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EDITORIAL

PONDERING AMIDST THE PANDEMIC

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Who would have thought that amidst the new year revelries last December, in Wuhan China, a different kind of explosion surfaced, which we now know as COVID-19. A month later, on 30 January 2020, the outbreak was declared a Public Health Emergency of International Concern. As history unfolds, we find ourselves each day seeking new information to cope with this pandemic.

There are several lessons to take from this crisis, and they are the same insights from of old:

..that human health is priceless, and each day is a gift and a blessing,

..that our health and that of our planet are inseparable,

..that a global threat needs a global response,

..that there is wisdom in the adage 'Prevention is better than Cure',

..that we all have a role to play in the battle of our lifetime, and

..that there is a need to unite through science to win this war.

In this issue we bring you relevant science on challenges which came way before COVID-19.

Flu is highlighted in 'Clinical Profile and Outcome of Admitted Pediatric Patients with Influenza'. Dengue is brought to the forefront in 'Development of A Clinical Risk Score to Diagnose Concurrent Bacterial Infections in Children with Dengue'.

Concerns with antimicrobial resistance are dealt with on 'Effectiveness and Adverse Effects of IV Colistin in Neonates with MDR Gram Negative Bacterial Infections' and 'Utility of Urine KOH in detecting Candiduria in Infants'.

Issues on vaccination are discussed in 'Validation of the Filipino Translated Questionnaire on Parent Attitudes About Childhood Vaccines'.

As the focus continues on COVID-19, we share with you PPS-PIDSP's collaborative outputs and guidelines on Screening and Treatment, Resumption of OPD Clinics, and Vaccination. Reflections in 'Scenarios After Enhanced Community Quarantine for COVID-19 Pandemic in the Philippines…What Can We Do as Filipinos?' caps this issue.

May we continue to utilize science as we seek for answers to our day to day problems. Where science yields no answer, may frequent pauses in our lives help us realize that not all questions need to be answered. In the end, what matters is our tireless search for the truth and the realization that not everything is within our control.

(Written with thoughts and in loving memory of Dr. Salvacion R. Gatchalian, mentor, colleague, friend)

FEATURE ARTICLE

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SCENARIOS AFTER ENHANCED COMMUNITY QUARANTINE FOR COVID 19 PANDEMIC IN THE PHILIPPINES… WHAT CAN WE DO AS FILIPINOS

To date, the Philippine lockdown has been successful. The country had a cumulative total of 9,223 cases, with 295 new ones, on May 3, 2020[1] while the U.S.A. had 1,133,069 cases and 30,000 new cases/day on May 1, 2020.[2] As the American lockdown was not uniformly done across the 50 states, the U.S. has done disproportionately much worse than the Philippines, considering that the former's population is only three times that of ours. Indeed, our 200-300 new cases per day, for a country of 110 million, is low; we cannot realistically achieve an actual figure of zero.

However, if this was a war, the lockdown was a unilateral cessation of hostilities declared by the government against an invisible vicious enemy, as our leaders realized that its soldiers and machinery were not prepared and equipped for a serious battle. In health care, the lockdown was a delaying tactic for an immunologically unequipped population. As the six-week respite dragged on, the number of confirmed COVID-19 cases on May 3, 2020 only comprised 0.008% of the country's total population. This means that a vast number of Filipinos will still not be immune to COVID-19 when they go out of their homes when the lockdown is lifted; people will still be at risk for infection. Put another way, the successful social distancing program, or lockdown, saved many people from illness and death, but has led to almost no immunity for the population.[3]

Indeed, the purpose for the government's extension of the lockdown to May 15, 2020, was mostly because the preparation of the local government units (LGUs), the capacity of hospitals and the health care system, and the knowledge of our people, were still far from adequate.

We need to continue to educate everyone that the COVID-19 virus has high infectivity, high pathogenicity, and high virulence, in a rarely-seen, propagative, pandemic setting, where the population has no pre-existing immunity. The feared polio virus, has high infectivity, but low pathogenicity & low virulence; only a small fraction of the infected develop paralytic disease.

On the other hand, like COVID-19, the measles virus has high infectivity, pathogenicity and virulence, but nearly twelve centuries of measles spread throughout the human population, in addition to an effective vaccine since 1963, have provided the world with herd immunity to measles long ago. No such herd immunity exists for COVID-19. It is estimated that two-thirds of the population have to become ill and recover, or be vaccinated, for herd immunity to be achieved, and for this pandemic to stop.[4]

What do we expect after May 15, when the enhanced community quarantine is lifted in Metro Manila? Take a look at what happens, if a small, urban city in the metropolis, has 20 infected & contagious people on that date, and these people go out of their homes without masks & do not practice physical distancing, with these scientific assumptions:[5] COVID-19's median incubation period is 6 days[6], reproduction number, the number of secondary cases arising from one index case is 2.5 people[6], and 80% of COVID-19 cases are asymptomatic or mildly ill and 20% will need hospitalization while 6.7% will die.[7]

Assuming this city has 20 people with active COVID-19 on May 15, how will this number grow over time? May 15: 20 cases; May 21: 20+50 = 70 cases; May 27: 70 + 125 = 195 cases; June 3: 195 + 313 = 508 cases; June 9: 508 + 783 = 1,291 cases; June 15: 1,291 + 1,958 = 3,249 cases; June 21: 3,249 + 4,895 = 8,144 cases; June 27: 8,144 + 12,238 = 20,382 cases; July 3: 20,382 + 30,595 = 50,977 cases.

If, of the 50,977 cases by July 3rd, 20% will need hospital care, this figure will be 10,195 between roughly May 21 to July 3, for a small urban city alone, and the deaths will total 3,415 by July 3. The above projection is based on the assumption that there will be no barriers (i.e., people do not wear masks, do not practice social distancing) for the spread of the highly infective virus in a community with no innate COVID-19 immunity. Since the country is made up of 7,000 islands, with rivers, straits, lakes, seas, hills, mountains, forests and homes, which are natural and physical barriers to spread, people in far-flung provinces like Batanes or Tawi-tawi, for example, are at less risk of COVID-19 today, just because of their physical distance away from Metro Manila. The virus has to travel, through infected people, by land, sea or air, to get from one point to the next. However, humans are not barriers because very few possess immunity, so that in urban areas like Cebu and Davao, where natural barriers are less, population density is high, and the ease of contagion is greater, spread will occur and will do so exponentially. This has happened in cluster outbreaks in Cebu and the penitentiaries.[7] When clusters are not contained, more sustained local spread will follow.

For the example above, no Philippine city has 10,000 beds to cater to such a demand over a span of six weeks. Even if the above projection is off by 90%, the hospital system will collapse. The National Capital Region (NCR) had a total bed (private and public) capacity of 29,723 in 2016; the total bed capacity of the whole country then was 101,688.[8] At present, the DOH counts that, with 95% of healthcare facilities reporting, the available COVID-dedicated beds in the Philippines are: 1,251 intensive care unit beds; 8,231 isolation beds; 2,587 ward beds and 1,825 mechanical ventilators. Community isolation facilities have a total of 12,413 beds.[9] With a total of 12,069 COVID-19-dedicated beds for the whole country, we have a bed capacity of 1.1 beds per 10,000 population.

Thus, with our limited hospital bed capacity, the only way that the above scenario can be avoided is if we, as a people, have the discipline and

determination, over months and years to come, to decrease the virus' spread when the lockdown is lifted. Meanwhile, administrators of government and private hospitals will have to make their best efforts to prepare, brace, equip, and boost the capabilities and capacities of our healthcare system, especially critical care capacity.[3] A new segment in this healthcare system is the quarantine facilities in each town and city, that will serve as hospital extenders.

To prepare our healthcare system, this is the healthcare bundle that each LGU ideally should have. These measures have been found to be effective in China.[10] The first seven are W.H.O. recommendations.[11, 12]

1. Every person who has COVID symptoms should be tested.[7] The Philippines has 20 laboratories doing over 5,000 tests per day. Will this be adequate for the whole country, considering that the total number of people tested since the pandemic started has been 126,124 as of May 3, or only 1.3% of the Philippine population?

2. Multiple COVID-19 tracking teams should account for all suspect, probable and confirmed COVID-19 patients, and their contacts. The W.H.O. prescribes the quarantining of COVID-19 contacts, but asymptomatic and mildly ill COVID-19 patients can also be placed in quarantine facilities to isolate them, if these individuals do not need hospital care.

3. Quarantine facilities have to be in place in each town. These sites are invaluable in stopping the propagation of cases in the community, especially by asymptomatic and mildly ill COVID-19-positive people and their contacts, should they otherwise decide to leave their homes because they do not feel ill.[13] At a point when there is large-scale community transmission, quarantining may no longer be practical and necessary, according to the W.H.O.,[14] but these facilities can be of use as spill-out units for hospitals at full capacity.

4. The LGU should identify and help beef up, with healthcare staff, equipment, medications and personal protective equipment (PPE), the government and private hospitals that will be taking in the very sick COVID-19 patients. Only the moderately and severely ill suspected, probable & confirmed COVID-19 patients should be admitted to these designated hospitals.

5. The government should help protect healthcare workers (HCWs) with provision of PPEs. Of the total confirmed COVID-19 people locally, 1,649 (19.7%) are HCWs, indicating that they are at high risk.[7] HCW's perception of inadequate support may increase the risk of their refusal to work, adding on to the current problem of a diminishing healthcare workforce brought about by forced quarantine from inadvertent COVID-19 exposure in the workplace.

6. The Department of Health should have an active surveillance system to monitor cases, clusters and spread, in coordination with the COVID-19 tracking teams.

7. The health care system should adjust and continue to provide medical care to people with non-COVID-19 illnesses.

8. The quarantine facilities are to be supported by LGU-private sector cooperation.

9. The government should support private hospitals; 53% of beds are in private hospitals.[8] With the lockdown, elective admissions and surgeries were put on hold, while people have been afraid to go to hospitals for non-COVID-19 illnesses. These have placed private hospitals' financial viability at great risk.

10. Hospitals should review and enhance their infection prevention and control practices, to decrease COVID-19 nosocomial transmission risk to HCWs and patients.[14]

11. The government should conduct a longitudinal surveillance of COVID-19 immunity, the knowledge of which may influence future policy-making, including the need for future lock-downs.[3]

Realistically, our healthcare system will be hard-pressed to come up with all the necessary preparations, but we have to do our best. Even

countries with advanced healthcare systems like the U.S., China, Spain and Italy have buckled in the face of the COVID-19 pandemic. For all Filipinos, after the lockdown is lifted, our mindset should be that: our home is our fortress - this is where we are in control and are safest; the new paradigm that should guide our everyday actions is - when I leave my home, I will cover my nose, mouth and eyes with a mask and eye shield as these three mucosal surfaces are the likely sites of viral entry. I will minimize the use of my hands, or glove them, or decontaminate them with alcohol, when I touch door knobs and other objects in my surroundings; and I will use my feet well by consciously keeping a safe distance from everyone else; anyone I encounter outside of my home may have asymptomatic COVID illness; in the Philippines, 12% of confirmed COVID-19 cases were asymptomatic.[7]; if I feel sick, I will not leave my home, I will promptly inform my workplace, and seek medical help for proper evaluation and treatment.

If we are not disciplined and our healthcare system is not properly set up when the lockdown is lifted, this is one probable scenario: infection rates will rise sharply after 4-6 weeks, hospitals and quarantine facilities will be unable to cope, people will die in large numbers, and the government will be forced to impose another lockdown. Intermittent lockdowns may be necessary when critical care capacity is threatened or exceeded.[3] This open-close lockdown can go on over 3-4 cycles, until a vaccine is, hopefully, available in 1 to 1.5 years, or an effective, oral, affordable anti-viral treatment is discovered.

We are Asians. Let us be as disciplined and educated about this like the Taiwanese and South Koreans are. As we do not have a healthcare system that these two countries possess, much of our ability to control the spread of COVID-19 will depend on our collective discipline as a people. Each person, each town, each city, and each province should regard the others beside him/it as a collection of links; each link is dependent on the next. The only way for us to survive this crisis is if we all work as one big family of Filipinos.

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ORIGINAL ARTICLE

UTILITY OF URINE KOH IN DETECTING CANDIDURIA IN INFANTS

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

4TH PRIZE 2020 PIDSP RESEARCH CONTEST

ABSTRACT

Background: Candida species are common cause of urinary tract infection in infants requiring medical care. Candida fungal elements may be demonstrated in urine using microscopic examination with potassium hydroxide (KOH). However, detection of these elements does not always correlate with candiduria.

Objectives: To establish the utility of urine KOH in identifying candiduria and to determine the risk factors, as well as urinalysis and CBC parameters associated with candiduria.

Methods: This prospective cross-sectional study included admitted infants 1 year and below with urine culture and with any risk factor/s for candiduria. Additional urine KOH testing was done using clean catch or catheter method. Urine culture was used as the gold standard.

Results: Among the 90 study participants with both urine culture and urine KOH, 13 (14%) had candiduria. The use of indwelling catheter, presence of urinary tract anomalies, positive leukocyte esterase in urinalysis, and increased monocyte counts in CBC are all associated with candiduria. Urine KOH has sensitivity of 100%, (CI 75.2-100%), specificity 59.7%, (CI 47.9-70.7%), PPV 29.5%, (CI 17.7-45.2%), and NPV 100%, (CI 92.2-100%) in detecting candiduria.

Conclusions: Negative urine KOH has excellent negative predictive value, while positive urine KOH result may warrant further investigation. Urine KOH results should be interpreted with caution depending on patient's risk factors, clinical status, and other laboratory results prior to initiation of empiric antifungal therapy. Positive urine KOH may not always require treatment.

KEYWORDS: *urine KOH, candiduria, Candida*

INTRODUCTION

Candida species are one of the common causes of urinary tract infection (UTI) in neonates and infants requiring medical care.[1] Fungal elements (e.g. yeast cells and pseudohyphae) may be seen in *Candida* infected body fluid specimens such as urine with microscopic examination using 10-20% potassium hydroxide suspension (KOH).[2] However, detection of these fungal elements in urine does not always correlate with candiduria or UTI. Urine KOH results are frequently used to diagnose candiduria in many clinical settings because it is affordable, readily available, and yields immediate results compared to urine culture, the gold standard for detecting candiduria. However, the role of KOH in urine for detection of candiduria has not been well studied. There was no available data or study conducted both locally and internationally that compared urine KOH to urine culture, hence this study was undertaken. This study will help and guide clinicians regarding the value of urine KOH in the diagnosis of candiduria in infants. If highly sensitive or specific, it may be a valuable screening tool for candiduria. However, if not sensitive, we will be able to prevent unnecessary urine KOH testing, and thus unnecessary expenses. And if shown that it is not specific, this will prevent unwarranted exposure of patients to antifungal therapy.

The main objective of this study is to establish the utility of urine KOH in identifying candiduria in infants. Specifically, to determine the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of urine KOH in detecting candiduria in infants compared with urine culture, to identify the risk factors significantly associated with candiduria in infants, and to detect association of urinalysis findings and CBC parameters with candiduria in infants.

Candiduria is defined by presence of $>10^3$ CFU/mL in urine culture (by suprapubic aspiration), $>10^4$ CFU/mL (by urethral catheterization), or $>10^5$ (by clean catch method), and a positive Urine KOH is the presence of fungal elements (yeast or hyphae) in urine specimen.

METHODOLOGY

This prospective cross-sectional study determined the utility of urine KOH in detecting candiduria in infants conducted from September 2017 – June 2018. The study commenced upon the approval of the Institutional Review Board and Ethics Committee of our institution. This study did not have any financial sponsors. No conflicts of interest are hereby declared.

Subject and Sample Size Computation

Inclusion Criteria: Admitted infants 1 year old and below, with urine culture request, and with any of the following risk factors: low birth weight (<2500g), prematurity (<37 weeks AOG), on prolonged steroids (>14 days), with congenital urinary tract anomalies, on broad-spectrum antibiotics (e.g. third and 4th generation cephalosporins, piperacillin tazobactam, vancomycin, carbapenems), on parenteral nutrition, admitted at ICU, on endotracheal intubation, with indwelling urinary catheter or on clean intermittent catheterization, those who underwent recent (≤ 1 month) abdominal, pelvic or urologic surgery, with hematologic malignancies, or those on immunosuppressive drugs (e.g. on chemotherapy). Patients on antifungal prophylaxis or previously given antifungal were included as long as they were able to fulfill the inclusion criteria.

Exclusion Criteria: infants with urine culture without any risk factor for candiduria, infants with cutaneous candidiasis on the pelvic/perineal area (i.e. satellite pustules with erythematous base,

and marginal scaling), and infants with diaper dermatitis.

Using Epi Info Version 7, the minimum sample size requirement is 90 based on the specificity of KOH smear in evaluation of fungal foot infection (62%)[16], with a margin of error 10% and confidence interval of 95%.

Study Procedure

Admitted infants (≤12 months old) with urine culture request were identified from the laboratory logbook daily. Once identified, the risk factors for candiduria were determined if present in these infants, which was done through history and physical examination of the patient and chart review by the principal investigator. If a risk factor was present, and the infant had no clinical signs of diaper dermatitis or cutaneous candidiasis on the pelvic or perineal area, an informed consent was obtained from the parents/guardian of the infant for inclusion in the study. Thereafter, urine collection for KOH testing was obtained for those infants without prior urine KOH test. Infants with recent KOH test (past 24 hours) were included in the study but no additional KOH testing was done. Urine specimen for KOH testing was collected either via clean catch method, or from catheter (in catheterized patients), within 24 hours of urine culture collection.

Data Processing and Analysis

Data analysis was performed in Stata SE version 13. Quantitative variables were summarized as mean and standard deviation, while qualitative variables were tabulated as frequency and percent. Accuracy of urine KOH in predicting candiduria were computed in terms of its sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Factors associated with candiduria was analyzed using logistic regression. The level of significance was set at 5%.

RESULTS

In our study, 69% (62) were males and 67% (60) were infants more than 1 month old. The most common risk factors identified for candiduria in the study participants were the use of broad-spectrum antibiotics in 72 of the 90 cases (80%), followed by admission to an Intensive Care Unit 59 (66%), and having endotracheal intubation 32 (36%) (Table 1).

Table 1. Risk factors Identified for Candiduria

Risk factors	**n = 90**	**%**
Low birth weight (<2500g)	24	27%
Prematurity (<37 weeks AOG)	18	20%
Prolonged steroids (≥14 days) use	1	1%
Congenital urinary tract anomalies	14	16%
Broad-spectrum antibiotics (e.g. 3rd and 4th generation cephalosporins, piperacillin, vancomycin, carbapenems) use	72	80%
Parenteral nutrition	5	6%
Admitted at Intensive Care Unit (ICU), Neonatal ICU (NICU)	59	66%
Endotracheal intubation	32	36%
Urinary catheter use	20	22%
Central vascular catheters (central lines)	17	19%
Recent (≤ 1 month) abdominal, pelvic or urologic surgery	11	12%
Hematologic malignancies	3	3%
Immunosuppressive drugs (e.g. on chemotherapy) use	1	1%
Others: Candidemia	3	3%

In our study, 56 (62%) did not have any growth in urine culture, 21 (23%) had bacterial growth, and 13 (14%) had candiduria. Among these, 10 (77%) were non-albicans *Candida* spp. and 3 (23%) were *Candida albicans.*

Of the 13 infants with candiduria, 8 (62%) were males, and 8 (62%) were more than 1 month old. The most common identified predisposing risk factor in those with candiduria was the use of broad spectrum antibiotics (100%), followed by admission to an Intensive Care Unit (69%), and having a urinary catheter (61%) (Table 2).

The presence of congenital urinary tract anomalies, or those with urinary catheter are the significant risk factors identified for candiduria in this study. The odds of developing candiduria is 4.72 if a patient has congenital urinary tract anomaly, and 8.67 if with urinary catheter (Table 2).

Table 2. Association of Patients' Characteristics and Risk factors with Candiduria

Characteristics Risk factors	***With*** candiduria n = 13	***Without*** candiduria n = 77	**Odds ratio**	**P value**	**C.I**
Sex (male)	8 (62%)	54 (70%)	0.68	0.538	0.20 – 2.30
Low birth weight	0	24 (31%)	-	-	-
Prematurity	0	18 (23%)	-	-	-
Prolonged steroids use	1 (8%)	0	-	-	-
Congenital urinary tract anomalies	5 (38%)	9 (12%)	4.72	0.021	1.27 – 17.60
Broad-spectrum antibiotics use	13 (100%)	59 (77%)	-	-	-
Parenteral nutrition	0	5 (6%)	-	-	-
Admitted at ICU/NICU	9 (69%)	50 (65%)	1.2	0.763	034 – 4.31
Endotracheal intubation	6 (46%)	26 (34%)	1.68	0.391	0.51 – 5.51
Urinary catheter	8 (62%)	12 (16%)	8.67	0.001	2.41 – 31.04
Central vascular catheters	2 (15%)	15 (19%)	0.75	0.728	0.15 – 3.75
Recent (≤ 1 mo) abdomen, urologic/pelvic surgery	1 (8%)	10 (13%)	0.56	0.594	0.06 – 4.77
Hematologic malignancies	0	3 (4%)	-	-	-
Immunosuppressive drugs use	0	1 (1%)	-	-	-

Of the 13 infants with candiduria, 1 (8%) showed positive nitrite results, and 9 (69%) showed positive for leukocyte esterase. The mean values for urine WBC (63/hpf) and RBC (62/hpf), as well as CBC parameters were also noted (Table 3).

