures, such as during nebulization, open suctioning of respiratory tract, intubation, bronchoscopy, cardiopulmonary resuscitation.
5. Can COVID-19 be caught from a person who has no symptoms?	The main way the disease spreads is through respiratory droplets expelled by someone who is coughing sneezing and talking. The risk of catching COVID-19 from someone with no symptoms at all is very low. However, many people with COVID-19 experience only mild symptoms. This is particularly true at the early stage of the disease. It is therefore possible to catch COVID-19 from someone who has, for example, just a mild cough and does not feel ill. There is ongoing research on the period of transmission of COVID-19 and findings may change based on the results.
6. Can COVID-19 be transmitted from the feces of someone with the disease?	Live virus has been cultured from feces but the risk of transmission through the fecal-oral route, particularly for infants and children who are not toilet-trained. appears to be low. There have been no reports of fecal−oral transmission of the COVID-19 virus to date. However, since there still is a possible risk, it is advised to clean hands regularly, especially after using the bathroom, handling soiled linens and before eating.
7. Can SARS-CoV-2 be transmitted by breastfeeding?	Breastfeeding offers several protective effects that may be able to protect against increased mortality and morbidity from infectious diseases. The risk of transmission from breastmilk is low because breastmilk samples from the mothers after the first lactation were found to be negative for SARS-CoV-2. However, because of the close contact between the mother and child during breastfeeding, droplet and contact transmission of the virus can occur.
8. What precautions can be taken by mothers who choose to continue breastfeeding?	Mildly symptomatic mothers who are suspected or confirmed to have COVID-19 who choose to breastfeed their infant should wear a surgical face mask at all times, cover nose and mouth during coughing or sneezing with tissue or flexed elbow, practice hand hygiene before and after touching or carrying the infant, and routinely clean and disinfect surfaces which the symptomatic mother has been in contact with. In symptomatic mothers with severe COVID 19 or who have complications that prevent her from caring for her infant, separation of the mother and infant may be necessary. The following feeding alternatives may be given to mothers who are not able to breastfeed or express

	breastmilk: relactation, wet nursing, donor human milk or appropriate breastmilk substitutes.
CLINICAL SYMPTOMS	
9. What are the symptoms of COVID-19 in children?	In the largest epidemiologic study involving 2143 pediatric patients with COVID-19 from Hubei province and the bordering provinces in China, majority were mild cases with only one mortality (*Dong Y, Mo X, Hu Y, et al. Pediatrics. 2020).* The severity of illness based on defined criteria were as follows: • 4.4 % were **asymptomatic** • 50.9 % had **mild disease**- symptoms of upper respiratory infection, i.e. fever, cough, sore throat, runny nose, sneezing; some presented only with digestive symptoms such as nausea, vomiting, abdominal pain and diarrhea • 38.8 % had **moderate symptoms**- pneumonia with no hypoxemia or lung lesions on chest CT • 5.9% were **severe and critical disease** - severe symptoms included progressing respiratory symptoms such as hypoxemia (oxygen saturation < 92%) and cyanosis which may be concomitant with gastrointestinal symptoms such as diarrhea; critical cases were children with respiratory failure, ARDS, shock, encephalopathy and organ dysfunction including myocardial injury or heart failure, coagulation dysfunction, and acute kidney injury. Most of those with severe or critical illness were pre-school children below 5 years old and infants below 1 year old.
10. Is hospital admission necessary for all children suspected or confirmed to have COVID-19 and who develop fever and mild respiratory symptoms?	Patients with mild disease do not require hospital interventions unless there is concern for rapid deterioration or an inability to promptly return to a designated COVID-19 hospital if they get worse. Patients should have none of the criteria for severe disease. Mild disease may include those with uncomplicated upper respiratory tract infection, those with non-specific symptoms such as fever, fatigue, cough with or without sputum production, anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, or headache. This also includes patients with diarrhea, nausea and vomiting who can be hydrated in the home setting. They should be instructed to comply with home isolation procedures according to local/regional public health protocols.

11. What isolation measures should be practiced at home for children with mild symptoms who are PUIs or confirmed COVID-19?	The following home isolation measures should be followed for children who are PUIs or COVID-19 with mild symptoms in order to prevent transmission within the household or community: ● 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 (i.e. open windows, 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 careaker 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 be provided with separate dishes, drinking glasses, cups, eating utensils, towels, and beddings for his / her own use ● The child and household members should wear a surgical face mask when in the same room or when interacting inside the home. ● 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.
12. Who among the children with suspected, probable or confirmed COVID-19 need hospital admission?	Patients with severe symptoms should be admitted to the hospital. Criteria for **Severe** symptoms are the following: 4. Any child with cough or difficulty of breathing PLUS at least ONE of the following: a. Central cyanosis or SpO2 <90% b. Severe respiratory distress (e.g. grunting, chest indrawing) c. Signs of pneumonia with a general danger sign: inability to breastfeed or drink, lethargy/movement only when stimulated, unconsciousness, or convulsions d. Other signs: chest indrawing, fast breathing (in breaths/min): a. <2 months: RR ≥60 breaths per minute