From the results of the study, the significant laboratory parameters associated with candiduria are presence of leukocyte esterase on urinalysis and elevated monocyte counts on CBC. The presence of leukocyte esterase in urinalysis increases the odds of having candiduria as well as increase in monocyte counts in CBC (Table 3).

Table 3. Association of Patients' Laboratory Parameters with Candiduria

Laboratory Parameters	***With*** candiduria Mean ± SD n = 13	***Without*** candiduria Mean ± SD n = 77	Odds ratio	P value	C.I
Urinalysis					
Nitrite (+)	1 (8%)	5 (6%)	1.20	0.873	0.12 – 11.18
Leukocyte esterase (+)	9 (69%)	17 (22%)	7.94	0.002	2.17 – 28.99
WBC	62.9 ± 122.0	23.3 ± 67.0	1.00	0.122	0.99 – 1.01
RBC	62.1 ± 158.0	112.4 ± 534.9	1.00	0.740	0.99 – 1.00
CBC					
Hemoglobin	11.7 ± 2.0	11.6 ± 2.6	1.02	0.697	0.81 – 1.28
Hematocrit	35.3 ± 5.9	34.5 ± 7.5	1.02	0.939	0.93 – 1.09
WBC	14.9 ± 7.0	21.0 ± 24.1	0.97	0.366	0.91 – 1.03
Neutrophil	55.6 ± 21.3	55.2 ± 22.6	1.00	0.957	0.97 – 1.02
Lymphocyte	30.3 ± 17.9	36.6 ± 22.9	0.98	0.350	0.95 – 1.01
Eosinophil	3.3 ± 5.01	1.9 ± 2.6	1.12	0.159	0.95 – 1.30
Monocyte	9.2 ± 4.2	5.1 ± 4.0	1.27	0.004	1.08 – 1.49
Platelet ($x10^3$)	398.0 ± 259.7	244.5 ± 164.9	1.00	0.010	1.00 – 1.00

As seen in table 4, of the 90 study participants, 44 patients (49%) had positive urine KOH while 46 patients (51%) had negative urine KOH. Of the 44 patients who tested positive for urine KOH, 13 infants (30%) had positive urine culture result. Thirty-one (31) patients (70%) who tested positive for urine KOH was negative for urine culture. Of the 46 patients who tested negative for urine KOH, all 46 patients (100%) were also negative for urine culture.

Table 4. Urine KOH and Urine Culture Results

	Urine CS (+)	Urine CS (-)	Total
Urine KOH (+)	13	31	**44**
Urine KOH (-)	0	46	**46**
	13	***77***	90

The sensitivity of urine KOH in detecting candiduria is 100%, which means that all patients with candiduria tested positive for urine KOH. The specificity of urine KOH is 59.74%, which means that 59.74% of patients without candiduria tested negative for urine KOH. The positive predictive value (PPV) of urine KOH is 29.55%, while the negative predictive value (NPV) of urine KOH is 100% (Table 5).

Table 5. Accuracy of Urine KOH in Detecting Candiduria

	Overall % (C.I)
Sensitivity	**100% (75.2-100%)**
Specificity	**59.7% (47.9-70.7%)**
PPV	**29.5% (16.7-45.2%)**
NPV	**100% (92.2-100%)**

DISCUSSION

Candida spp. are commensal organisms commonly found in the gastrointestinal and genitourinary tracts of healthy individuals.[3] *Candida* is the most important cause of fungal infection in health care settings, including those of the urinary tract. In the majority of asymptomatic persons, the presence of yeast in the urine indicates contamination or colonization. However, in symptomatic patients or those with risk factors for candiduria, the presence of yeast may indicate true infection.

In the study by Gholamipour et al, the highest frequency of candiduria was seen in patients who had received more than 2 or 3 antibiotics during their hospitalization (37% and 24%, respectively).[4] Other risk factors identified in their study include admission in ICU (24.5%) and NICU (12%), those with cardiovascular disorder (18%), with urinary catheter (12%), respiratory diseases (10%), anomaly of the urinary tract (10%), gastrointestinal and liver diseases (9%) and neurologic disorders (8.5%). In relation to this, this study has identified the use of broad-spectrum antibiotics in all (100%) patients who developed candiduria. Furthermore, other common risk factors for candiduria that were identified in this study include the following: admission to intensive care unit (69%), use of indwelling urinary catheter (61%), on endotracheal intubation (46%), and presence of congenital urinary tract anomaly (38%).

In the study of Paul et al, prior antimicrobial use was documented in 92% with candiduria (OR 9.1; 95%; CI 2.1-31.9) [5], while in this study as mentioned above, prior antimicrobial use was documented in 100% of patients with candiduria. Furthermore, Alfouzan et al. reported that aside from long term urinary catheterization, prior antibiotic use is the next most significant risk factor for candiduria.[6] In this study, the most frequently used antibiotic in patients with candiduria were cephalosporins (3rd and 4th generations).

The use of broad-spectrum antibiotics leads to alteration of the normal bacterial flora, that results to a more conducive environment for the growth of yeasts. The higher number of candiduria cases noted in ICU patients are probably secondary to others factors such as underlying diseases, relative immunodeficiency status, multiple manipulations by health care team and altered bacterial flora secondary to use of broad-spectrum antibiotics.[7]

In this study, the odds of developing candiduria increases in the presence of urinary tract anomaly, or use of indwelling urinary catheter. Urinary tract anomalies noted in patients with candiduria in this study included horseshoe kidneys, cloacal exstrophy, prune belly syndrome, and bladder exstrophy. Alfouzan et al. also reported that long-term urinary catheterization is considered to be the most significant risk factor for candiduria.[6]

The presence of pyuria, hematuria, or leukocyte esterase in urinalysis maybe useful in distinguishing infection from contamination or colonization.[3] In this study, urinalysis and CBC parameters were compared between those with candiduria and those without candiduria. Significantly, the presence of positive leukocyte esterase in urine specimen increased the odds of a patient having candiduria. Monocytes, along with neutrophils and macrophages are important antifungal effector cells. Residing phagocytes in infected organs are involved in the killing of invading Candida, whereas neutrophils and monocytes are recruited to the site of infection.[3] The mean percentage of monocyte in infants is 5%.[8] In our study, increase in monocyte counts was noted to be associated with increased odds of having candiduria. The presence of low platelet count has been associated to candidemia in several studies, especially in the neonates.[9,10] In our study, platelet counts has no significant association with the presence or development of candiduria, probably because our study population involved more infants than neonates.

Among the 13 *Candida* species isolated in our study, 10 were non-albicans *Candida* spp. (77%), and 3 were *Candida albicans* (23%). In the study of Malhotra et al, *C. albicans* were isolated in 37 of 333 cases (11.1%) and non-albicans *Candida* spp. were noted in 35 patients (10.5%). [11]

The accuracy of urine KOH in its ability to detect significant candiduria has not been well studied. There is scarcity in data regarding the use of urine KOH in predicting candiduria when compared to urine culture as the gold standard. In this study, the sensitivity of urine KOH was noted at 100%, implying that all patients with candiduria tested positive with urine KOH. On the other hand, the specificity of urine KOH was noted at 59.74%. The 100% sensitivity also means that urine KOH will detect virtually every infant who has candiduria but its low specificity means that it will be falsely positive for a number of infants who actually don't have candiduria. Comparison of urine KOH with the standard urine culture is important, since urine KOH is a cheaper, readily available especially in remote areas, and yields more rapid results.

From the results of the study, not all patients with positive urine KOH implies candiduria. Of the 44 patients with positive urine KOH, only 13 (30%) showed with positive urine culture results. Thus, it is prudent to not immediately treat patients with positive urine KOH result with antifungals such as fluconazole, unless correlated with urine cultures and clinical status of the patient. Correlation of the patient's clinical status is also important, as not all infections are detected by urine culture even though it is the gold standard in detecting candiduria. Furthermore, exposure of patients to unnecessary drugs or antimicrobials (antifungals included), has its drawbacks and disadvantages.

First, unnecessary exposure of patients to antifungals may lead to emergence of resistant strains of *Candida* species such as *C. glabarata* and *C. krusei*. In the study of Prasad et al, they identified that patients older than 2 years, those with recent surgical procedure, and prior fluconazole use were independent risk factors for infection with *C. glabrata* and *C. krusei* in children.[12] Second, the general recommendation for treatment of candidemia is the use of Amphotericin B, which is usually nephrotoxic and may cause electrolyte imbalances (e.g. hypercalciuria, hypokalemia, hypomagnesemia), renal tubular acidosis, renal failure, acute hepatic failure, and hypotension.[8] In relation to this, patients who are not on prior azole use (e.g. fluconozaole) and not critically ill may use fluconazole for treatment of candidemia with susceptible isolates.[2] However, in the instance that a patient was previously treated with fluconazole because of other conditions (e.g. positive urine KOH), then we can no longer use fluconazole (a relatively safer agent compared to amphotericin B) to treat candidemia; amphotericin B will be given and continued for at least 14 days, thereby increasing the risk for possible detrimental side effects of this antifungal as previously mentioned.

Lastly, unnecessary use of antifungals such as fluconazole provides additional economic burden to patient's family. Locally, IV fluconazole approximately costs 1,500 pesos per vial of 2mg/ml (100ml), while oral fluconazole capsule costs 400 pesos per 200mg tablet.

Fluconazole is highly water soluble and is mainly excreted in the urine as an active drug (urinary concentrations are more than 10-fold compared to those in serum). With this, fluconazole is considered the drug of choice for both candida cystitis and pyelonephritis.[13] For asymptomatic candiduria, elimination of predisposing factors such as indwelling urinary catheters catheter is strongly recommended. Antifungal treatment is not recommended unless patients has high risk of candidemia (blood stream infection), such as neutropenia, very low birth weight, and patients who will undergo urologic manipulation.[2] In patients with indwelling catheter, removal of the device maybe adequate to resolve the candiduria without antifungal therapy.[3] It is recommended that asymptomatic catheter-associated bacteuria or

candiduria should not be treated while the catheter remains in place since this may lead to evolution of resistant flora.[14]

In the review of Lundstrom et al., management of candiduria depends on the clinical manifestations of patients. For those with asymptomatic candiduria, modification of risk factors such as catheter removal, or rational use of broad-spectrum antibiotics, is sufficient to address the condition. For those who are symptomatic with cystitis (dysuria, hematuria, frequency, urgency, and suprapubic tenderness), or those with pyelonephritis (fever, leukocytosis, costovertebral angle tenderness), treatment with fluconazole is given.[15] Thomas et al., supported this management concept for candiduria and indicated that antifungal therapy is only required in symptomatic or high-risk cases, because spontaneous resolution is common in patients with asymptomatic colonization.[16]

Based from the recommendations of other literatures and the results of this study, this study recommends the following approaches which may be done in patients with positive urine KOH:

1. For patients *without* risk factor for candiduria, who are *asymptomatic,* and with positive urine KOH, no treatment is necessary and observation or monitoring for clinical signs and symptoms suggestive of urinary tract infection maybe done.
2. On the other hand, for patients *with* risk factor/s for candiduria, who remain to be *asymptomatic*, and with positive urine KOH, a urine culture should be done to verify presence of candiduria; treatment is then directed once urine culture and sensitivities are available. Furthermore, for patients with risk factors such as presence of urinary tract abnormality or those with indwelling catheter (which were both found to increase the odds of developing candiduria in this study), an antifungal therapy maybe started pending urine culture. Treatment is then directed once urine culture results are available.
3. Lastly, for patients *with* risk factor/s for candiduria, who are *symptomatic* (e.g. febrile, frequency, dysuria) or critically ill (e.g. admitted at ICU, intubated), and with positive urine KOH, antifungal therapy with fluconazole maybe empirically started with urine collection for culture. Treatment is then continued, stopped, or directed once urine culture result and sensitivities are available, with correlation on the clinical status of the patient.

CONCLUSION AND RECOMMENDATIONS

The most common risk factors seen with candiduria are prior use of broad-spectrum antibiotics, admission to intensive care units, and use of indwelling urinary catheter. The use of indwelling catheter, presence of urinary tract anomalies, the positive leukocyte esterase in urinalysis, and elevated monocyte counts in CBC are all associated with increased odds of developing candiduria. When compared to urine culture, a negative urine KOH has excellent negative predictive value, while a positive urine KOH result will warrant further investigation with urine culture and correlation with patient's condition, prior to initiation of empiric antifungal therapy.

This study recommends that urine KOH results be approached individually with caution depending on patient's risk factors and clinical status to prevent emergence of resistant candida strains, promote rational use of antifungals, and avoid additional economic burden to the family with the use of unnecessary antifungals.

The study recommends to extend the scope of population to VLBW babies since candiduria is significant in these age group, as well as in older children (beyond infancy > 1 year old) so as to determine value of urine KOH in candiduria in this age group. Comparison of use of urine KOH for those without risk factors for candiduria against those with risk factors is also recommended for future studies.

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ORIGINAL ARTICLE

EFFECTIVENESS AND ADVERSE EFFECTS OF INTRAVENOUS COLISTIN IN NEONATES WITH MULTI-DRUG RESISTANT GRAM-NEGATIVE BACTERIAL INFECTIONS

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

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ABSTRACT

Background: The global burden of multi-drug resistant gram-negative bacterial (MDR-GNB) infections has been increasing. Neonates are at a particularly high-risk and there is limited treatment option. The use of colistin has been re-introduced for this population. However, data on its use in neonates is scarce.

Objective: To determine the effectiveness and adverse effects of intravenous colistin in neonates with multidrug-resistant gram-negative infections.

Design: This is a retrospective cohort study of the clinical profile and outcome of neonates with MDR-GNB infections given colistin for a minimum of 3 days conducted from April 2015 to April 2019.

Results: A total of 175 pediatric patients had MDR-GNB infections. 75 (43%) neonates met the inclusion criteria and received intravenous colistin. Of the 75 patients with MDR-GNB infections- that included sepsis, pneumonia, urinary tract infection and abscess, 37 (49.3%) were alive and 38 (50.7%) patients died. Nephrotoxicity was seen in 4% if patients and 2.6% patients had hypersensitivity reaction. MDROs isolated were Acinetobacter baumanii, Klebsiella pneumoniae and Pseudomonas aeruginosa.

Conclusion: Intravenous colistin is 50% effective and is relatively safe to use in neonates.

KEYWORDS: *colistin, MDR-GNB, neonates*

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INTRODUCTION

Sepsis is one of the major causes of hospital admission and mortality in neonates. A serious concern in the management of neonatal sepsis is antibiotic resistance. Multi-drug resistance among bacterial organisms are emerging and problematic because treatment options with antimicrobial agents for these strains are often limited. [1]

Multi-drug resistant gram-negative bacteria (MDR-GNB) have been reported in different parts of the world. It is a major threat to neonatal care, carrying a high rate of morbidity and mortality. The presence of MDR-GNB and the lack of new antibiotics to treat them have led to the revival of polymyxins, an old class of cationic, cyclic polypeptide antibiotics. Colistin, mainly colistimethate sodium (polymyxin E), has been predominantly used for infections caused by these organisms before the advent of newer safer antibiotics. While colistin is the treatment of choice, few studies have reported its use in neonates. [2]

Colistin was first introduced in 1952 and was used until the early 1980's for the treatment of infections caused by gram-negative bacilli. In vitro, colistin has demonstrated excellent activity against various gram-negative rod-shaped bacteria, including multidrug-resistant Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae. The mechanism of action of colistin is on the bacterial cell membrane. It binds to lipopolysaccharides and phospholipids in the outer cell membrane of gram-negative bacteria that leads to disruption of the outer cell membrane leading to the leakage of intracellular contents and eventual bacterial death. [3]

Data on the use of colistin in the pediatric population remain scarce. Safety and effectiveness data regarding colistin in pediatric patients especially in the neonates are limited. The optimal dosage has not been defined. However, according to a multicenter study in recent years, 2.5 - 5 mg/kg/day is safe in the pediatric age group.[4] Some studies reported using 50,000-75,000 IU/kg/day (1 mg colistimethate sodium = 12,500 IU) in newborns and preterm infants. The most frequent adverse effect of intravenous colistin is nephrotoxicity. Toxicity is dose-dependent and reversible on discontinuation of treatment.[3] The exact molecular mechanism of toxicity is, however, not known. Other reported side effects include neurotoxicity, electrolyte imbalances.[4] The 2019 International Consensus Guidelines for the Optimal Use of Polymyxins states that the magnitude of polymyxin exposure is the most important risk factor for polymyxin-associated acute kidney injury. The recommended dose is no more than 5 mg/kg/day (equivalent to ~152,000 IU/kg/day). A risk factor in multiple analysis identified that advanced age is co-related with nephrotoxicity, although the so-called cut-off age for increased risk is inconsistent. Administration of concomitant nephrotoxic agents is also a consistent risk factor for acute kidney injury in patients receiving polymyxin therapy.[5]

In the Philippines, colistin use is limited. However, due to the increasing number of MDR-GNB at a tertiary government training hospital in Manila, the drug has been used since 2015. To date, there are no local studies on the effectiveness and adverse effects of colistin use in neonates. This study aims to determine the effectiveness and adverse effects of colistin in neonates with multidrug-resistant gram-negative bacterial infections. Data on the neonates' clinical characteristics, outcome, and adverse effects, as well as the MDRO antimicrobial susceptibility were collected and analyzed.

Operational Definition of terms:

1. Multi-drug resistant organism - is defined as microorganism with non-susceptibility to at least one agent in three or more antimicrobial categories.[2]
2. Extended neonatal period – is defined as corrected gestational age for prematurity plus another 28 days. Age of viability is at 24 weeks thus a maximum of 118 days of life was considered.[6]
3. Nephrotoxicity (drug-induced) - 0.5 mg/dL or 50% rise in serum creatinine over 24–72 h time frame and a minimum 24–48 h of drug exposure or any of

the following: decreased urine output, increased BUN, proteinuria, hematuria or casts in the urine.[4,7]

4. Neurotoxicity – severe neurotoxic effects include seizures, hypertonicity, spasms, change/decrease in sensorium reported during treatment with colistin not explained by any other co-morbidity (meningitis, hypoglycemia, hypoxia, etc.).[4,10]

5. Hypersensitivity reaction – includes but not limited to generalized pruritus, urticaria, rash during or after administration of colistin any time during treatment.

6. Survived – patients who are alive after 14 days of treatment completion with colistin and whose repeat cultures are negative.

7. Died – patients given more than 3 days of colistin treatment and died within 14 days of treatment.

METHODOLOGY

A. Study design and setting

This is a retrospective cohort study of the clinical profile and outcome of neonates with MDR-GNB given colistin that were admitted in the pediatric wards, pediatric intensive care unit (PICU) and neonatal intensive care unit (NICU) from April 2015 to April 2019. The study was done at a tertiary government training hospital with the largest facility and referral center that serves more than 600,000 patients yearly.

B. Study population and sampling plan

A minimum of 57 patients was computed for this study based on a 35.9% prevalence of mortality among neonates with sepsis with 5% level of significance and 12.5% half-width of the confidence interval.[1]

Admitted patients < 118 days of corrected age with MDR-GNB isolates on blood, endotracheal aspirate, urine, cerebrospinal fluid (CSF), abscess on initial or repeat cultures and given colistin for a minimum of 3 days in order to properly assess antibiotic treatment response or failure were included.[6]

Exclusion criteria were as follows:

- Patients beyond 28 days of life or >118 days of age based on an extended neonatal definition of corrected age for prematurity
- Duration of colistin use is < 3 days
- Cultures positive for gram-positive pathogen, fungal infection, and mixed organisms

C. Data collection and procedure

The use of colistin in our center is highly restricted. It requires approval from the Section of Infectious and Tropical Diseases in Pediatrics (INTROP) prior its administration. The list of pediatric patients given colistin was obtained from the section's list and patient records. Medical charts and laboratory data of these patients were reviewed. All information needed was recorded in a case report form.

D. Data processing and analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables, median and interquartile range for non-normally distributed continuous variables and mean and SD for normally distributed continuous variables. Fisher's exact test was used to determine the difference between patients that survived or died in terms of concomitant antibiotics given during colistin administration. Shapiro-Wilk was used to test the normality of the continuous variables. Odds ratio and corresponding 95% confidence intervals from binary logistic regression were computed to determine significant factors of mortality. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at 0.05α-level of significance. STATA 13.1 was used for data analysis.

E. Ethical Issues

An approval from the Research Ethics Board (REB) was obtained before the conduct of this study. Review of medical records and its anonymity were maintained in accordance with our National Ethical

Guidelines of Health and Health-related Research 2017.

The data was collected solely by the principal investigator. All patient information and data collected in this study were kept confidential.

RESULTS

A total of 175 pediatric patients had MDR-GNB infection from April 2015 to April 2019. 75 (43%) neonates met the inclusion criteria and received intravenous colistin. The median age was 15 days old with a mean weight of 1500 grams. Almost 74% (55) of the patients in this study were pre-term. Sixty-three patients (84%) with MDR-GNB were admitted at the NICU due to sepsis (82.7%). The summary of the other clinical characteristics of patients is presented in Table 1.

Table 1. Clinical profile of patients with MDR-GNB treated with colistin (n=75)

	Frequency (%); Mean ± SD; Median (IQR)
Age (days)	15 (9 to 23)
Term	20 (26.66)
Pre-term	55 (73.33)
Weight (grams)	1500 (940 to 2495)
Sex	
Male	36 (48)
Female	39 (52)
Admission ward	
Ward 9	7 (9.33)
Ward 11	4 (5.33)
PICU	1 (1.33)
NICU	63 (84)
Underlying disease	
Sepsis	62 (82.67)
Pneumonia	9 (12)
Ventriculitis	6 (8)
UTI	3 (4)
NEC III/abscess	1 (1.33)

Clinical manifestations of patients are presented in table 2, the most common signs and symptoms seen in patients with MDR-GNB were poor activity (94.7%), abdominal distention (60%), tachypnea (53.3%), tachycardia (42.7%) and fever (37.3%).

Table 2. Clinical manifestations of patients with MDR-GNB prior to treatment with colistin

Signs and symptoms	**Frequency (%)**
Temperature	
> 38.5^{0}C	28 (37.33)
Normal	30 (40)
< 36^{0}C	17 (22.67)
Respiratory	
Tachypnea	40 (53.33)
Normal	18 (24)
Apnea	17 (22.67)
Cardiac	
Tachycardia	32 (42.67)
Normal	24 (32)
Bradycardia	19 (25.33)
Hypotension	8 (10.67)
Seizure	6 (8)
Decreased urine output	1 (1.33)
Skin and subcutaneous manifestations	
Mottling	8 (10.67)
Rashes	10 (13.33)
Sclerema	10 (13.33)
Normal	47 (62.67)
Gastrointestinal manifestations	
Feeding intolerance	7 (9.33)
Poor suck	0
Abdominal distention	45 (60)
Normal	23 (30.67)
Irritability	4 (5.33)
Poor activity	71 (94.67)

Patients with MDR-GNB in this study presented with thrombocytopenia (90.5%) and leukocytosis (45.3%). Details of the laboratory findings are seen in table 3.

Table 3. Laboratory findings of patients with MDR-GNB prior to treatment with colistin

Laboratory	Frequency (%)
WBC count	
< 4,000 x10^9 cells/L	34 (45.33)
Normal	15 (20)
> 30,000 x10^9 cells/L	26 (34.67)
Platelet count < 100,000 x10^9 cells/L (n=74)	
Yes	67 (90.54)
No	7 (9.46)
CRP (n=21)	
< 12 mg/dL	10 (47.62)
> 12 mg/dL	11 (52.38)
Glucose	
Hyperglycemia	1 (1.33)
Normal	62 (82.67)
Hypoglycemia	12 (16)

There were 83 MDR-GNB isolated from different sites, the top 3 isolates were A. *baumannii* (57.83%), *K. pneumoniae* (26.51%) and *P. aeruginosa* (4.82%). As shown in Table 4, the majority of the MDR-GNB was isolated in the blood (65). Out of the 75 patients, 41(61.29%) neonates had A. *baumannii* and 19 (29.23%) neonates had *K. pneumoniae* in their blood culture. *Acinetobacter baumannii* was also the most common organism seen in the endotracheal aspirate and cerebrospinal fluid culture. Other isolated MDR-GNB were *E. coli*, *S. maltophilia*, and *D. acidorovans*.

Table 4. Pathogens isolated from specific sites in neonates treated with colistin

	Blood (n=65)	Respiratory (n=9)	Urine (n=3)	Abscess (n=1)	CSF (n=5)	Total (n=83)
	Frequency (%)					
Acinetobacter baumannii	41 (61)	6 (66.)	0	1 (100)	3 (60)	48(57)
Klebsiella pneumoniae	19 (29)	1 (11)	1 (33)	0	1 (20)	22(26)
Pseudomonas aeruginosa	2 (4)	1 (11)	1 (33)	0	0	4(4)
Others	3 (4)	1 (11)	1 (33)	0	1 (20)	4(4)
Total	65(78)	9(10)	3(3)	1(1)	5(6)	

Cultures were obtained from all patients prior to the initiation of intravenous colistin. Figure 1 shows the blood isolates and antibiotic resistance rates. The most common organism isolate was *A. baumannii* with noted high resistance to meropenem, aztreonam, and amikacin. However, it was susceptible to colistin. Nineteen patients had *K. pneumoniae* in their blood culture with noted resistance to aztreonam, piperacillin-tazobactam and high resistance rates to ciprofloxacin, meropenem, and amikacin. Although there were only two *P. aeruginosa* organisms isolated in the blood, it was resistant to all antibiotics except for colistin.

Figure 1.1 Resistance rates of Acinetobacter baumannii isolates (n=41)

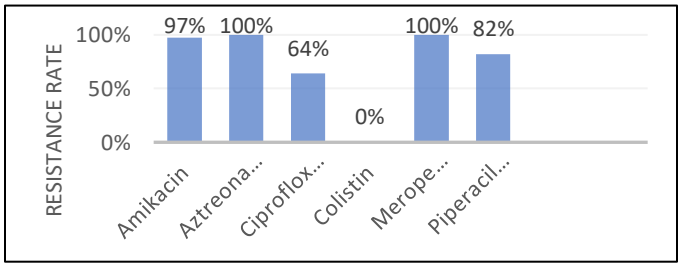


Figure 1.2 Resistance rates of Klebsiella pneumoniae isolates (n=19)

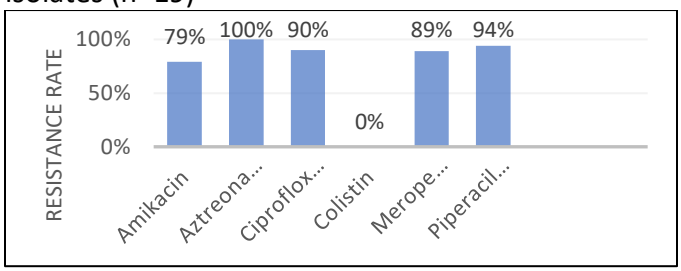
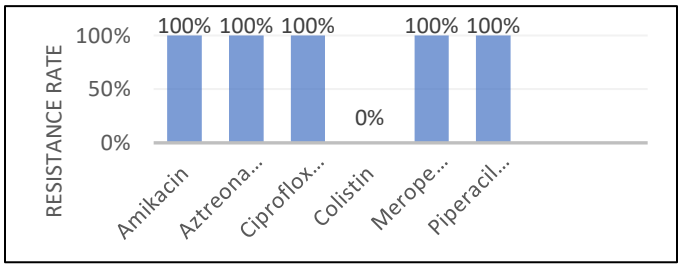


Figure 1.3 Resistance rates of Pseudomonas aeruginosa isolates (n=2)



For the urine isolates, the two most common MDR-GNB isolated were *K. pneumonia* and *P. aeruginosa*. These organisms were sensitive to colistin but were resistant to all other antibiotics. Both patients were term infants born with lumbosacral myelomeningocele with probable concomitant neurogenic bladder.

Antibiotic sensitivity of the endotracheal aspirates was also determined in neonates with severe pneumonia. Standard cultures of the endotracheal aspirates upon intubation were performed and the two most common organisms isolated were *A. baumannii* and *K. pneumoniae*, with similar resistance rate to aztreonam, ciprofloxacin, and piperacillin-tazobactam but colistin showed good activity on these MDR-GNB.

Only three CSF MDR-GNB isolates were recorded in this study, *A. baumannii*, *K. pneumoniae* and *E. coli.* They were resistant to all the listed antibiotics but were sensitive to colistin. Patients who had MDR-GNB ventriculitis have Arnold Chiari II malformation that underwent operative repair of their lumbosacral mass.

Abscess isolates were obtained in two patients, one patient was a full-term infant who had ruptured myelomeningocele upon delivery who underwent surgical repair and developed multi-drug resistant *K. pneumoniae* sepsis and soft tissue abscess on the left forearm secondary to burn. Incision and drainage of the abscess were done revealing multi-drug resistant *K. pneumoniae* on culture. The second patient was a 27-week old infant admitted due to respiratory distress secondary to prematurity, later had necrotizing enterocolitis III-B with abdominal abscess formation. The culture of the abdominal abscess revealed multi-drug resistant *A. baumannii*.

Table 5 presents the antibiotics used prior to colistin administration, the two most common antibiotics were ciprofloxacin (41%) and meropenem (41%). These antibiotics were mostly used in combination with an aminoglycoside (amikacin). Before the utilization of colistin in our institution in 2015, combination therapy with meropenem + ciprofloxacin (8%) were given to MDR-GNB infections.

Table 5. Antibiotics used prior to Colistin treatment

Antibiotics	**Frequency (%)**
Ciprofloxacin	31 (41.33)
Meropenem	31 (41.33)
Meropenem+Ciprofloxacin	6(8.00)
Piperacillin-Tazobactam	4 (5.33)
Cefepime	1 (1.33)
Cefotaxime	1 (1.33)
Meropenem+Vancomycin	1 (1.33)

Table 6 shows the outcome of patients with MDR-GNB treated with colistin. Of the 75 patients with MDR-GNB infections, 37 (49.3%) survived and completed the course of their colistin treatment while the other 38 (50.7%) patients died. The majority of the deaths were attributed to severe sepsis (29) despite adequate antimicrobial treatment. Other causes of death were respiratory

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failure (6) and multiple organ dysfunction syndrome (3).

Table 6. Outcome of patients with MDR-GNB treated with colistin

Outcome	Frequency (%)
Died	38 (50.67)
Survived	37 (49.33)

Univariate analysis on factors associated with mortality including sex, weight, location of admission, underlying disease, isolated organism, and adverse effects was performed. The only factor that was associated with mortality was the duration of intravenous colistin in days this is shown in table 7. The result of the univariate analysis showed that for every day increase in the duration of colistin treatment, the odds of mortality decreases by 19.56%. Since there is only one variable that was significant on univariate analysis, multivariate analysis was no longer done.

Table 7. Univariate analysis of factors associated with mortality (n=75)

Variable	Crude odds ratio	95% CI	P-value
Duration of IV colistin treatment in days	0.8044	0.7187 to 0.9002	**<0.001**

Combination therapy with colistin and another antimicrobial was based on the organism isolated and their culture susceptibility results. Since the most common MDR-GNB isolated was *A.baumannii*, intravenous colistin was given in combination with ampicillin-sulbactam (44%) because of its synergistic in-vitro activity to *A.baumannii*. Table 8 shows the antibiotics given in combination with colistin. Concomitant antibiotics given during colistin administration were analyzed and revealed no statistical association with the outcomes. The mean duration of intravenous colistin treatment was 11.45 ± 5.81 days.

Table 8. Concomitant antibiotics given with colistin and their outcomes

Antibiotics	Total (n=75)	Expired (n=38)	Alive (n=37)	P-value
	Frequency (%)			
Amikacin	3 (4)	0	3 (8.11)	0.115
Ampicillin-Sulbactam	33 (44)	19 (50)	14 (37.84)	0.355
Meropenem	11 (14.67)	8 (21.05)	3 (8.11)	0.191
Ciprofloxacin	17 (22.67)	9 (23.68)	8 (21.62)	1.000
Aztreonam	21 (28)	7 (18.42)	14 (37.84)	0.075

Renal function tests that includes blood urea nitrogen, serum creatinine and urine output monitoring were done prior to and during colistin treatment. It was repeated every 3 to 5 days while ongoing colistin administration until the completion of treatment. Acute kidney injury manifestations were seen in 3 patients, two of which had an increase in serum creatinine as early as the 3rd day and the other patient had decreased urinary output. These patients were referred to a pediatric nephrologist and appropriate adjustment on the colistin dose was done based on their creatinine clearance. In this study, two neonates developed maculopapular rashes after colistin administration typical for hypersensitivity reaction (2.7%). Desensitization to colistin was done on both patients. These adverse effects are shown in table 9.

Table 9. Adverse effects of patients with MDR-GNB treated with colistin

Adverse effects	Frequency (%)
Nephrotoxicity	3 (4)
Neurotoxicity	0
Electrolyte imbalance	0
Hypersensitivity	2 (2.70)

DISCUSSION

The increasing global burden of MDR-GNB infections in pediatric patients is emerging. The prevalence of this disease is also seen in our country. Neonates are at the highest-risk for developing MDR-GNB infections. A mortality rate of 78% was documented in pediatric patients with MDR-GNB infections compared to 41% mortality rate among patients with non-MDR-GNB.[9] Treatment options to these infections are limited, because of this, an old drug was re-introduced. Colistin belongs to the Polymyxin group and it was widely used for its efficacy in gram-negative infections both in adults and children but owing to its nephrotoxicity and availability of newer, safer drugs, it was abandoned. Although there are some studies on colistin use in neonates, the effectiveness of this drug is not well established. The efficacy of colistin in those studies range from 50% to 98%.[4,8]

In our study, there was a 49.3% survival rate with intravenous colistin use. The majority of deaths were secondary to severe sepsis. Several confounders like age, weight, co-morbidities, etc. were not found to be significant to their outcome.

In a similar study on the safety and efficacy of intravenous colistin use in neonates by Tekgunduz et.al, the clinical and microbiological response to colistin and its adverse effects were evaluated. Included in that study were 12 neonates with mean 31.8 ± 3.5 weeks gestational age. Eleven (91.7%) patients showed microbiological clearance with intravenous colistin. However, only 6 (50%) patients survived. Despite high microbiological clearance there were 6 (50%) mortalities, contributing factor to mortality was probably secondary to their underlying co-morbidity (congenital cystic adenomatoid malformation, CHARGE syndrome, congenital heart disease, William syndrome, NEC). Although no statistical analysis on the significance of the co-morbidity was done in that study.[4] Comparing this to our study, a similar survival rate (49.3%) was seen. Also, in Tekgunduz study, 91.7% were pre-term with a median birth weight of 1482 grams in contrast to our study of having 73.3% pre-term neonates with MDR-GNB infections with a similar median birth weight of 1500 grams.

A review of neonates who received intravenous colistin admitted to a NICU in India was done in 2012. A total of 62 neonates received intravenous colistin for the treatment of *A. baumannii*, *K. pneumonia* and *P. aeruginosa* infections. Of the total 62 neonates, 41 (66.12%) survived and 21 (33.87%) died. No adverse effect was reported in that study.[10] In that study by Jasani et.al, analysis of variables with the outcome was done. Significant association in mortality was observed in lower birth weight (<1000gm), early pre-term neonates (<32 weeks), duration of colistin use (10 days) and sepsis due to *Klebsiella.* Similar analysis of variables with the outcome was also done in our study, the only similar significant variable in the analysis is the duration of colistin use. In contrast to the study in India, a more specific classification in weight, prematurity, type of sepsis (early or late), timing of initiation and duration of colistin use were analyzed.

A retrospective single-center study was conducted in Turkey in 2018 by Ilhan, et.al, it aimed to compare the efficacy and safety of intravenous colistin among very low birth weight preterm infants and non-low birth weight infants. The efficacy of colistin between the two groups was comparable with 89.3% vs 86.8% efficacy. During colistin treatment, adverse effects were monitored, serum magnesium and potassium levels were significantly lower in the very low birth weight infants than in the non-low birth weight infants during colistin therapy.

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[11] In the study of Ilhan, demographic characteristics and outcome were analyzed, gestational age, weight and apgar score were found to be significant. Clinical characteristics were determined, it was reported that only 27 (40.9%) of 66 patients were intubated probably owing to the low mortality rate (27%) and high efficacy rate (89.3%) in that study. Monitoring of adverse effects including electrolyte imbalance were likewise done in our study but in contrast to the study of Ilhan no abnormalities in electrolytes were documented in our patients.

Nephrotoxicity, neurotoxicity, and electrolyte imbalance were the most commonly reported adverse effects of intravenous colistin use. [3,5,11,12,13] In this study, 3(4%) patients developed nephrotoxicity secondary to intravenous colistin. Only 1 patient presented with decreased urine output while the 2 other patients presented with an increase in serum creatinine on serial monitoring after 3 days of intravenous colistin. In other clinical studies, the incidence of colistin-associated neurotoxicity reported was about 7%.[11] In this study, seizure (8%) episodes observed in six patients manifested prior to colistin administration and these were attributed to their underlying CNS disease (meningitis, ventriculitis, hydrocephalus, etc.). Also, important to note was the development of hypersensitivity reaction to colistin on 2 (2.6%) patients presenting as maculopapular rash. Electrolytes were monitored during colistin treatment and no abnormalities were seen.

Studies involving pediatric patients given colistin including one study on neonates reported nephrotoxicity rates that ranged from 1.6% to 22% while neurotoxicity rates range from 0% to 4%.[12] The colistin monograph reports the incidence of reversible renal toxicity with polymyxins ranging from 20 to 60 %, although this wide range depends on several factors including dose, existing renal dysfunction, severity of illness, confounding advanced chronic diseases, and the high use of concomitant nephrotoxins in patients receiving polymyxins. These data are probably the basis why colistin has been used sparingly in the recent years. Our study showed a significantly lower nephrotoxicity profile compared to the ones mentioned in literatures. Hypersensitivity reactions have also been reported in 2% of patients.[13]

Nephrotoxicity rate of concomitant medications used in this review includes amikacin with 10-20%, aztreonam with 6%, ampicillin-sulbactam with <1%. [14] The nephrotoxicity rate reported in literatures for amikacin, a commonly used drug in the population included in this study is higher than the nephrotoxicity rate computed for colistin in this study. It should lead us to question if amikacin use is safer than colistin use in our study population. These relatively low rates of adverse events with the use of colistin would make a physician more comfortable in using this drug in our study population. Especialy important to note is the fact that in most of these patients, only colistin is found to have in-vitro sensitivity to the MDR-GNB isolated.

Efficacy of colistin in MDR-GNB varies in different studies, the organisms involved play a huge factor in the patients' survival. In this study, all MDR-GNB isolates showed high resistance to almost all the antibiotics usually given in the NICU. Perhaps this is one of the reasons why there is only 50% survival of the patients in this study. Prior to colistin use, 41% these patients were on broad-spectrum antibiotics, that may have predisposed them to having MDR-GNB. The different combination of antibiotics that were given, as we have seen in the results of this study, had no significant effect on the outcome of patients. The only significant factor affecting outcome was the days of colistin given. This is probably explained by the fact that the longer you give colistin, bacterial eradication is continued thus probably translates to patient getting better and surviving from the MDR-GNB infection.

Since this is a retrospective study, the lack of a control group and not being able to do a multi-variate analysis of the contributing factors to the outcome are some of the limitations of this study. Likewise, bacterial clearance, long-term effects of colistin were not explored. However, overall, the

result of this study with regards to the effectiveness and adverse effects of intravenous colistin in neonates is quite similar to the other studies.

CONCLUSION

This study showed that neonates with MDR-GNB treated with intravenous colistin had almost 50% effectiveness measured in terms of survival. Although there was note of nephrotoxicity (4%) and hypersensitivity (2.6%), it is within the reported rates based on other studies and is actually much lower.

Neonates are at high-risk to the emerging MDR-GNB infections and with the limited antibiotic options, intravenous colistin is safe and can be used in this age-group until a new drug is available for MDR-GNB organisms.

RECOMMENDATION

Prospective studies are recommended to evaluate efficacy of intravenous colistin in the sterilization of cultures. Likewise, a prospective randomized comparative study on the outcome or efficacy using colistin in combination with different anti-microbials is worthwhile.