	b. 2-11 months: RR ≥50 breaths per minute c. 1-5 years: RR ≥40 breaths per minute 5. Any child with suspected or proven infection and ≥2 SIRS criteria, of which one must be abnormal temperature or white blood cell count (sepsis) 6. Any child presenting with septic shock, defined as hypotension (SBP <5th centile or >2SD below normal for age) or at least 2 of the following: a. Altered mental state b. Tachycardia or bradycardia (HR <90 bpm or >160 bpm in infants and HR <70 bpm or >150 bpm in children) c. Prolonged capillary refill (>2 sec) or warm vasodilation with bounding pulses d. Tachypnea e. Mottled skin or petechial or purpuric rash f. Increased lactate g. Oliguria h. Hyperthermia or hypothermia
CLINICAL EVALUATION	
13. How should children with suspected COVID 19 who are asymptomatic or have mild symptoms be evaluated without bringing them to the hospital?	The healthcare provider can interview the asymptomatic / mildly symptomatic PUI (or his / her adult caregiver) by telephone, text monitoring system, or video conference. Temperature monitoring could be reported by phone or shown to a provider via video conferencing. Those who do not improve despite supportive or specific measures after 2-3 days should be instructed to inform the healthcare provider for further evaluation.
DIAGNOSIS	
14. What is the recommended diagnostic test to confirm the diagnosis of COVID -19?	The diagnosis of COVID-19 can only be confirmed via detection of the causative agent SARS-CoV-2 using nucleic acid testing such as reverse transcriptase polymerase chain reaction (RT-PCR) or other PCR-based test. The preferred specimen is the nasopharyngeal swab; oropharyngeal swab may be added.
15. What is the role of antibody tests (IgM/IgG) in the diagnosis of COVID-19?	Specific antibodies (IgM and IgG) against the SARS-CoV-2 are produced after infection and can be detected by a variety of methods, e.g. immunochromatography, ELISA, chemiluminescence immunoassay, etc. However, these tests are not useful for early detection of disease because IgM is detectable 5-10 days after symptom onset and IgG is detectable 21 days after symptom onset. Currently there are several Philippine FDA-registered IgM/ IgG rapid diagnostic tests. Based on DOH guidelines, these tests are to be used in limited settings and in conjunction with RT-PCR tests.

MEDICATIONS	
16. Are antibiotics effective in preventing or treating the COVID-19?	Antibiotics do not work against viruses; they only work on bacterial infections. COVID-19 is caused by a virus, so antibiotics generally do not work. Chloroquine or hydroxychloroquine (antimalarial drugs) combined with azithromycin (an antibiotic) has been tried based on in-vitro studies showing anti-viral activity against SARS-COV-2 and immunomodulatory properties. Preliminary studies have demonstrated viral clearance but further investigation is warranted. Due to the risk of adverse effects, these drugs should only be used upon the recommendation of a physician.
17. Are there any medicines or therapies that can prevent or cure COVID-19?	While some western, traditional or home remedies may provide comfort and alleviate symptoms of COVID-19, there is no evidence that current medicine can prevent or cure the disease. Currently there are investigational antibiotics, antivirals, etc being recommended but since they need futher investigation and bec the disease is generally mild in children we only recommend them for severe disease, and that recommendations may change as we gain more evidence. WHO does not recommend self-medication with any medicines, including antibiotics, as a prevention or cure for COVID-19. WHO will continue to provide updated information as soon as clinical findings are available.
DISINFECTION AND SANITATION	
18.How long does the virus survive on surfaces?	It is not certain how long the virus that causes COVID-19 survives on surfaces, but it seems to behave like other coronaviruses. Studies suggest that coronaviruses (including preliminary information on the COVID-19 virus) may persist on surfaces for a few hours or up to several days (e.g. up to 72 hours on plastic and stainless steel surfaces). Viability of the virus vary under different conditions (e.g. type of surface, temperature or humidity of the environment). If you think a surface may be infected, household disinfectants can kill the virus and protect yourself and others. If surfaces are dirty, they should be cleaned using a detergent or soap and water prior to disinfection. For disinfection, diluted household bleach solutions (5 tablespoons bleach +1 gallon of water), alcohol solutions with at least 70% alcohol, and most common household disinfectants should be effective.

	After disinfecting surfaces, clean your hands with an alcohol-based hand rub or wash them with soap and water. Avoid touching your eyes, mouth, or nose.
19. What is the proper way to handle soiled beddings, towels and clothes from PUIs or confirmed COVID-19 patients?	The following are recommended when handling soiled beddings, towels and clothes from PUIs or confirmed COVID-19 patients: ● Do not shake dirty laundry; this minimize the possibility of dispersing virus through the air. ● Clothes/beddings/pillows/stuffed toys used by the child must be washed separated. • Machine wash 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 excreta are on surfaces of linen or towels, the excreta 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 while handling soiled items. Place all used disposable gloves, facemasks, 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.

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