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2ND PRIZE 2020 PIDSP RESEARCH CONTEST

ORIGINAL ARTICLE

VALIDATION OF THE FILIPINO TRANSLATED QUESTIONNAIRE ON PARENT ATTITUDES ABOUT CHILDHOOD VACCINES

ABSTRACT

Objective: To determine the content validity and test-retest reliability of the Filipino Translated Questionnaire on Parent Attitudes About Childhood Vaccines.

Methodology: Eligible parents of patients seen at the Pediatric Outpatient Department, Pediatric Emergency Room and Pediatric Wards of the Philippine General Hospital were recruited into the study. The original survey tool was translated to Filipino by the Sentro ng Wikang Filipino. A focus group of four experts in the field of vaccination rated the content of each item on the questionnaire based on its relevance. Ten Filipino speaking participants were then recruited to check its face validity. This was then implemented to 67 Filipino speaking participants to check its test-retest reliability.

Results: The overall item content validity index of the questionnaire was computed to be 0.95. All items had a 100% rating in terms of clarity and simplicity. The high intraclass correlation coefficient of 0.970 supports the tool's test-retest reliability. However, the test had a low Cronbach's α coefficient of 0.687 which could be increased to 0.711 with the removal of one item from the question pool.

Conclusion: The Filipino Translated Questionnaire on Parent Attitudes About Childhood Vaccines has face and content validity with an acceptable internal consistency. This can serve as a framework for future researches on vaccine hesitancy.

KEYWORDS: *immunization, vaccination, questionnaires, Filipino*

INTRODUCTION

Childhood vaccination is regarded as one of public health's groundbreaking accomplishments. Development of immunization policies have significantly decreased child morbidities and deaths related to certain diseases globally. The success of these programs relies heavily on vaccine compliance in lessening vaccine-preventable diseases (VPD). Immunized children benefit directly from vaccinations and significant community vaccination coverage rates have added protection via herd immunity.[1] Despite the proven efficacy of vaccination and its acceptance worldwide, a growing proportion of parents have refused vaccinating their children for different reasons.[2] Diminished trust in vaccination has led to outbreaks in diseases. This has put hindrances towards global elimination of diseases such as polio which have sparked political discussions in different nations worldwide.[3] The World Health Organization (WHO) defined 'vaccine hesitancy' as the delay in acceptance or refusal of vaccination despite availability of vaccination services.[4]

Given the rising global issue of vaccine hesitancy, the WHO launched the Strategic Advisory Group of Experts (SAGE) Working Group on Vaccine Hesitancy. They were tasked to approach this problem and deliver evidence-based analyses and solutions.[4] The SAGE Working Group saw the necessity to outline the reasons for vaccine hesitancy. Development of this matrix of determinants involved extensive review of literature.[5] Factors were subdivided into different categories exploring the scope of vaccine hesitancy. The work of Opel *et. al.* was among the first to develop and validate a survey tool specific to vaccine hesitancy, the Parent Attitudes About Childhood Vaccines (PACV) survey. This tool was developed by incorporating results from previous studies in order to add to the item pool. Screening and content validation were conducted by a group of experts in the field of immunization, and pre-testing the validated tool on a group of parents.[6] A prospective cohort study on 437 parents of children under an integrated health care system based in Seattle showed that scores on the PACV predict childhood immunization status and have high reliability. It was recommended that results be validated in different geographic and demographic samples of parents.[7]

The Department of Health (DOH) of the Republic of the Philippines was alarmed that a significant number of parents refused to avail of the government's various vaccination programs following the issue regarding the newly introduced dengue vaccine.[8] Several studies related to vaccine hesitancy, its determinants, and its impact in the different regions of the world are already available but there is a dearth of investigations done in the Philippines. With this in mind, efforts have been made to address the growing hesitancy and refusal of parents for vaccine administration to their child. To increase the possibility of success in this endeavor, the development of a means of measuring vaccine hesitancy in certain population groups is necessary to determine reasons contributing to it. This study was undertaken to determine the content validity, face validity and test-retest reliability of a Filipino Translated Questionnaire on Parent Attitudes About Childhood Vaccines.

MATERIALS AND METHODS

Description of the Study Setting

This is a tool validation study. Convenience sampling was done. Parents/legally authorized representatives of patients 15 months to 6 years seen at

the Outpatient Department or admitted at the Pediatric Wards and Emergency Room were enrolled in this study. The hospital has a 1,500-bed capacity with 200 patients admitted at the UP-PGH Department of Pediatrics. Each month, there are at least 600 new pediatric admissions and 1000 outpatient consults.

Participants

Tagalog-speaking parents of Filipino children aged 15 months to 6 years who consulted at the Philippine General Hospital Pediatrics Outpatient Department Section, Pediatrics Emergency Room and Pediatrics Wards 9 and 11 from July 2019 to August 2019 were eligible to participate in the study. The minimum age was set at 15 months as it is expected that a child would have been given all the vaccine doses prescribed in the National Immunization Program by that age if the parents are fully compliant. A maximum age of 6 years was set to account for catch-up immunization. Parents of patients requiring resuscitation, in cardiorespiratory distress, or were immunocompromised, were excluded from this study.

Potential respondents were identified through the census in the pediatric wards, emergency room and outpatient department. Available respondents were recruited into the study by the principal investigator. The age and clinical status of the child were identified during the recruitment of respondents. Among eligible subjects, only those who gave consent were included in this study.

Tool Validation and Data Collection

Approval from the main author of the PACV survey was sought before study initiation. The English questionnaire was translated into Filipino by a linguist from *Sentro ng Wikang Filipino-Manila*. This office located in the University of the Philippines in Manila, undertakes translation, writing and publication of materials into Filipino. The translated questionnaire underwent assessment for content validity by 4 experts in the field of vaccination. Each of the non-demographic questions (15 items) were assessed using a 4-point ordinal scale: 1 = not relevant, 2 = somewhat relevant, 3 = quite relevant, 4 = highly relevant. Items with low content validity index (CVI) were revised based on comments or suggestions of the 4 experts. CVI was computed again for the revised items in the translated PACV survey.

The revised translated PACV survey were then administered to ten parents/ legally authorized representatives to assess the face validity of each question based on clarity and simplicity. Agreement was assessed using yes or no responses and the level of agreement was computed.

The final translated PACV survey was administered using a test-retest design to a sample of parents/ legally authorized representatives who consented for the study. The initial assessment was done right after the informed consent process. The second assessment was done during the next patient follow-up which was at least 2 weeks from initial assessment. Privacy was ensured for all respondents while answering the questionnaire and they were provided 10 to 15 minutes to answer all items. The responses of participants during the re-test assessment were used to determine the acceptability and internal consistency reliability of the translated PACV survey.

Sample Size

The minimum sample size needed was computed using an online software by Arifin (2018).[9] Based on the expected test-retest reliability coefficient of 0.844 from the study of Opel et. al. 2011, a minimum acceptable reliability of 0.7, 80% power,

95% confidence interval, and an adjustment of 10% drop-out rate, the needed minimum sample size was 67. [10]

STATISTICAL ANALYSIS

The respondents' characteristics were described using frequencies and proportion. Content validity was determined using the item content validity index (I-CVI), based on the expert panel's rating on item relevance. A CVI greater than 0.78 per item was considered as acceptable.[11] Face validity was determined by computing for the level of agreement among the ten respondents based on clarity and simplicity. The level of agreement was computed by the proportion of "yes" response per item. Items with at least 75% level of agreement were considered acceptable.[12] Test-retest reliability was determined by computing for the Intraclass correlation coefficient. A cut-off value of 0.70 was considered evidence of acceptable reliability.[13] Acceptability was determined by obtaining the percentage of no response per item. Finally, Cronbach's alpha was computed for the 10 items using 5-point likert scales to determine internal consistency. A value of at least 0.70 was considered acceptable.[14]All analyses was done using Microsoft Excel and SPSS v23.

RESULTS

Population

A focus group of four experts in the field of vaccination rated the content of each item based on its relevance. Two of the experts are physicians who work in the field of public health while the other two are pediatricians, one of which is an Infectious Disease Specialist. Seventy-seven participants from the Pediatric OPD, Pediatric Emergency Room and Pediatric Wards who fulfilled the inclusion criteria were recruited. Ten of the participants rated each item on the level of agreement based on its simplicity and clarity. The sixty-seven participants then answered the questionnaire for its test-retest reliability. Majority (70.12%) of participants were females. The mean age of participants was 34.5 years with 63% of participants aged 30 years and above. Thirty five percent of participants were married, while 66% were in a common law relationship. The highest educational status attained by majority of participants is secondary education at 66%. (See Table 1).

Table 1 Sociodemographic profile of respondents

Variables	Population n = 77	Percentage %
Parent of child		
No	**1**	**1.2**
Yes	**76**	**98.8**
Parent's age ≥30 years		
No	**24**	**31.1**
Yes	**53**	**68.8**
Parent's marital status		
Single, separated, widowed, or divorced	**1**	**1.2**
Married	**25**	**32.4**
Living with a partner	**51**	**66.2**
Household income		
< 10,000	**46**	**59.7**
10,000 – 20,000	**23**	**29.8**
20,000 – 30,000	**3**	**3.8**
>30,000	**5**	**6.4**
Parent's educational level		
≤High school graduate	**64**	**83**
Some college	**13**	**17**
No. of children in household		
1	**14**	**18.1**
≥2	**63**	**81.9**

Content and Face Validity

Table 2 shows that majority (3-4) gave a high content validity rating on all questions. The content validity index for each question is high at 0.75 to 1.0 and the overall CVI is 0.95 which supports the content validity of the questionnaire.

All questions had 100% rating in terms of clarity and simplicity which supports the face validity of the tool.

Table 2. Content validity indices of the items in the final translated PACV survey

Item #	Rater 1	Rater 2	Rater 3	Rater 4	CVI
1	2	4	4	4	0.75
2	4	3	4	4	1
3	1	3	4	4	0.75
4	3	4	4	4	1
5	4	4	4	4	1
6	1	4	4	4	0.75
7	3	4	4	4	1
8	4	4	4	4	1
9	3	4	4	4	1
10	3	3	4	4	1
11	4	4	4	4	1
12	4	3	4	4	1
13	4	4	4	4	1
14	4	4	4	4	1
15	4	4	4	4	1
S-CVI/AVE = 0.95 Total agreement= 12					

Test-retest reliability

The questionnaire had a high test-retest Pearson's correlation (0.970) which supports the reliability of the tool. Cronbach's alpha is low at 0.687. Item number 5 can be removed to increase alpha to an acceptable rating of 0.711.

The fifteen non-demographic items with the corresponding responses are listed in Table 3. These 15 items were translated from the original PACV questionnaire which were developed from three domains. Items 1-3,11 and 12 were developed under the domain Immunization Behavior in the original study. These sets of responses are generally non-hesitant with percentage of answers ranging from 77.6 – 95.5%. In the domain, Beliefs about Vaccine Safety and Efficacy (Items 4-10), there is a higher percentage of hesitant responses per item ranging from 13.4 – 46.3 %. The Trust domain comprised the remaining items 13-15 which had the highest non-hesitant set of responses ranging from 88 -97%.

Table 3. Summary of responses to the final translated PACV survey

Item Number	Not hesitant (N;%)	Not sure (N;%)	Hesitant (N;%)
1. Nangyari na bang hindi mo pinabakunahan sa tamang oras ang iyong anak kahit wala siyang sakit o allergy?	52 (77.6)	2 (3.0)	13 (19.4)
2.May pagkakataon bang nagpasya ka na hindi pabakunahan ang iyong anak sa ibang kadahilanan maliban sa sakit o allergy?	56 (83.5)	6 (9.0)	5 (7.5)
3. Gaano ka kasigurado na ang ipinapayong iskedyul ng bakuna ay makababuti sa iyong anak?	55 (82.1)	0 (0.0)	12 (17.9)
4. Ang mga bata ay nabibigyan ng bakuna na sobra sa kung ano ang makababuti sa kanila.	27 (40.3)	15 (22.4)	25 (37.3)
5. Naniniwala ako na ang mga sakit na naaagapan ng bakuna ay malulubhang sakit.	44 (65.7)	10 (14.9)	13 (19.4)
6. Mas mabuti na magkasakit sa natural na paraan ang anak ko kaysa sa magpabakuna	53 (79.1)	5 (7.5)	9 (13.4)
7. Mas maigi na mabigyan ang mga bata ng mas kaunting bakuna sa isang pagkakataon.	40 (59.7)	11 (16.4)	16 (23.9)
8. Gaano ka nag-aalala na maaaring magkaroon ng masamang epekto ang bakuna sa iyong anak?	35 (52.2)	3 (4.5)	29 (43.3)
9. Gaano ka nag-aalala na maaaring hindi ligtas ibigay ang bakuna sa iyong anak?	32 (47.8)	6 (8.9)	29 (32.3)

DISCUSSION

Vaccine hesitancy has context specific determinants which span different regions in the world. These sentiments have been extensively studied in other countries as mentioned by Larson et al. [3] Tools have been created as a result of decreasing vaccination rates to identify such determinants. Tool development has since then helped understand the generally positive response of some regions toward vaccination. In the Philippines there is a looming need to address vaccine hesitancy from a public health perspective given the recent drops in vaccination rates. [15] Despite the vast majority of studies done in this field, there are no tools developed to measure vaccine hesitancy in the Philippines. Translated from an accepted and validated PACV survey, this tool was validated with the goal of developing a means of assessing vaccine hesitancy in the Philippine setting.

In this study, the Filipino Translated Questionnaire on Parent Attitudes About Childhood Vaccines showed high content validity among the 4 experts with overall agreement in 12 of the 15 non-demographic items in the tool. The remaining three items were reworded to improve readability among laypeople. Upon administration to the first ten participants, there was a unanimous agreement among parents that the survey items were clear and simple to understand (N=10). This was then administered to the 67 participants which showed that the translated PACV has a high test-retest reliability as supported by a high intraclass correlation coefficient of 0.970.

The internal consistency however had a low Cronbach's α coefficient with an overall coefficient of 0.687. On review of responses and feedback of patients, some of the respondents' answers would have incongruences under similar domains. The original validation study by Opel et. al. had three domains identified in its questionnaire. [2] These were Immunization Behavior, Vaccine Safety and Efficacy, and Trust. In this study, the internal consistency for individual domains were low ranging from 0.468-0.632. On data analysis, removal of item number 5 "Naniniwala ako na ang mga sakit na naaagapan ng bakuna ay malulubhang sakit." would increase the overall coefficient to 0.711 (See Table 3).

LIMITATIONS

The team recognizes that this study has limitations. The test-retest phase of tool development was completed after the measles epidemic. The timing of the survey may have affected parents' responses to the questionnaire. In addition, all participants were derived from one institution in the National Capital Region limiting the generalizability of results. The sample population were obtained from convenience sampling. This questionnaire was translated to Filipino and will still bring about different contextual meanings. Although this test has been administered globally, the team understands the need for tools to be available in the native tongue. The study team attempted to preserve each item's readability and inherent meaning by having it officially translated by the Sentro ng Wikang Filipino as well as having it screened by both an expert panel and the target study population.

CONCLUSION

The translated Filipino PACV is a useful 21-item tool to identify possible reasons for vaccine hesitancy among Filipino parents. The remaining 14 non-demographic items on the Filipino Translated Questionnaire on PACV have face and content validity with an acceptable internal consistency.

RECOMMENDATIONS

Future studies can be done geared towards improving internal consistency in the questionnaire by adjusting item phrasing to improve readability. Expanding the study sites to include communities outside a tertiary hospital setting will also bring about a broader study population. The next phase of this study should test the tool's predictive and content validity. Focus should be placed on further psychometric evaluation to measure association of sociodemographic features and vaccine hesitancy. This is already being done globally in the original PACV survey. This study can serve as a framework for future studies in correlating behaviors affecting vaccine hesitancy. Original tool development should be contemplated by future researchers to uncover domains and behaviors towards vaccine hesitancy which are more appropriate to the Filipino context.

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Figure 1. Validated Filipino Translated Questionnaire on Parent Attitudes and Vaccine Survey

1. Siya ba ang panganay mong anak? ☐**Oo** ☐**Hindi**

2. Ano ang relasyon mo sa kanya? ☐**Ina** ☐**Ama** ☐**Iba:**_____

3. Nangyari na bang hindi mo pinabakunahan sa tamang oras ang iyong anak kahit wala siyang sakit o allergy?	**Oo** ☐	**Hindi** ☐	***Hindi ko alam*** ☐
4. May pagkakataon bang nagpasya ka na hindi pabakunahan ang iyong anak sa ibang kadahilanan maliban sa sakit o allergy?	**Oo** ☐	**Hindi** ☐	***Hindi ko alam*** ☐

5. Gaano ka kasigurado na ang ipinapayong iskedyul ng bakuna ay makabubuti sa iyong anak? Sagutan ang panukatan na 0 hanggang 10, kung saan ang 0 ay *Hindi talaga sigurado* at ang 10 ay *Siguradong sigurado.*

Hindi talaga sigurado — **Siguradong sigurado**

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

	Mahigpit na sumasang-ayon	**Sumasang-ayon**	**Hindi sigurado**	**Hindi sumasang-ayon**	**Lubos na hindi sumasang-ayon**
6. Ang mga bata ay nabibigyan ng bakuna na sobra sa kung ano ang makabubuti sa kanila.	☐	☐	☐	☐	☐
7. Mas mabuti na magkasakit sa natural na paraan ang anak ko kaysa sa magpabakuna	☐	☐	☐	☐	☐

8. Mas maigi na mabigyan ang mga bata ng mas kaunting bakuna sa isang pagkakataon.	☐	☐	☐	☐	☐
	Hindi nag-aalala	**Hindi gaanong nag-aalala**	**Hindi sigurado**	**Medyo nag-aalala**	**Sobrang nag-aalala**
9. Gaano ka nag-aalala na maaaring magkaroon ng masamang epekto ang bakuna sa iyong anak?	☐	☐	☐	☐	☐
10. Gaano ka nag-aalala na maaaring hindi ligtas ibigay ang bakuna sa iyong anak?	☐	☐	☐	☐	☐
11. Gaano ka nag-aalala na maaaring hindi rin mapipigilan ng bakuna ang sakit?	☐	☐	☐	☐	☐

12. Kung magkakaanak ka ulit ngayon, gugustuhin mo bang mabigyan siya ng lahat ng inirerekomendang bakuna?	**Oo**	**Hindi**	***Hindi ko alam***
	☐	☐	☐

13. Sa pangkalahatan, gaano ka nag-aalinlangan sa mga bakunang pambata?	**Hindi Nag-aalinlangan**	**Di masyadong Nag-aalinlangan**	**Hindi sigurado**	**Nag-aalinlangan**	**Sobra Pag-aalinlangan**
	☐	☐	☐	☐	☐
14. Nagtitiwala ako sa mga impormasyong natatanggap ko ukol sa bakuna.	**Lubos ayon sumasang ayon**	**Sumasang-sigurado**	**Hindi sumasang-ayon**	**Hindi na**	**Lubos na sumasang--ayon**
	☐	☐	☐	☐	☐
15. Malaya kong nasasabi sa doktor ng aking anak ang mga bumabagabag sa akin tungkol sa bakuna.	☐	☐	☐	☐	☐

16. Matapos isaalang-alang ang lahat ng bagay, gaano ka nagtitiwala sa doktor ng iyong anak. Sagutin ang panukatan na 0 hanggang 10, kung saan ang 0 ay *Hindi talaga nagtitiwala* at ang 10 ay *Tiwalang-tiwala.*

Hindi talaga nagtitiwala — **Tiwalang-tiwala**

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Ang mga susunod na katanugan ay tungkol sa'yo. Pumili lamang ng isang sagot at lagyan ito ng check mark.

17. Ilang taon ka na?
☐ 18-29 taong gulang
☐ 30 taong gulang o mahigiy

18. Ano ang iyong estadong sibil?
☐ Walang asawa
☐ Kasal
☐ May kinakasama
☐ Nabalo
☐ Hiwalay

19. Ano ang pinakamataas na antas ng edukasyon ang natapos mo?
☐ Elementarya
☐ Hayskul, ngunit hindi nakapagtapos
☐ Nakapagtapos ng hayskul
☐ Nakatungtong ng kolehiyo ngunit hindi nakapagtapos o nakatapos ng 2-year degree
☐ Nakapagtapos ng kolehiyo (4-year course)
☐ Higit pa sa 4 na taong digri sa kolehiyo

20. Gaano kalaki ang kinikita ng inyong pamilya sa loob ng isang buwan?
☐ P10,000 o mas mababa pa
☐ P10,000-20,000
☐ P20,000-30,000
☐ P30,000 o mahigit pa

21. Ilan ang bata sa iyong sambahayan?
☐ Isa
☐ Dalawa
☐ Tatlo
☐ Apat o mahigit

ORIGINAL ARTICLE

DEVELOPMENT OF A CLINICAL RISK SCORE TO DIAGNOSE CONCURRENT BACTERIAL INFECTIONS IN CHILDREN WITH DENGUE

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

3RD PRIZE 2020 PIDSP RESEARCH CONTEST

ABSTRACT

Background: The clinical course of dengue can be adversely affected by bacterial coinfection. Because of this, clinical manifestations may be severe and may lead to morbidity and mortality. Little is known about this dual infection in the pediatric population.

Objectives: This study was conducted to evaluate the clinical characteristics and risk factors of patients with dengue infection and coinfection and subsequently develop a scoring system to diagnose bacterial coinfection in patients with dengue.

Methods: A prospective cross-sectional observational study was conducted among hospitalized pediatric patients with confirmed dengue infection between January 2019 to August 2019. Baseline characteristics, risk factors, clinical parameters, laboratory findings, management and outcomes were recorded. Cases with concurrent bacterial infections were further analyzed. A scoring system was created which assigned 1 point each for the following risk factors - age ≤9 years, fever >5 days, dengue severe, and 2 points for CRP >12 mg/l)

Results: A total of 154 pediatric dengue patients were enrolled with a mean age of 8.54 ± 4.15 years, and 99 patients (64%) had bacterial coinfection. Patients with coinfection were A total of 154 pediatric dengue patients were enrolled with a mean age of 8.54 ± 4.15 years, and 99 patients (%) had bacterial co-infection. Patients with co-infection were younger, have prolonged fever (>5 days), and were more frequently observed to have hypotension, tachycardia, desaturations and bleeding. Patients with coinfection also had higher white blood cell counts (>8 x109 cells/L), higher neutrophil counts (58.80 ± 18.42 % count), and elevated CRP (>12 mg/l) and procalcitonin (>4.01 ng/L). Utilizing the scoring system developed, a score of ≥3 had a sensitivity of 66.67% and specificity of 76.36%, in diagnosing concurrent bacterial infection in children with dengue.

Conclusions: Patients with dengue and bacterial coinfections were younger with comorbidities. They presented with significantly abnormal vital signs, physical examination findings, and elevated acute phase reactants. Using age ≤ 9 years, fever >5 days, dengue severe, and CRP >12mg/l, a scoring system was developed to diagnose bacterial coinfection in patients with dengue. A score of ≥3 can help diagnose patients with dengue and bacterial coinfection who will most likely need early empiric antimicrobial therapy.

KEYWORDS: *Dengue, Concurrent Bacterial Infection, Risk Score*

INTRODUCTION

Dengue is a fast-emerging pandemic-prone viral disease affecting many parts of the world [1]. Globally, it is responsible for nearly 500,000 hospitalizations and 3.6 billion people remain at risk. In the Philippines, dengue illness is considered one of the country's eight pervasive infectious diseases [2]. Of the ten Association of Southeast Asian Nations (ASEAN) member countries, the Philippines ranks fourth in the number of dengue cases.

Dengue virus infection in humans is often inapparent[1] but can lead to a wide range of clinical manifestations that vary according to age and severity[3] and often with unpredictable clinical evolution and outcome [4]. The severity of infection depends on several factors related to the virus and host. Fluid management and antipyretic therapy with paracetamol is preferred during the febrile phase. Judicious fluid administration remains the mainstay of treatment during the critical phase [5]. However, optimal management of dengue may differ once it is confounded by bacterial coinfection. In addition, the clinical course of dengue infection can be adversely affected by bacterial coinfection. Due to complex interactions between pathogens [6], clinical manifestations may be severe and may lead to morbidity and mortality.

The problem in managing patients with dengue is identification of patients with concurrent bacterial infections. The clinical and laboratory presentation of dengue and some other bacterial infections such as leptospirosis, salmonellosis and bacteremia overlap [6, 7, 8], hence they are easily overlooked in a dengue endemic setting [9]. The diagnosis of coinfections proves to be challenging especially during dengue outbreaks [10]. This may lead to missed diagnosis due to unusual clinical presentations and may lead to delays in antibiotic therapy [6].

To identify concurrent bacterial infection among patients with confirmed dengue infection, serum inflammatory markers such as C-reactive protein (CRP) and Procalcitonin (PCT) may be utilized. Studies on the use of these inflammatory markers in pediatrics are still limited compared to studies performed in adults. The normal serum value of PCT is <0.1 ng/mL. The greatest elevation of serum PCT are seen in bacterial infections. In a study by Chen et. al. in adult patients with dengue and bacterial coinfections admitted in the ICU, they found the sensitivity and specificity of procalcitonin to be 81.5% and 59.5% respectively using a cutoff value of 1.14 ng/mL [11]. The NPV can be up to 89.8% in these situations, and this finding suggest that procalcitonin can be used for excluding concomitant bacteremia among dengue patients in the ICU.

On the other hand, CRP is a non-specific, acute-phase protein that increases 4-6 hours after exposure to an inflammatory trigger (infectious or not) and has an 8-hour doubling time, peaking from 36 to 50 hours after trigger stimulus. [12]. It is not a specific biomarker for differentiating infection from inflammation or for identifying specific infectious agents. [13]. Due to the limited specificity of CRP, the combined use of CRP with other biomarkers such as procalcitonin is being done [13].

There are several studies on the clinical characteristics and risk factors of patients with dengue infections and concurrent bacteremia [6, 9] however these studies were exclusively done in adults. Little is known about the incidence and risk factors for this dual infection in the pediatric population, thus this study was done to evaluate the clinical characteristics of patients with dengue infection and concurrent bacterial infections and to identify risk factors for these dual infections. It intended to create a scoring system to diagnose concurrent bacterial infection in patients with dengue to help clinicians start timely antibiotic therapy in patients with dengue infection.

MATERIALS AND METHODS

This was a prospective cross-sectional observational study conducted from July 2018 to August 2019 at a tertiary hospital in Metro Manila. The study participants were pediatric patients 1

month to 18 years old and 365 days admitted for a period of <72 hours. Those who were clinically diagnosed with dengue based on the 2009 WHO Dengue Case Classification *or* has laboratory confirmation of dengue through a positive anti-dengue immunoglobulin M (IgM) antibody (enzyme-linked immunosorbent assay [ELISA]) *and/or* dengue non-structural protein 1 (NS1) antigen *and* fever of >7 days and/*or* clinical deterioration despite treatment based on standardized dengue care pathways and/*or* alterations in laboratory parameters such as hyponatremia, elevated leukocyte count for age, high neutrophil counts for age, and elevated creatinine (from kidney failure due to shock) were included. Patients were excluded if they were previously hospitalized in another institution in the last 10 days or was a clinically and laboratory confirmed dengue case but admitted for more than 72 hours in our institution.

Subject Enrollment and Collection of Patient Data

Subjects who were eligible were enrolled after the informed consent process. A complete history was obtained and thorough physical examination was done. Patient's age, sex, height, weight, education, co-morbidities, and dengue vaccine history, were recorded on the data collection form. Clinical data collected included signs and symptoms such as presence and duration of fever, abdominal pain, persistent vomiting, mucosal bleeding, rash, aches and pains, difficulty of breathing, headache, loose stools, dysuria, cough and chest pain. Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, temperature, oxygen saturation), presence or absence of fluid accumulation, spontaneous bleeding, and liver enlargement were also recorded. Laboratory data collected were hemoglobin, hematocrit, white blood cell count, neutrophils, lymphocytes, platelet count, albumin, alanine transaminases (ALT) and aspartate transaminases (AST), sodium, potassium, calcium, chloride, creatinine, blood urea nitrogen (BUN), CK-MB, and glomerular filtration rate (GFR).

Concurrent bacterial infection was defined as any clinical diagnosis of bacterial infection (e.g. pneumonia) and/or any bacteremia or bacteriuria from cultures taken within 72 hours from admission. Conventional blood and urine cultures were done, with the former supplemented by an automated BacT/Alert System (bioMerieux SA, Durham NC, USA). Patients with blood or urine cultures positive for coagulase-negative staphylococci were considered to have concurrent bacterial infection if the following were conditions were met: (1) with two or more positive blood cultures from different anatomic sites, (2) a positive culture from blood and another usually sterile site with identical antimicrobial susceptibility patterns, (3) growth in continuously monitored blood culture system within 15 hours of incubation, (4) clinical findings of infection, (5) an intravascular catheter has been in place for 3 days or more, and (6) similar or identical genotypes among isolates[14].

Acute phase reactants such as procalcitonin and CRP were also taken upon enrollment of patients. Quantitative determination of procalcitonin was measured using a homogenous immunoassay method (Thermo Scientific B·R·A·H·M·S PCT sensitive KRYPTOR, Hennigsdorf, Germany) with the procedure performed according to manufacturer's instructions. The detection limit for the PCT assay was 0.02 ng/mL. C-reactive protein (CRP) was determined semi-quantitatively using latex agglutination (rheumajet CRP, Biokit). The detection limit was 6 mg/l of C-reactive protein.

Candidate variables that were reliably measured and readily available at the time of presentation were selected for the diagnostic model.

ETHICAL CONSIDERATIONS

The research protocol was approved by the Institutional Review and Ethics Committee of the Philippine Children's Medical Center. The study adhered to ethical considerations and principles set out in relevant guidelines, including the Declaration

of Helsinki, WHO guidelines, International Conference on Harmonization-Good Clinical Practice, Data Privacy Act of 2012, and National Ethics Guidelines for Health Research.

STATISTICAL ANALYSIS

The minimum computed sample size was 279 subjects. This value gives 90% power to detect an effect size of 0.417 at 0.05 α-level of significance. The value used for this sample size computation was based on a study by See et. al. in 2013 [15]. However, the sample size achieved was only 154 subjects.

Descriptive statistics was used to summarize the general and clinical characteristics of participants. Frequencies and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables. Independent T-test, Mann-Whitney U test, and Fisher's exact/Chi-square test was used to determine the difference of mean, median, and frequencies between patients with concurrent bacterial infection versus those without, respectively.

Multivariate analysis and formulation of the scoring system

Crude and adjusted odds ratio and the corresponding 95% confidence intervals from binary logistic regression were computed to determine predictors of concurrent bacterial infection. The corresponding coefficients in the regression were used to create a scoring system to assess the risk of having infection, following the method described by Tai and Machin in 2014 [16]. The regression coefficients were used as a basis for the scoring system. First, the constant term was dropped then the coefficients were divided to the least figure. Next, all coefficients were rounded off to the nearest integer. A constant value equivalent to the sum of all negative points was then added to avoid a negative point (e.g. for a point system $y = -4x_1 + 3x_2 + -2x_3$, a constant equal to +6 was added). For this data set, there were no negative coefficients and thus did not require a constant value.

All valid data were included for analysis while missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05α-level of significance. STATA 15.0 was used for data analysis.

RESULTS

We included in our study a total of 154 pediatric patients comprising 76 males and 78 females, with a median age of 8 years old. Most patients (55.19%) are in elementary (Table 1). Thirty-three percent were positive for Dengue NS1, while 94% of the patients who were tested with dengue immunoglobulin M (IgM) were positive. Most of the patients (87.66%) were classified as dengue severe.

Table 1. Demographic and clinical profile of patients (n= 154)

	Total (n = 154)	With co-infection (n = 99)	Without co-infection (n = 55)	*p*
	Frequency (%); Median (Range); Mean ± SD			
Age, years	8.54 ± 4.15	7.76 ± 3.82	9.94 ± 4.37	**0.002***
<12 months	5 (3.25)	4 (4.04)	1 (1.92)	
1 – 5 years	31 (20.13)	23 (23.23)	8 (14.55)	
6 – 9 years	58 (37.66)	41 (41.41)	17 (30.91)	
10 – 12 years	33 (21.43)	22 (22.22)	11 (20)	
13 – 15 years	16 (10.39)	5 (5.05)	11 (20)	
16 – 17 years	11 (7.14)	4 (4.04)	7 (12.73)	
Sex				0.962†
Male	76 (49.35)	49 (49.49)	27 (49.09)	
Female	78 (50.65)	50 (50.51)	28 (50.91)	
Education				**0.031‡**
Out of school	4 (2.60)	4 (4.04)	0	
Elementary	85 (55.19)	57 (57.58)	28 (50.91)	
High school	31 (20.13)	14 (14.14)	17 (30.91)	
College	1 (0.65)	0	1 (1.82)	
Others	33 (21.43)	24 (24.24)	9 (16.36)	
Co-morbidities				
CHD	7 (4.55)	7 (07.07)	0	0.051‡
Asthma	1 (0.65)	1 (1.01)	0	1.000‡
CKD	1 (0.65)	1 (1.01)	0	1.000‡
Others	4 (2.60)	3 (3.03)	1 (1.79)	1.000†
Symptoms				
Fever, days	5.60 ± 1.51	5.94 ± 1.62	4.98 ± 1.03	**<0.001***
Abdominal pain	106 (68.83)	67 (67.68)	39 (70.91)	0.678†
Persistent vomiting	102 (66.23)	63 (63.64)	39 (70.91)	0.360†
Aches and pains	53 (34.42)	33 (33.33)	20 (36.36)	0.704†
Headache	39 (25.32)	22 (22.22)	17 (30.91)	0.235†
Cough	30 (19.48)	26 (26.26)	4 (7.27)	**0.004†**
Mucosal bleeding	28 (18.18)	20 (20.20)	8 (14.55)	0.383†
Weakness	19 (12.34)	14 (14.14)	5 (9.09)	0.361†
Rash	13 (8.44)	8 (8.08)	5 (9.09)	1.000‡
Decreased urine output	11 (7.14)	7 (7.07)	4 (7.27)	1.000‡
Others	36 (23.38)	25 (25.25)	11 (20)	0.461†
Dengue vaccine	7 (4.55)	3 (3.03)	4 (7.27)	0.249‡
Previous dengue infection	1 (0.65)	1 (1.01)	0	1.000‡

CHD- congenital heart disease; CKD- chronic kidney disease
*Statistical Tests Used: * - Independent t-test; † - Chi-square Independent test; ‡ - Fisher's Exact test*

Patients presented with fever after a median of 5.6 days (sd ± 1.51). Of the 154 pediatric patients

who were included, 99 (64.29%) were classified as having bacterial co-infections (Table 2).

Table 2. Dengue features of patients (n = 154)

	Frequency (%)
Dengue fever testing	
Dengue NS1	51 (33.12)
Dengue IgM	119 (77.27)
Negative	7 (5.88)
Positive	112 (94.12)
Dengue classification	
Dengue Severe	135 (87.66)
Dengue with Warning Signs	19 (12.34)
Without concurrent bacterial infection	55 (35.71)
With concurrent bacterial infection	99 (64.29)
Pneumonia	88 (88.89)
LCBSI	11 (11.11)
UTI	9 (9.09)
Leptospirosis	1 (1.01)
Cellulitis	1 (1.01)
Meningitis	1 (1.01)

LCBSI – Laboratory-confirmed bloodstream infections;
UTI – Urinary tract infection

Of these 99 patients with bacterial co-infections, 88 (88.89%) had pneumonia, 11 (11.11%) had laboratory confirmed blood stream infection (LCBSI), 9 (9.09%) had culture confirmed urinary tract infection (UTI), and the rest had either leptospirosis, cellulitis, or meningitis. Pneumonia cases were diagnosed based on the presence of radiological features and accompanying symptoms (eg. cough, tachypnea, rales, chest pain, etc.). Leptospirosis was diagnosed based on molecular detection (Real-Time PCR) of pathogenic *Leptospira spp*. DNA from the blood of the patient. The diagnosis of meningitis was based on the presence of seizures and decreased sensorium and cerebrospinal fluid (CSF) findings of low sugar level along with an increased white blood cell count and increased protein. Lastly the diagnosis of cellulitis was based on physical examination findings of the skin or soft tissue which showed swelling, erythema, tenderness and warmth. There were no other infections noted. Of the patients with positive blood cultures, *Escherichia coli* was isolated in 2 patients, and one of each grew Methicillin-sensitive *Staphylococcus aureus, Streptococcus mitis, Salmonella sp., Klebsiella pneumoniae, Acinetobacter baumanii, Sphingomonas paucimobilis* and *Aeromonas hydrophilia* and were isolated singly from different patients. In those with positive urine cultures, Escherichia *coli* was isolated in seven patients, and *Acinetobacter baumanii* and *Morganella morganii, were isolated one* from each patient.

On the average, dengue patients with coinfection were significantly younger (7.78 $\pm$ 3.83 vs 9.87 $\pm$4.37, p = 0.002). Only 13 patients (8.4%) have a comorbidity and seven had congenital heart disease. Other comorbidities noted were asthma (2), chronic kidney disease (2), abnormal uterine bleeding (1), hypoxic ischemic encephalopathy (1), and neurogenic bladder (1). Fever duration was also longer in patients with coinfection, 5.9 days versus 4.9 days (p<0.001).

The group with coinfections had significantly higher cardiac and respiratory rates, and significantly lower blood pressure (Table 3). Abnormal physical examination findings were noted more frequently among patients with coinfection, such as fluid accumulation (68% versus 33%, p <0.001), spontaneous bleeding (44% versus 20%, p=0.002), liver enlargement (53% versus 24%, p=0.001), prolonged capillary refill time (CRT) (77% versus 62%, p=0.049), and poor pulses (71% versus 38%, p<0.001). Average WBC and neutrophil counts were also higher in those with coinfection (Table 3). In addition, among those with coinfections, 40 (40.40%) patients required blood transfusion (vs. 10.91%, p<0.001), and 51 (51.52%) patients required mechanical ventilator (vs. 16.36%, p<0.001) (Table 4).

Table 3. Physical examination/laboratory investigations upon enrollment of patients (n = 154)

	Total (n = 154)	With coinfection (n = 99)	Without coinfection (n = 55)	p
	Mean ± SD; Median (Range) Frequency (%)			
Vital signs				
CR	118.40 ± 22.07	122.92 ± 21.51	110.27 ± 20.85	**0.001***
RR	26 (10 – 58)	28 (10 – 58)	25 (18 – 45)	**0.012§**
SBP	85 (0 – 120)	80 (0 – 120)	90 (0 – 110)	**0.001§**
DBP	60 (0 – 95)	50 (0 – 90)	60 (0 – 95)	**0.002§**
Temperature	37.9 (35 – 40)	38 (35 – 40)	37 (36.2 – 39.7)	**0.011§**
Oxygen saturation	0.98 (0.8 – 1)	0.98 (0.8 – 1)	0.98 (0.9 – 1)	**0.019§**
Within normal ranges				
Blood pressure	24 (15.58)	16 (16.16)	8 (14.55)	0.791†
Cardiac rate	26 (16.88)	11 (11.11)	15 (27.27)	**0.010†**
Respiratory rate	31 (20.13)	15 (15.15)	16 (29.09)	**0.039†**
Fluid accumulation	86 (55.84)	68 (68.69)	18 (32.73)	**<0.001†**
Spontaneous Bleeding	55 (35.71)	44 (44.44)	11 (20)	**0.002†**
Liver enlargement	65 (42.21)	52 (52.53)	13 (23.64)	**0.001†**
Size (cm)	2 (2 – 6)	2.5 (2 – 6)	2 (2 – 6)	0.135§
CRT				**0.049†**
<2 secs	44 (28.57)	23 (23.23)	21 (38.18)	
>2 secs	110 (71.43)	76 (76.77)	34 (61.82)	
Pulse				**<0.001†**
Poor	91 (59.09)	70 (70.71)	21 (38.18)	
Full	63 (40.91)	29 (29.29)	34 (61.82)	
Complete blood count				
Hemoglobin	130.5 (53–208)	130 (53 – 208)	132 (99 – 186)	0.465§
Hematocrit	39.5 (14 – 63)	38 (14 – 63)	41 (32 – 56)	0.108§
WBC (10^9 cells/L)	6.45 (1.5 – 34)	8 (1.5 – 25)	4.7 (1.5 – 34)	**<0.001§**
Lymphocytes (% count)	34 (2 – 91)	30 (3 – 80)	41 (2 – 91)	**0.012§**
Neutrophils (%count)	55.48 ± 18.73	58.80 ± 18.42	49.51 ± 17.95	**0.003***
Platelet (10^9 cells/L)	31 (4 – 254)	29 (4 – 254)	36 (8 – 242)	0.062§
Within normal ranges				
Hemoglobin	44 (28.57)	26 (26.26)	18 (32.73)	0.458†
Hematocrit	64 (41.56)	36 (36.36)	28 (50.91)	0.079†
WBC	49 (31.82)	27 (27.27)	22 (40)	0.104†
Lymphocytes	30 (19.48)	20 (20.20)	10 (18.18)	0.762†
Platelet	11 (7.14)	4 (4.04)	7 (12.73)	0.056‡
Neutrophils	32 (20.78)	25 (25.25)	7 (12.73)	0.066†

CR- cardiac rate; RR- respiratory rate; SBP- systolic blood pressure;
DBP- diastolic blood pressure;
CRT- capillary refill time; WBC- white blood cell
*Statistical Tests Used: * - Independent t-test; † - Chi-square Independent test; ‡ - Fisher's Exact test; § - Mann Whitney U test*

Table 4. Management of patients with dengue (n = 154)

	Total (n = 154)	With coinfection (n = 100)	Without infection (n = 54)	p
	Frequency (%)			
Required blood transfusion	46 (29.87)	39 (39.80)	7 (12.50)	**<0.001†**
Required mechanical ventilator	60 (38.96)	50 (51.02)	10 (17.86)	**<0.001†**
Required inotropes	101 (65.68)	69 (70.41)	32 (57.14)	0.096†
Hemodialysis	13 (8.44)	10 (10.20)	3 (5.36)	0.377‡
Hemoperfusion	13 (8.44)	10 (10.20)	3 (5.36)	0.377‡

Statistical Tests Used: † - Chi-square Independent test; ‡ - Fisher's Exact test

Cephalosporins, specifically cefotaxime (Table 5), were the most common empiric antibiotics given to patients despite absence of a documented coinfection (69.09%). This was followed by aminoglycosides (24.03%) and penicillins (7.79%). In our institution the primary physician decides on the need for an antibiotic if there are abnormal laboratory results pointing to an infection or if patients are not responding to the usual dengue management.

Table 5. Antibiotics used in dengue patients (n = 154)

Cephalosporins	110 (71.43)	83 (84.69)	27 (48.21)	**<0.001†**
Cefotaxime	76 (69.09)	58 (69.88)	18 (66.67)	
Ceftriaxone	25 (22.73)	21 (25.30)	4 (14.81)	
Cefuroxime	9 (8.18)	4 (4.82)	5 (18.52)	
Aminoglycosides	34 (24.03)	27 (29.59)	1 (14.29)	**0.032†**
Gentamicin	33 (89.19)	26 (89.66)	7 (87.50)	
Amikacin	1 (2.70)	1 (3.45)	0	
Penicillin	12 (7.79)	9 (9.18)	3 (5.36)	0.538‡
Penicillin G	7 (58.33)	5 (55.56)	2 (66.67)	
Oxacillin	3 (25)	2 (22.22)	1 (33.33)	
Ampicillin	2 (16.67)	2 (22.22)	0	
Meropenem	8 (5.19)	7 (7.14)	1 (1.79)	0.259‡
Vancomycin	6 (3.90)	6 (6.12)	0	0.087‡
Azithromycin	1 (0.65)	1 (1.02)	0	1.000‡
Fluconazole	1 (0.65)	1 (1.02)	0	1.000‡
Other antibiotics	2 (1.30)	2 (2.0)	0	0.534‡

Statistical Tests Used: † - Chi-square Independent test; ‡ - Fisher's Exact test

As to clinical outcomes (Table 6), evidence was insufficient to make a conclusion as to length of hospital stay. However, those with coinfection had a higher mortality rate versus those without (35.35% vs 9.09%, p=0.001) with an overall mortality of 26%. All mortality were classified as severe dengue cases. (Table 7).

Table 6. Clinical outcomes of patients with dengue (n= 154)

	Total (n = 154)	With coinfection (n = 99)	Without co-infection (n = 55)	p
	Frequency (%); Median (Range); Mean ± SD			
Admission				0.062‡
Ward	24 (15.58)	11 (11.11)	13 (23.64)	
PICU	129 (83.77)	87 (87.88)	42 (76.36)	
IICU	1 (0.65)	1 (1.01)	0	
Length of hospital stay	6 (1 – 56)	6 (1 – 42)	5 (2 – 56)	0.784§
Mortality	40 (25.97)	35 (35.35)	5 (9.09)	**0.001†**

PICU- Pediatric Intensive Care Unit; Intermediate Intensive Care Unit
Statistical Tests Used: † - Chi-square Independent test; ‡ - Fisher's Exact test; § - Mann Whitney U test

Table 7. Survival rate according to Dengue classification (n=154)

	Non-survivor (n = 40)	Survivor (n = 114)	*p*
Dengue classification			**0.004**
DWS	0	19 (16.67)	
DS	40 (100)	95 (83.33)	

DS- Dengue Severe; DWS- Dengue with Warning Signs

Development of a Scoring System

Upon binary logistic regression analysis, the variables age of ≤9 years, fever of more than 5 days, dengue severity, WBC of ≥5 x 109/L, procalcitonin of >0.5 ng/mL, and CRP of >12mg/L, were found to be significantly associated with concurrent bacterial infection (Table 8).

Table 8. Factors associated with concurrent bacterial Infection (n = 154)

	Crude Odds Ratio (95% CI)	*p*	Adjusted Odds Ratio (95% CI)	*p*
Age, years				
≤9	2.447 (1.24 – 4.82)	**0.010**	2.922 (1.30 – 6.59)	**0.010**
>9	Reference	-	Reference	-
Fever, days				
≤5	Reference	-	Reference	-
>5	3.333 (1.63 – 6.80)	**0.001**	**4.120 (1.80 – 9.42)**	**0.001**
Dengue classification				
DWS	Reference	-	Reference	-
DS	4.798 (1.71 – 13.49)	**0.003**	**3.876 (1.07 – 14.02)**	**0.039**
WBC				
≤5 (10^9 cells/L)	Reference	-		
>5 (10^9 cells/L)	2.074 (1.06 – 4.07)	**0.034**		
Procalcitonin				
≤0.5 ng/mL	Reference	-		
>0.5 ng/mL	7.530 (2.32 – 24.48)	**0.001**		
CRP				
≤12 mg/l	Reference	-	Reference	-
>12 mg/l	6.043 (2.48 – 14.72)	**<0.001**	6.028 (2.31 – 15.71)	**<0.001**

WBC- White Blood Cell; CRP- C-Reactive Protein
Adjusted R^2 = 23%; p<0.001

The adjusted model explained 23% in the variation of the prevalence of concurrent bacterial infection (p<0.001). A scoring system was derived based on the regression coefficients of the variables, using the method described by Tai and Machin in 2014 [16]. With this method, age of ≤9 years, fever of more than 5 days, dengue severe, CRP of >12mg/L were used for the final risk score. The item scores ranged from 1 to 2, and the total score ranged from 0 to 5 (Table 9). Overall, among 154 pediatric patients enrolled for the scoring, 16.2% scored 0 or 1, 27% scored 2, and 56.49% scored 3 or more.

Table 9. Proposed scoring system to determine concurrent bacterial infection among pediatric dengue patients

	Reference value	Regression Coefficient	Crude point	Final point
Age ≤9 years	No = 0	**1.072**	0	0
	Yes = 1		1	1
Fever >5 days	No = 0	1.416	0	0
	Yes = 1		1.32	1
Dengue Severe	No = 0	1.355	0	0
	Yes = 1		1.26	1
CRP >12 mg/l	No = 0	1.796	0	0
	Yes = 1		1.68	2

CRP- C-Reactive Protein

Figure 1 and Table 8 show the diagnostic performance at each cut-off points. The maximum Youden's index indicates the optimal cut-off point, and in this case, the optimal cut-off was at 3 points. This means that by using the scoring system defined earlier, a patient with a score of at least three has the optimal discriminative power to distinguish between those with and without bacterial infection, with a sensitivity of 66.67% and specificity of 76.36%.

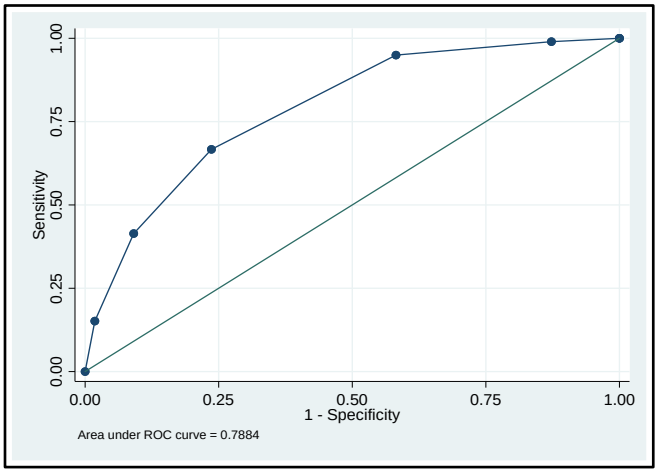

Figure 1. Receiver operating characteristic curve of the proposed scoring system

Optimal Cut-Off of Procalcitonin

Since procalcitonin was not included in the final risk scoring system, we computed for the optimal cut-off of procalcitonin in predicting coinfection among dengue patients. Figure 2 shows the ROC curve of procalcitonin in predicting coinfection among dengue patients. Based on the

highest J index, the suggested optimal cutoff of procalcitonin is > 2.5 ng/mL, with a sensitivity 67.68%, specificity 83.33%, accuracy 73.20%, and Youden's index 51.01%.

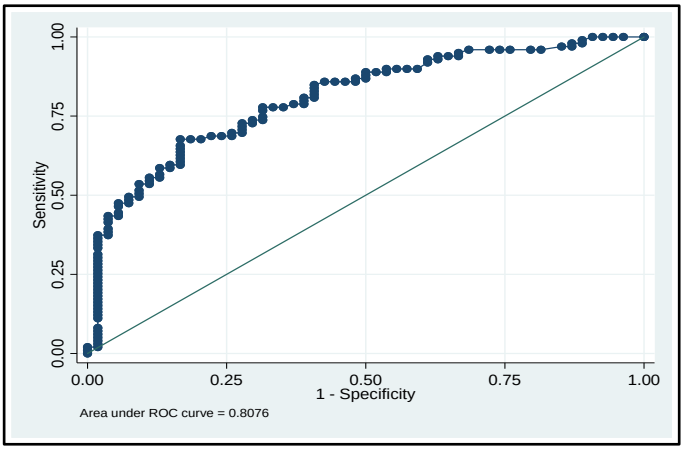

Figure 2. Receiver operating characteristic curve of procalcitonin in predicting concurrent infection

DISCUSSION

Concurrent bacterial infections in patients with dengue are uncommon yet important as they are also associated with mortality [6]. This occurrence was seldom discussed in the past and so hindered widespread awareness of concurrent bacterial infections in patients with dengue [17]. Only four studies investigated on the presence of concurrent bacterial infections in patients with dengue and these were all retrospective [6, 18, 19, 20]. In children, published studies have mostly been case reports. As to our knowledge, this is the first prospective study done to investigate concurrent bacterial infections in children with dengue.

Concurrent bacterial infections in our patients with dengue is associated with high mortality compared to those without concurrent bacterial infections. This is also true in previous studies, although done in adults.[6, 18, 19, 20]. In our study, 64% of enrolled patients were diagnosed with concurrent bacterial infection compared with other studies with a lower occurrence of concurrent bacterial infection at 4-7%. We predicted our data to be high because we did not include all patients with dengue who were admitted at our institution regardless of a suspicion of coinfection. Like others have shown, majority of laboratory confirmed blood stream infections were due to gram-negative organisms [7, 18, 20]. It is postulated that this occurs due to the disintegration of the mucocutaneous barrier due to vascular leakage [19, 21, 22] which results in seepage of bacteria or in microbial translocation (MT) into the bloodstream [22, 23, 24]. This then leads to aberrant cytokine cascade mostly mediated by gram-negative bacteria leading to a worse outcome in dengue patients with coinfection [25]. Other probable reasons for coinfections are rapid urbanization and increased population density, frequent travel, poor sanitation, changing season, and poor infrastructure and inadequate vector control measures [26]. These may explain the wide range of other infections that we found in our study such as pneumonia, meningitis and leptospirosis which have only been highlighted mostly in case reports.

We identified several clinical and laboratory risk factors in dengue patients with concurrent bacterial infection. In our study, younger age (≤9 y) was an important risk factor for concurrent bacterial infection. Age has been a well-established epidemiological risk factor when it comes to disease severity in dengue [27, 28] and has been associated with a poor prognosis [29]. This is probably because of increased microvascular fragility seen in younger children [27].

Similar to the findings of Premaratna, R. et al and Lee et al, our study showed that patients with prolonged fever (>5 days) are at high risk for possible coinfection. The febrile phase usually lasts for 5-7 days [23], however in those with prolonged fever > 5 days, it could be that at the time when they enter the critical phase, increased permeability of the epithelial lining may facilitate entry of microorganisms leading to sepsis [30]. Contrary to the findings of Premaratna, R. et al and Lee et al, See et al did not find fever to be a reliable sign of possible coinfection.

We found that dengue patients with

coinfection have more severe clinical manifestations compared to those without coinfection. In our analysis, patients with coinfection have more fluid accumulation, spontaneous bleeding, and low blood pressure. All these results from excessive plasma leakage due to increased vascular permeability. This group of patients also exhibited lower albumin levels reflecting the severity of plasma leakage. These results share similar findings with a previous study done by Thein et al where patients with dengue and coinfection were more likely to be critically ill with lower albumin levels [6].

Similar to other studies, our results also showed that white blood cell and neutrophils counts were significantly higher in dengue patients with bacterial coinfections [25, 31]. Studies have shown that patients with dengue had significantly higher white blood cell and neutrophil counts [32] and an elevated count may indicate other etiology of febrile illnesses or a superimposed bacterial infection.

Interestingly, we included the use of acute phase reactants to see their usefulness and benefit in patients with dengue and bacterial coinfection. In a systematic review, CRP has an estimated 77% sensitivity and 79% specificity and diagnostic accuracy for bacterial infection in children with fever. However, its predictive value increases with the number of serial measurements, thus rendering it possibly useful to assess response to therapy [13]. The addition of CRP to the scoring system that we created is of novel use because this is the only risk score study in dengue patients with coinfection that included inflammatory markers.

Procalcitonin (PCT) is currently used as a novel biomarker for diagnostic and prognostic purposes [20, 33]. PCT has been assessed as a biomarker for local and systemic inflammatory responses, disease severity, and necrosis related to organ failure, particularly in patients with bacterial infection. To date, the greatest elevation of serum PCT are seen in bacterial infections. In previous studies, the level of PCT in viral diseases is <0.5 ng/mL [34, 35]. In our study, CRP and PCT was found to be significantly elevated in dengue patients with coinfection compared to dengue without coinfection. A CRP value > or = 12 mg/l was observed in 95 out of 99 patients (95%) with coinfection. Procalcitonin, on the other hand, has an optimal cutoff value of > 2.5 ng/mL in predicting coinfection among dengue patients, with sensitivity of 67.68% and specificity of 83.33%. A study done by Chen et al in adult patients admitted in the ICU showed that procalcitonin has a sensitivity and specificity of 81.5% and 59.5% respectively for diagnosing bacteremia using 1.14 ng/mL as a cutoff [20]. It should be noted that our study included localized and systemic bacterial infections, hence, further studies need to be done to determine the discriminative power of CRP and PCT in detecting bacterial infections between local and systemic infections in patients with dengue. Nevertheless, the addition of CRP and PCT as adjunct tests in diagnosing bacterial coinfection in dengue patients may be of value.

PCT has also been associated with dengue shock and/or multiple organ failure [33, 36, 37]. Thanachartwet, et al. showed that PCT > 0.7 ng/mL was independently associated with dengue shock and/or organ failure. It is probable that the increased levels of PCT during dengue virus infection is due to widespread inflammation in multiple organs [33]. Another study explained that organ failure may be due to the broader tropism of dengue virus leading to drastic lesions and damage in several organs [38].

Physicians are often faced with a dilemma whether or not to initiate antimicrobial treatment in dengue patients, especially in those with severe manifestations. In our study, majority of patients were given antibiotics. The most common indication for initiating antibiotics is pneumonia and a consideration of sepsis due to recurrent shock. Similar to other studies, Syue, et. al. [39] and Hadinegoro, et. al. [40] have noted that hypotension/shock or recurrent shock might be a clue to the occurrence of bloodstream infections

and suggested that cultures be obtained and antibiotics be administered in these settings. In our study, Cephalosporins, specifically cefotaxime, is the most common antibiotic used empirically for dengue patients suspected with coinfection. Since majority of bacteremic pathogens are gram-negative enteric bacteria, the use of 3rd generation cephalosporin maybe appropriate pending the results of cultures. In other studies, although done in adults, empiric antibiotic regimen recommended is levofloxacin, cefepime, or piperacillin/tazobactam [39].

It is important to correctly identify patients with dengue who are likely to have bacterial coinfections. To help us identify patients who are likely in need of empirical antibiotics and distinguish patients who will benefit most from early intervention and initiation of antimicrobial therapy, we created a scoring system to help us diagnose coinfection in dengue patients, especially in patients with no obvious focus of bacterial infection. This is the first study done in the pediatric population to determine a scoring system to diagnose coinfection in dengue patients. Previous scoring systems have been done but studied exclusively the adult population. See et. al., [19] created and validated a Dengue Dual Infection Score (DDIS) for early identification of dengue patients in need of empirical antibiotic treatment. The DDIS was a summation of five variables (each scored as 0 or 1) which were pulse rate ≥90 bpm, total leukocyte count ≥6, 000/μL, hematocrit <40%, sodium <135 mmol/L, and urea ≥5 mmol/L). A DDIS score of ≥4 was associated with coinfection in 94.4% of cases. In our study, the scoring system created had an AUC of 0.7884 in the derivation set. Only about 6% of patients with a score of 0-1 had bacterial coinfection, whereas 73.7% of patients with score of ≥ 3 had bacterial coinfections. Given this data, and using this simple scoring system, it is possible to identify patients who are likely to need close monitoring and early empiric antimicrobial therapy. We neither recommend the indiscrimate use and administration of empiric antibiotic nor the overutilization of cultures on every dengue infected patient meeting the cutoff point without carefully considering other relevant clinical and laboratory parameters. On the contrary, in cases where antibiotics are not given, patients may deteriorate and die. We should carefully use this scoring system on every dengue patient we encounter, especially those admitted in healthcare settings where all the diagnostic tests are available.

CONCLUSION

In conclusion, we have found a significant portion of dengue cases with various bacterial coinfections (64.29%). Patients with dengue and bacterial coinfections were younger with comorbidities. They presented with significantly abnormal vital signs, physical examinations findings, and elevated acute phase reactants. Using age ≤ 9 years, fever >5 days, dengue severe, and CRP >12mg/l, a scoring system was developed. A score of ≥3 can help diagnose patients with dengue and bacterial coinfection who will most likely need early empiric antimicrobial therapy.

LIMITATIONS

There are some limitations in this present study. First, the sample size is limited to 154 children and this may not be representative of all Filipino children with dengue. Second, it was conducted at a single tertiary medical center, and the patient population and clinical characteristics may not be generalizable to other settings such as in primary, or secondary hospitals and community hospitals. Lastly, we did not determine if mortalities can be prevented through early antimicrobial therapy of patients with bacterial coinfection.

RECOMMENDATIONS

We recommend further prospective studies to obtain information on clinical characteristics of dual infections in the pediatric population, especially since this is the first study of its kind.

Prospective validation of the risk scoring is also recommended to investigate its usefulness and effectiveness so that we can be more confident of its wider application in our setting.

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ORIGINAL ARTICLE

CLINICAL PROFILE AND OUTCOME OF ADMITTED PEDIATRIC PATIENTS WITH INFLUENZA

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

ABSTRACT

Background: Influenza is one of the most common illnesses pediatricians face. Children are especially at risk for contracting influenza. Aside from fever, cough and colds, the disease may present differently in children. Complications due to influenza are varied and anti-virals may be useful if given early in the course of illness.

Objectives: To determine the clinical profile of admitted pediatric patients with influenza based on rapid testing and determine its prevalence, outcome and complications.

Methods: Cross sectional study of pediatric patients who had nasopharyngeal swab for influenza by antigen rapid detection test were included. Retrospective chart review was done on patients with influenza-like illness admitted from 2013-2019.

Results: There were 244 patient charts reviewed, the mean age of patients was 5 – 9 years old and majority had no influenza vaccine during the year of admission. Patients presented with fever, cough, colds and non-specific symptoms. Ear pain, difficulty of breathing and myalgia were found to be associated with a positive influenza infection. Of the 244 suspected patients, 133 (54%) were positive for influenza rapid testing, 33% were influenza B positive and 21.3 % were influenza A positive. The most common clinical complication for influenza positive patients was pneumonia. 1 patient had respiratory failure, 5 had febrile convulsions and 7 developed viral myositis. 19% of the subjects had asthma as co-morbidity. Only 11% of the population had their annual influenza vaccine.

Conclusion: 54% of pediatric patients tested for influenza had positive tests for either Influenza A or B. Although generally a mild illness, it contributes to morbidity and mortality in children. Complications are not uncommon in the pediatric population as seen in this study. Vaccination remains an important preventive measure to curb influenza cases.

KEYWORDS: *Influenza, Seasonal Flu, Influenza A, B*

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INTRODUCTION

Influenza is one of the most common illnesses physicians face yearly. It is responsible for seasonal epidemics of pediatric respiratory diseases each year resulting in substantial morbidity, mortality and increased health care utilization. Children, especially those younger than two years of age have high rates of influenza cases, similar to the rates of hospitalization among the elderly.[1] Classic influenza infection is characterized by sudden onset of high fever, coryza, cough, headache, malaise and inflammation of the upper respiratory tree and trachea. Acute symptoms and fever often persist for 7 to 10 days. In younger children, croup, bronchiolitis and pneumonia are all possible clinical presentations of influenza. Gastrointestinal symptoms are uncommon in adults but can be the primary symptoms in children.[2] It may present immediately as a case of acute respiratory distress syndrome, acute myositis, encephalitis or viral myocarditis, most of which are not seen in adults. It is imperative that physicians be aware of these atypical presentations of influenza in children for rapid diagnosis and treatment. Common complications of influenza among children are well documented including bronchiolitis, otitis media, and pneumonia.[1] Laboratory diagnosis is the mainstay in the diagnosis of influenza infection. Clinical findings alone are insufficiently sensitive or specific to diagnose influenza, especially in younger children who less often have classic findings.[3] PCR remains the gold standard for testing. Rapid diagnostics tests have sensitivities of approximately 70% and specificities of 90%. Children may yield higher sensitivities than adults since children tend to harbor larger quantities of virus in their respiratory tracts making them easily detectable. Patients who may benefit the most from rapid influenza testing include children and adults with lower respiratory tract illness who have underlying medical conditions placing them at risk for secondary complications of influenza.[4]

Influenza disease presents differently in various populations. Most of the clinical signs and symptoms reported are based on Western population, where most journals or researches are published and where seasonal influenza is being monitored.[2] Currently there are still minimal local studies on clinical profile of influenza in the local population especially in children. A local study done by Lucero et al. monitored the circulating strains of influenza in the country from 2006 to 2012. This study focused on analyzing seasonality, and influenza strains for 5 years. The study was used by the World Health Organization (WHO) in predicting seasonal thresholds and epidemic curves.[5] Investigating clinical symptoms, complications and sequelae in the local pediatric population will help understand the impact and severity of the disease in the local setting.

Influenza is highly treatable and antiviral for influenza is most effective within 48 hours after the onset of signs and symptoms. Awareness of the clinical manifestation of influenza in pediatric patients would lead to early diagnosis, early treatment, shorter hospital stay, decreased antibiotics use, prevention of complications and hasten recovery. This study aims to determine the clinical profile of admitted pediatric patients in a tertiary hospital in Metro Manila who were suspected to have influenza and underwent rapid influenza testing.

MATERIALS AND METHOD

A. Study design and participants

This is a cross sectional study, using a retrospective chart review of pediatric patients admitted at a tertiary hospital in Metro Manila who were tested for influenza via rapid antigen detection kit from 2013 to 2019.

B. Inclusion and exclusion criteria for subject selection:

This study enrolled consecutive pediatrics patients (< 19 years old) admitted for suspected influenza and underwent influenza testing (with positive or negative results). Patients who were already undergoing treatment for influenza prior to rapid testing were excluded from the study.

C. Description of study procedure

Between 2013- 2019, records of pediatric patients who were tested for influenza using the *EZER*^{TM} Influenza A and B viral antigen rapid test device were included. The test kit was manufactured in Hangzhou China, sensitivity for influenza A is 94.7%, specificity of 94%, while sensitivity for influenza B is 91.7% and a test specificity of 97.5%. The test has no cross reactions with the following viruses: adenovirus, coxsackie, cytomegalovirus, echovirus, enterovirus, parainfluenza, poliovirus, respiratory syncytial virus, rhinovirus. Characteristics and variables such as age, sex, influenza vaccination status, clinical presentations, underlying medical conditions were collected. Outcome and complications of those who tested positive for influenza were likewise analyzed. The prevalence of influenza (A and B) and the signs and symptoms associated with either influenza A and B were studied.

D. Sample Size Estimation

Sample size was calculated based on the population proportion estimation. Sample size was calculated using signs and symptoms of nasal congestion symptom since it yielded the largest sample size. Assuming that the proportion of the patient is 52.7 with a maximum allowable error to 5%, and a reliability of 90%, sample size calculated is 269.

E. Mode of Data Analysis

Determination of the clinical profiles, clinical outcomes and prevalence of influenza A and B among participants were done using frequency and percentage for qualitative variables and mean and standard deviation for quantitative variables. Association of the different clinical profiles with the prevalence of influenza and with clinical outcomes were analyzed using univariate statistics. Chi square test were utilized for qualitative and quantitative clinical profiles respectively. Level of significance will be set at alpha = 0.05

F. Ethical considerations

This research upholds the highest ethical standard of confidentiality, transparency and integrity in processing personal information. The study abided by the principles of the Declaration of Helsinki (2013) and is conducted along the Guidelines of the International Conference on Harmonization – Good Clinical Practice (ICH-GCP). The Clinical Protocol and all relevant documents were approved by the Institutional Ethics Review Committee as well as the data privacy officer on July 9, 2019. Given that this research is dealing with vulnerable population (children), provisions were made to ensure their protection, anonymity and confidentiality of their medical information at all times. Patient confidentiality was respected by ensuring anonymity of patient records. Each patient document is coded and does not contain any identifying information in order to ensure confidentiality. The chart review was done by the author, and was done at the hospital premises. All study data were recorded and investigators are responsible for the integrity of the data i.e. accuracy, completeness, legibility, originality, timeliness and consistency. The manner of disseminating and communicating the study results guarantees the protection of the confidentiality of patient's data. All study- related documents such as the all versions of the protocol, ethical clearance, data collection forms, hard copies of source documents, is kept and stored by the principal investigator in strict confidentiality; after which they will be shredded**.** Data collections commenced upon approval of the research protocol by the Institutional Review Board and Institutional Ethics Review Committee. This paper was self-funded and the authors deny any conflict of interest.

RESULTS

A total of two hundred forty-four patient charts were reviewed for this study. Table 1 shows the characteristics of admitted patients suspected to have influenza and underwent influenza rapid test. The most common co-morbid condition seen was bronchial asthma followed by seizure disorder. Majority of suspected cases were female comprising

52.5% compared to males at 47.5%, and most of which are in the age group of 5- 9 years old. Eighty eight percent of influenza suspect patients did not receive their yearly influenza vaccine. Majority of suspected cases presented with symptoms of fever, cough and colds (Table 2).

Table 1. Characteristics of patients suspected to have Influenza

		N=244	Percentage
Sex	Female	128	52.5%
	Male	116	47.5%
Age group	0-5 months	4	1.6%
	6 -23 months	38	15.5%
	23-59 months	87	35.6%
	5- 9 years old	89	36.4%
	> 10 years old	36	14.7%
Vaccination status	With vaccine	28	11.5%
	Without vaccine	216	88.5%
Exposure to influenza	With exposure	53	21.7%
	Without exposure	191	78.3%
Comorbidities			
Asthma		47	19.3%
Congenital heart disease		2	0.8%
Seizure disorder		7	2.9%
Malignancy		0	0%

Table 2. Clinical Presentation of patients admitted for influenza-like illness

Symptoms	N=244	Percentage
Fever	239	98.4%
Cough	208	86%
Colds	185	75.8%
Sore throat	10	4.1%
Ear pain	6	2.5%
Abdominal Pain	22	9.0%
Loose stools	45	18.4%
Vomiting	53	21.7%
Myalgia	17	7.0%
Difficulty breathing	18	7.4%
Seizures	12	4.9%
Altered Consciousness	0	0%

Out of two hundred forty-four patients who underwent influenza testing one hundred thirty-three (54%) patients were positive for influenza. Eighty-one (33.2 %) patients were positive for influenza B, while 52 (21.3 %) were influenza A. Of these 133 patients who were confirmed influenza, 39 patients developed complications, the most common was pneumonia at 13.6%, other complications seen were myositis and benign febrile convulsion (Table 3, 4)

Table 3. Prevalence of Influenza

	N=244	**Percentage (%)**
Negative for Influenza	111	45.5%
(+) Influenza A	52	21.3%
(+) Influenza B	81	33.2%

Table 4. Clinical Complications of influenza positive patients

Clinical Complications	N = 39	%
Respiratory failure	1	1.5%
Pneumonia	18	13.6%
Secondary bacterial infection	8	6.1%
Encephalitis	0	0
Febrile convulsions	5	3.8%
Viral myositis	7	5.3%
Myocarditis	0	0

Majority of flu like symptoms such as fever, cough and colds were seen in both influenza positive and influenza negative patient. Non-specific systemic symptoms such as abdominal pain, loose stools, vomiting, myalgia and ear pain were likewise observed in patients either with influenza positive or negative results. A pearson chi-square showed the association of confirmed influenza positive patients with some signs and symptoms, setting the level of significance at 0.05. These signs and symptoms were ear pain, myalgia and difficulty of breathing had a p value < 0.05, making it statistically significant. (Table 5)

Table 5. Signs and Symptoms associated with positive and negative Influenza test

	Influenza A	%	Influenza B	%	Negative	%	Chi square (P < 0.05)
Fever	52	100%	80	98.8%	107	97.3%	0.417
Cough	47	90.4%	72	88.9%	89	81.7%	0.213
Colds	40	76.9%	62	76.5%	83	74.8%	0.94
Sore throat	3	5.8%	4	5.0%	3	2.%	0.583
Ear Pain	3	5.8%	3	3.7%	0	0%	**0.058**
Abdominal Pain	4	7.7%	9	11.1%	9	8.1%	0.72
Loose stools	11	21.1%	13	16%	21	18.9%	0.749
Vomiting	17	32.7%	16	19.8%	20	18.0%	0.093
Myalgia	2	3.9%	12	14.8%	3	2.7%	**0.003**
Difficulty breathing	1	1.9%	2	2.5%	15	13.5%	**0.004**
Seizures	4	7.7%	3	3.7%	5	4.5%	1.203
Altered consciousness	0	0%	0	0%	0	0%	0.548

Influenza A positive patients were shown to have higher rates of pneumonia, secondary bacterial infection and febrile convulsions, while patients who were influenza B positive were shown to develop viral myositis. (Table 6) All patients who were influenza positive were given oseltamivir. Eight patients were given parenteral antibiotics for concomitant bacterial infections, such as pneumonia and otitis media. All patients who were confirmed for influenza eventually recovered with an average hospital stay of four days. A patient who had cerebral palsy, seizure disorder, had concomitant bacterial and fungal infection stayed at the hospital for 52 days.

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Table 6. Clinical complications of patients positive for influenza A or B

	Influenza A	Influenza B
Respiratory failure	0%	1%
Pneumonia	17.30%	11.30%
Secondary bacterial infection	7.70%	5.00%
Encephalitis	0%	0%
Febrile convulsion	5.8%	2.5%
Viral myositis	3.8%	6.3%

DISCUSSION

Influenza has been a major cause of morbidity and mortality among children. Suspected patients typically present with symptoms such as fever, cough and colds. Other signs and symptoms include abdominal pain, loose stools, myalgia and ear pain. In this study, symptoms such as ear pain, difficulty of breathing and myalgia were found to be associated with a positive influenza result. Influenza in children ranges from subclinical illness to complicated disease. It is difficult to diagnose influenza in young children on the basis of clinical grounds because no specific signs or symptoms exist, and because other viral respiratory infections that present with fever also occur frequently during influenza season. In separate studies done by Machado et. al in Brazil,[6] Peltola et al in Finland[7] and Tran et al in Canada[8] they showed that there were no differences in clinical findings between influenza A positive and influenza B positive patients. Systemic symptoms such as myalgia, abdominal pain and loose stools were seen frequently in influenza B positive patients. According to the study done by Dilantika et al done in Indonesia, it is possible that the influenza B virus might bind to α 2, 6 sialic receptors in the human gastrointestinal tract and infect, actively replicate within the cells of the gastrointestinal tract causing abdominal pain and loose stools.[2]

The most common clinical complication of influenza seen in this study is pneumonia. Influenza A positive patients were prone to develop pneumonia. This is also seen in a similar study by Daley et. al, done in Sydney Australia where infection with influenza A was associated with severe pulmonary symptoms such as pneumonia or bronchitis.[9] However, one patient in this study developed respiratory failure secondary to influenza B infection and was subsequently intubated. Research done by Tran et. al concluded that mortality was greater for influenza B disease and were more likely to require ICU admission.[8] Our results also showed that influenza B positive patients were prone to develop viral myositis (6.3% vs 3.8%). A study done in Germany[10] showed a large outbreak of influenza B associated benign acute childhood myositis. It is an infrequently and poorly known complication of influenza and according to a research done in Taiwan a small glycoprotein unique in influenza B may render it to be more myotropic than influenza A, although further studies still need to be done to conclude on this hypothesis.[11]

Based on the WHO global influenza surveillance and response system, the predominant strain in the Philippines is influenza A.[12] This was also reported in the Global Influenza Initiative last 2017 where it was reported that influenza A remains to be the predominant strain in the Asia Pacific region, although there were sporadic outbreaks of influenza B during some weeks.[13] Out of two hundred forty-four admitted patients in the study seen to have influenza like illness, one hundred thirty-three (54%) were influenza positive. Thirty three percent (33%) were influenza B positive while only twenty one percent (21%) were influenza A positive. Traditionally, attention has been directed towards influenza A as a major source influenza infection. However the results of the Global influenza B study showed that influenza B represents roughly 20% of all cases reported to national influenza centers in 26 countries around the world, being the most common in the tropics and affecting younger age groups.[14] This was also similarly reported by Clotilde et al in a research on the epidemiology of influenza in the Asia Pacific region, that showed influenza B represented 31.4% of cases in Asia from 2010 to 2017 which was a

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higher proportion than reported elsewhere.[15] A study done by Kamigaki et al., in Baguio city showed similar reports where influenza B infections were higher among age groups 5-14 years. Influenza – related hospitalizations were higher for influenza B than influenza A.[16] This was similarly reported by Tran et al that one- third (1/3) of hospitalizations were due to influenza B.[8] Chia- Yu C et al, postulated that influenza B positive pediatric patients may have increased severity of the disease. This is because of the genetic differences between the Hemagglutinin receptor of the Yamagata lineage virus and Victoria lineage virus might alter the affinity of attachment to airway epithelium and along with young age and a naïve immune system, be responsible for the increased severity of the disease.[11] Another reason for a higher proportion of influenza B positive patients would be a possible vaccine mismatch. An influenza B vaccine mismatch is defined as a mismatch between the influenza lineage included in the vaccine and the linage that cause majority of cases in a season with significant circulation of influenza B. In a paper by Jennings et al (2018), that reviewed the epidemiology of influenza B in 15 countries in the Asia Pacific region (including the Philippines), significant or complete mismatch between the circulating and trivalent vaccine type B strain were observed on numerous occasions in countries. Influenza vaccine efficacy is reduced when there is a mismatch as is likely to be associated with a higher clinical disease burden. Evidence also suggests that younger age groups are frequently infected with influenza B. Extensive use of quadrivalent vaccines lagged until 2015 or later, and was mostly used in developed countries.[17] Although, it would be hard to conclude a vaccine mismatch based on the given data, and not within the scope of this paper.

Vaccines play a major role in the prevention of influenza. The recommended target population for influenza vaccination according to the WHO include pregnant women, healthcare workers, children aged 6-59 months, elderly and those with high risk conditions. [13] This study revealed that only 11.5% of patients received their yearly influenza vaccination. Among the twenty-eight patients (11.5%) who received their yearly vaccine, eleven were diagnosed to be influenza positive. The clinical effectiveness of influenza vaccines can vary by year and setting. This is driven by a number of factors such as virus dynamics, including vaccine match to circulating viruses and the overall influenza attack rate in the study population.[18] Vaccination is an important tool to reduce the burden of illness, especially in high risk groups. It is especially important in children as naïve immune systems respond less effectively, children are more likely than adults to become sick and to remain sick for longer periods of time. Children also have a higher viral load than adults and the period during which children can actively transmit infections to others is longer, thus increasing spread of disease. Because childhood transmission is a major driver of annual influenza epidemics, increasing vaccination uptake among children may therefore limit the widespread dissemination into the community.[19] According to the Global Influenza Initiative, disease burden in the Philippines is highest in young children, with the highest proportion of death in adults > 60 years and children aged < 5 years. Barriers to vaccination including geography, logistics, funding, lack of vaccine awareness and education. In the Philippines, insufficient or absent public funding are major barriers in doing mass influenza vaccinations. For the Philippines, influenza seasonality is from June to November, making the ideal time to administer influenza vaccine should be from April to May, with the quadrivalent vaccine having a more impact on influenza control.[13] Results of the study also showed that a proportion of admitted patients were influenza B positive. Since younger children have a higher probability of being infected with influenza B viruses, this group is more likely to benefit more from a quadrivalent vaccine containing B lineages.[17]

The genetic characteristics of influenza viruses facilitate the generation of novel strains with the potential to cause human disease. The influenza

virus contains its own RNA polymerase, which lacks proof reading functions leading to point mutations with regular frequency during genome replication. An accumulation of point mutations is known as antigenic drift and is responsible for seasonal variation of influenza A strains that cause annual epidemics. Antigenic shift is an abrupt, major change in the influenza virus proteins and enters the human population. A pandemic occurs if this newly generated strain causes disease in humans and can efficiently spread from person to person and throughout the world.[3] As the flu virus changes rapidly per year, surveillance schemes enables the WHO to evaluate the success of the yearly flu vaccine as well as recommend which influenza strains should be included in the yearly vaccine formulations. Surveillance is also important in monitoring pandemics and emerging anti-viral resistance.[20]

Influenza is an unrecognized burden in young children. In a study by Xin et al. on the global burden of respiratory infection associated with influenza in children under 5 years, in 2018 globally, there were an estimated 109.5 million influenza episodes, 10. 1 million influenza acute lower respiratory tract infection, 870, 000 influenza associated hospital admissions, and 15, 300 in hospital deaths. Research by Ruf and Knuf done in Germany showed that children age less than 5 years have greater rates of hospitalizations and complications than their older counterparts.[21] Influenza- associated complications contribute significantly to the disease burden. Common complications include otitis media, respiratory tract infections, the most important of which is pneumonia, encephalitis, and less commonly acute myositis- all these were seen in this study. Influenza illness causes children to lose school time, their parents to lose work, causing a socioeconomic as well as clinical burden.[22] In a study by Krow et al done in Utah, Salt lake City, 325 children were hospitalized for influenza for over 3 viral seasons, 16% had pneumonia and 15% were in the ICU, with 8% requiring mechanical ventilation. In the study, mortality rate was at 0.6% where 2 children died of influenza.[23] This was similarly seen in the study where complications included pneumonia, otitis media, acute myositis, and febrile convulsions. Although there was no reported mortality, the study had a patient who developed respiratory failure secondary to influenza related lower respiratory tract infection.

CONCLUSION AND RECOMMENDATION

In conclusion, majority of patients with influenza present with upper respiratory tract infections such as cough, colds and fever. This may be accompanied by other systemic symptoms such as myalgia, abdominal pain, loose stools and vomiting. Symptoms such as myalgia, difficulty of breathing and ear pain were significantly associated with a positive influenza result. Majority of cases admitted were influenza B positive. The most common clinical complication seen was pneumonia, and most of the patients did not receive yearly influenza vaccines.

The major limitation of this study is that it was done as a retrospective chart review and only included admitted patients. Suspected patients who were screened for influenza on an out-patient basis were not included in the study. Including these patients in a future study may give researchers a broader insight regarding influenza in children. This will also help track the trend of influenza in children within the community. Another limitation is the use of a rapid antigen detection kit and not the gold standard, PCR. Since the study revealed that majority of pediatric patients did not receive their yearly influenza vaccine, it is recommended that we re-educate parents regarding influenza and the benefits of yearly vaccination. Further research on influenza B in the Philippines, it's epidemiology and virologic characteristics are worthwhile. The study also recommends that influenza testing should be accessible to all patients, especially those with severe symptoms and in the high-risk group. Earlier testing, leads to earlier treatment,

decreasing morbidity and mortality among patients.

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PPS and PIDSP Recommendations

GUIDELINES

VACCINATION DURING THE COVID-19 PANDEMIC: PPS and PIDSP RECOMMENDATIONS

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INTRODUCTION

The COVID-19 pandemic is sweeping across the globe with extreme ferocity, leaving many countries grappling to contain its transmission and the healthcare system struggling to protect the yet uninfected. As this crisis intensifies, many health facilities are left with no choice but to identify which services to forego, delay, or re-schedule, and re-align infrastructure and resources to prepare for the surge in COVID-19 cases. A lot of basic care services such as immunization, thus, become neglected.

Having witnessed the surge of vaccine preventable diseases (VPD) locally in the past two years, namely measles and polio, the decision to continue immunization services remains important and should be maintained while observing proper infection control measures to prevent transmission of SARS COV-2.1

On a national scale, implementation of immunization services should be the responsibility and one of the top priorities of each local government unit. Decision-making would be largely dependent on the current situation of the community, availability of resources including infection control measures, logistics including but not limited to vaccine supply and manpower, and containment of community transmission.

Disruption in the provision of immunization services increases the number of susceptible individuals in the community. This can lead to outbreaks of VPDs as well as VPD-related deaths, and further burden the already exhausted healthcare resources due to the rise in COVID-19 cases.[1]

I. Guide for the pediatrician on scheduling vaccinations

While maintaining timely administration of vaccines is necessary especially during a pandemic, health providers should also keep in mind that protecting themselves and their patients is of utmost importance. Existing guidelines on the prevention of SARS COV-2 transmission during vaccination visits should be followed.

If a health facility is catering to COVID-19 cases, it is recommended for healthcare providers to direct their well child visits to another clinic where no COVID-19 or PUI admissions are entertained. Should the COVID-19 response measures in the health facility not allow safe implementation of vaccination and no alternative location is feasible, immunization providers may consider delaying vaccination and start identifying the cohorts of children who have missed their vaccine doses and develop an action plan for tailor-made catch-up immunization.[1]

The PPS and PIDSP drafted the following guidelines on immunization of well pediatric patients during the COVID-19 pandemic. These guidelines do not cover vaccination of special groups (immunocompromised patients and those on immunosuppressive therapy).

1. Before scheduling a child for vaccination, ensure that the child is well and:
   - not suffering from fever, cough, colds, diarrhea, and influenza-like illness
   - has had no significant exposure to a positive or suspected COVID-19 case in the last 14 days
   - does not reside in an area with localized transmission or local community under enhanced quarantine. Check DOH updates to confirm if the child's community is classified as such. Note also if there is household clustering of influenza-like illnesses, or if the child resides in a community with sustained community transmission.
   - has no absolute contraindications to vaccination
2. Whenever possible, limit the child's companion to just 1-2 caregivers. Ensure that they are also free of COVID-19 symptoms (no respiratory illness and/or diarrhea).
3. Ensure that you, as the pediatrician, and your assistants, are also cleared from symptoms suggestive of COVID-19 before attending to the patient.
4. Follow the recommended schedule and administration of vaccines included in the PIDSP-PPS-PFV 2020 Childhood Immunization Schedule.
5. Prioritize completion of primary immunization series and administration of vaccines against epidemic-prone diseases such measles, polio, diphtheria and influenza. Pneumococcal and rotavirus vaccinations are highly recommended as well.

For missed vaccine doses, catch-up immunization is essential. (Refer to annotations in the PIDSP-PPS-PFV 2020 Childhood Immunization Calendar

6. Schedule patient visits as much as possible to minimize crowding and exposure in your clinic.
7. Consider triaging through pre-clinic calls, scheduling well baby consults separately from sick consults.[4]
8. On scheduled consultation, allot time to emphasize the importance of keeping the child's vaccine schedule up to date, and reinforce the importance of adhering to frequent hand washing, cough etiquette, and physical distancing.
9. Observe strict infection control measures. Clinics should be adequately disinfected prior to receiving patients, and periodically done until the last patient has been attended to.

Procedures on hand hygiene, use of personal protective equipment, prevention of needle-stick or sharps injury, waste management, cleaning and disinfection of equipment and environment,

should be followed and adapted according to your local COVID-19 situation.[1]

10. Ideally, the location of vaccination room/area should be far from heavy foot traffic such as Emergency Rooms, and Triage Areas. Pediatricians are encouraged to dedicate specific/separate rooms for sick and well visits; or for those with multiple practice sites to consider using one office location to see all well visits.[5]

11. Vaccines routinely given at birth such as BCG and Hepatitis B should be continued as scheduled, preferably given within 24 hours after delivery and prior to the baby's discharge from the hospital.[6]

12. In special circumstances such as after potential exposure to rabies or tetanus, efforts must be made to avoid delay and provide the appropriate vaccine following routine recommended schedule.[6]

13. For HCWs who are taking part in the epidemic control and have had contact with suspected and/or confirmed COVID-19 cases, it is advised that they do not participate in immunization activities during the pandemic, and delegate immunization tasks to colleagues who are unexposed to cases.[6]

II. General principles for delayed vaccinations during COVID-19 pandemic

Routine immunization is an essential component of health services and thus should be maintained as long as COVID-19 response measures allow. Considerations for providing immunization should be guided by a detailed assessment of the risk of outbreaks of VPDs (such as measles and polio) and the epidemiologic situation of COVID-19 and containment measures in the community.[1] Should the risk of the current circumstances outweigh the benefits of immunization, temporarily delaying vaccination services may be considered, and a catch up plan put in place.[6]

For catch up vaccinations, the best approach is to ascertain the antigens required for their current age, subtract any already given, and then develop the individual's catch-up schedule. If the immunization status of a child is uncertain or unknown, plan the catch-up schedule assuming the vaccines have not been given.[2]

1. For vaccines not given on time, the due dose should be given at the earliest scheduled visit. It is not necessary to restart the series or add doses of any vaccine due to extended interval between doses.[3]

2. Vaccine doses should not be administered at intervals less than the recommended minimal intervals or earlier than the acceptable minimum age for a specific vaccine. However, doses administered up to 4 days before the minimum interval or age can be counted as valid (except for rabies vaccine due to its unique dosing schedule). Doses administered outside this "grace period" of 4 days should not be counted as valid doses and should be repeated as age appropriate. The repeat dose should generally be spaced after the invalid dose by an interval at least equal to the recommended minimum interval for the specific vaccine.[3]

3. Use combination vaccines as appropriate. This allows for optimizing the opportunity to provide protection to the child against multiple diseases during a single clinic visit.

4. Simultaneous administration of all vaccines for which a child is eligible increases the probability that a child will be fully immunized at the appropriate age, and is allowed.

However, in children with functional or anatomic asplenia, PCV13 and MCV4-D should be separated by at least 4 weeks, giving priority to the administration of PCV ahead of MCV4-D.[3] (Note: There are no studies on interference with simultaneous administration of PCV10 and MCV4-D.)

5. For non-simultaneous administration of different vaccines, live parenteral vaccines not given during the same visit should be spaced by at least 4 weeks.[3] Live vaccines administered per orem may be given at any time before or after each other. Live oral vaccines may be given at any time before or

after live parenteral vaccines.[3] All other combinations of two inactivated vaccines, or live and inactivated vaccines, may be given at any time before or after each other.[3]

6. Physicians should be knowledgeable on the contraindications and precautions for vaccination.

7. Physicians must follow proper vaccine preparation and administration procedures.

8. Observe the patients closely after vaccine administration. All adverse reactions should be noted and addressed timely and appropriately (especially anaphylactic reactions). Due to ongoing COVID-19 transmission in the country, there may be an increased risk of coincidental AEs post vaccination. A system should be in place for reporting and investigation of causality assessment of these reactions, particularly SAEs.[1]

9. Physicians should maintain an accurate record of the child's vaccination.

10. Physicians must ensure proper storage of vaccines and maintain proper cold chain at all times.

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GUIDELINES

PPS/PIDSP INTERIM GUIDELINES ON RESUMPTION OF OUT- PATIENT PEDIATRIC CLINICS POST– ENHANCED COMMUNITY QUARANTINE DURING COVID PANDEMIC

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BACKGROUND

The World Health Organization (WHO) recommends the use of additional precautions (droplet and contact and, whenever applicable, airborne precautions) on top of standard precautions during COVID pandemic. 1 Nevertheless, the majority of outpatient settings are not designed to implement all of the isolation practices and other Transmission-Based Precautions (e.g., Airborne Precautions for patients with suspected tuberculosis, measles or chicken pox) that are recommended for hospital settings. Thus, facilities should develop, customize, and implement systems for early detection and management of potentially infectious patients at initial points of entry to the facility, during patient visits, and after clinics are done. [3]

The basic principles of infection prevention and control (IPC) and standard precautions should be applied in all health care facilities, including outpatient care and primary care. For COVID-19, the following measures should be adopted: [1]

- Triage and early recognition;
- Emphasis on hand hygiene, respiratory hygiene, and appropriate masks to be used by patients, companions, and medical personnel;
- Proper use of contact and droplet precautions for all suspected cases;
- Prioritization of care of symptomatic patients;

- Provision of separate waiting area for symptomatic patients if they are required to wait;
- Education of patients and families about the early recognition of symptoms, basic precautions to be used, and to which health care facility they should go.

This guidance is intended for health care workers /personnel (HCWs/HCPs), health care managers, and Infection and Prevention Control (IPC) teams at the out -patient facility level. The HCP is advised to adapt according to his/her own specific set up and needs, adhering to the same infection control principles.

RECOMMENDATIONS
GENERAL SOPs:

1. Standard Precautions are the minimum infection prevention practices that apply to all patient care, regardless of suspected or confirmed infection status of the patient, in any setting where healthcare is delivered. These practices are designed to both protect HCPs and prevent them from spreading infections among patients, and include:[2]

- Hand hygiene
- Use of personal protective equipment (e.g., gloves, gowns, masks)
- Injection safety (e.g. proper vaccination practices, administration of intramuscular/parenteral medications)
- Safe handling of potentially contaminated equipment or surfaces in the patient environment
- Respiratory hygiene/cough etiquette.

2. Training of the clinic staff[5]

- Ensure that clinic personnel know the proper ways to put on, use, and take off Personal Protective Equipment (PPE) safely. The PPE required for staff is determined by the level of potential exposure to patients and contaminated surfaces.
- Teach the staff about recognition of symptoms—fever, cough, shortness of breath, and others
- Make sure that staff members implement procedures to quickly triage and separate sick patients.
- Emphasize hand hygiene and cough etiquette for everyone.
- Ask staff to stay home if they are sick.
- Send workers home if symptoms develop at work.

3. Ensuring triage, early recognition, and source control

- Clinical triage includes a system for assessing all patients before or upon entry/admission, allowing for early recognition of possible COVID-19.
- Source Control is the immediate isolation of patients with suspected disease in an area separate from other patients.

HOSPITAL /CLINIC SOPs:

1. ENTRY TO THE HEALTHCARE FACILITY

To facilitate the early identification of cases of suspected COVID-19, health care facilities should:

A. Whenever possible, screen and triage patients via digital/telehealth methods already prior to actual patient visits.

B. Institute the use of screening questionnaires according to the updated case definition.

C. Establish a well-equipped triage station at the entrance to the facility. If there is more than one entrance to the facility, all entrances should have proper triaging of all persons.

D. Place trained staff who are skilled with a high level of clinical suspicion and recognition.

E. Check temperature upon arrival and entrance to the building where clinics are located.

F. Patients who fail screening should never be allowed to enter the outpatient healthcare facility, but isolated and managed at home or sent to the ER.

G. Require all personnel, patients, and visitors to wear masks that cover mouth and nose, except children ≤2 yrs. of age.

H. Limit non-patient visitors, companions, or caregivers.

I. Post visible signs in public areas to direct patient flow and remind symptomatic patients to alert HCWs.

2. RECEPTION AREAS/ WAITING AREAS

Well patients should always be separated from sick patients, physically and temporally whenever possible. Provide space and encourage persons with symptoms of respiratory infections to sit as far away from others as possible. Create separate spaces in waiting areas for sick and well patients.

A. Whenever possible, pre-screen patients before arrival at the clinic such that well child visits are scheduled separately from sick child visits.

B. If available, facilities may wish to place symptomatic patients in a separate area while waiting for care. [2]

C. Separation of at least 1-2 meters (3-6 feet) should be maintained between all patients and caregivers. Both spatial separation and adequate ventilation can help reduce the spread of many pathogens in the health care setting.[4]

D. Provide supplies – tissues, alcohol-based hand rub, soap at sinks and trash cans.[5] Provide separate trash cans for infectious waste.

E. Remove toys, reading materials or other communal objects, otherwise ensure that these are regularly cleaned. [5]

F. Provide resources and reminders for performing hand hygiene, respiratory hygiene and cough etiquette in or near waiting areas.

3. DOCTOR'S CLINIC- HCPS AND HCWS

Each outpatient facility should evaluate the services they provide to determine specific needs and to assure that sufficient and appropriate engineering controls and PPE are available for adherence to Standard Precautions, Droplet and Contact Precautions (and Airborne Precautions where applicable).

All HCPs and staff at the facility should be educated regarding proper selection and use of PPE. The rational, correct, and consistent use of PPE also helps reduce the spread of pathogens. PPE effectiveness depends strongly on adequate and regular supplies, adequate staff training, appropriate hand hygiene, and appropriate human behaviour.[1]

A. Design and install engineering controls to reduce or eliminate exposures by shielding HCP, staff and other patients from infected individuals. Examples of engineering controls include:

- Physical barriers or partitions to guide patients through triage areas and ensure appropriate distancing.
  - Physical barriers (e.g., glass or plastic windows, acrylic shields) at reception areas may be considered to limit close contact between triage personnel (who may not be equipped with full PPE) and potentially infectious patients. However, these barriers may be of little use and are not encouraged inside doctors' clinics, as doctors still need to go around these to perform physical examination of patients, while using proper PPE. Moreover, these barriers need to be disinfected after patient visit.
- Air-handling systems (with appropriate directionality, filtration, exchange rate, etc.) that are properly installed and maintained. Air should ideally flow AWAY from HCP and healthcare staff.

o Airborne Infection Isolation Rooms (AIIRs)- AIIRs are single-patient rooms at negative pressure relative to the surrounding areas, and with a minimum of 6 air changes/hour (12 air changes/hour are recommended for new construction or renovation).[1]Air from these rooms should be exhausted directly to the outside or be filtered through a high-efficiency particulate air (HEPA) filter directly before recirculation. Doors should be kept closed except when entering or leaving the room, and entry and exit should be minimized.

o The role of an AIIR, or negative pressure room, as an intervention to increase safety for HCP caring for suspected or known COVID-19 patients is unclear, with the exception of those involved in aerosol-generating procedures (AGPs) (e.g. nebulization, suctioning). To date, there are no data to suggest that SARS-CoV-2 is routinely spread via long- distance airborne nuclei during routine care or following AGPs.[6]

- Modified doorknobs and drawers to minimize handling of common surfaces (e.g. change doorknobs so elbows may instead be used, etc.).
- Covered waste bins/trashcans to protect against aerosolized particles
- Provision of proper waste disposal measures for PPEs and disinfection materials.
- Designated area for donning and doffing of PPEs.

B. Follow requirements for PPEs.

Adherence to CDC evidence-based guidelines for masks, hand hygiene, and environmental hygiene enhances the safety for health care workers. [3] All patients ≥ 2 yrs. of age and visitors should be required to wear masks for source control; for asymptomatic individuals, cloth masks may be sufficient; for symptomatic patients, surgical masks are preferred.

However, the Infectious Disease Society of America (IDSA) Guidelines recommend that health care personnel caring for patients with suspected or known COVID-19, use either a surgical mask or N95 (or N99 or PAPR) respirator as part of appropriate PPE which include gown, gloves and eye protection.[6] (Strong recommendation, moderate certainty of evidence)

Key recommendations for use of PPE in outpatient settings:

1. Facilities should assure that sufficient and appropriate PPE is available and readily accessible to HCP and staff.
2. Basic PPE for the HCP in a typical pediatric outpatient clinic (assuming no aerosol-generating procedures will take place) would include: medical mask (surgical mask or N95), gown, eye protection (face shield or goggles), and gloves.
3. Educate all HCP on proper selection and use of PPE.
   a. PPE, other than respirators, should be removed and discarded prior to leaving the patient's room or care area. If a respirator is used, it should be removed and discarded (or reprocessed if reusable) after leaving the patient room or care area and closing the door.
   b. Hand hygiene should be performed immediately after removal of PPE.
4. Wear gloves for potential contact with blood, body fluids, mucous membranes, non-intact skin or contaminated equipment.
   a. Do not wear the same pair of gloves for the care of more than one patient.
   b. Do not wash gloves for the purpose of reuse.
5. Wear a gown to protect skin and clothing during procedures or activities where contact with blood or body fluids is anticipated.
   a. Do not wear the same gown for the care of more than one patient.
   b. Non-disposable gowns may be removed (taking care to minimize the possibility of dispersing the virus through the air), sealed or soaked in detergent, and laundered for reuse.
6. Wear mouth, nose and eye protection during procedures that are likely to generate splashes or sprays of blood or other body fluids.
7. Avoid wearing jewelry and use of cellphones/gadgets.
8. Use closed shoes.

C. Implement measures to contain respiratory secretions in patients who have signs and symptoms of a respiratory infection.

D. HCWs should apply WHO's My 5 Moments for Hand Hygiene approach [1]

- Hand hygiene includes either cleansing hands with an alcohol-based hand rub or with soap and water.
- Alcohol-based hand rubs are preferred if hands are not visibly soiled.
- Wash hands with soap and water when they are visibly soiled.

Key recommendations for hand hygiene in outpatient settings:

Key situations where hand hygiene should be performed include:

1. Before contact with a patient.
2. Before performing an aseptic task (e.g., insertion of IV, preparing an injection).
3. After contact with the patient or objects in the immediate vicinity of the patient.
4. After contact with blood, body fluids or contaminated surfaces.
5. If hands will be moving from a contaminated-body site to a clean- body site during patient care.
6. After removal of personal protective equipment (PPE).

E. Use of disposable materials is preferred (e.g. paper tape measure, bed covers, replaceable ear tips for thermometers).

F. Provide at-home care instructions to patients with respiratory symptoms.

G. Consider telehealth options for pre-screening and/or follow up.

- This will minimize direct contact with patients.

H. Notify your health department of patients with suspected COVID-19 infection.

- Follow DOH guidelines for notification and management of suspected COVID-19 patients.

I. After patients leave, clean frequently touched surfaces (e.g. counters, doorknobs, beds, seating), medical devices (thermometers, stethoscopes) using detergent and water, and disinfectants.

CLEANING AND DISINFECTION OF THE DOCTOR'S CLINIC

Cleaning refers to the removal of visible soil and organic contamination from a device or environmental surface using the physical action of scrubbing with soap or detergent and water, or an energy-based process (e.g., ultrasonic cleaners) with appropriate chemical agents. This process removes large numbers of microorganisms from surfaces and must always precede disinfection.[2]

Disinfection is generally a less lethal process of microbial inactivation (compared to sterilization) that eliminates virtually all recognized pathogenic microorganisms but not necessarily all microbial forms (e.g., bacterial spores).[2]

A. Ensure that cleaning and disinfection procedures are followed consistently and correctly. Cleaning environmental surfaces with water and detergent and applying commonly used hospital disinfectants (such as sodium hypochlorite) is effective and sufficient. [1]

B. If surfaces are dirty, clean using a detergent or soap and water prior to disinfection.

C. EPA-registered disinfectants or 1:100 dilution of household bleach and water should be used for disinfection of surface and on noncritical patient-care equipment. Follow manufacturer's instructions for application, ensuring a contact time of at least 1 minute, and allowing proper ventilation during and after application.

D. Never mix household bleach with ammonia or any other cleanser.

E. Common low- and intermediate-level disinfectants that can be used for environmental surfaces in healthcare settings include:

1. quaternary ammonium compounds
2. alcohol (ethyl or isopropyl)
3. chlorine releasing agents (e.g., bleach)
4. improved hydrogen peroxide

F. Use appropriate PPE while carrying out cleaning and disinfection procedures.

G. Ideally, frequently touched surfaces should be cleaned and disinfected (with detergent and disinfectant) between each patient consultation/ examination.

Hard (Non-porous) Surfaces:

1. Wear disposable gloves when cleaning and disinfecting surfaces.
2. Gloves should be discarded after each cleaning.
3. If reusable gloves, should be dedicated for cleaning and disinfection of surfaces for COVID-19 and should not be used for other purposes.
4. Consult the manufacturer's instructions for cleaning and disinfection products used.
5. Clean hands immediately after gloves are removed.

Soft (Porous) Surfaces:

1. Remove visible contamination if present and clean with appropriate cleaners indicated for use on these surfaces- carpeted floor, rugs, and drapes

(taking care to minimize the possibility of dispersing the virus through the air).

2. After cleaning: Launder items as appropriate in accordance with the manufacturer's instructions. If possible, launder items using the warmest appropriate water setting for the items and dry items completely.

Electronics:

1. For electronics such as cell phones, tablets, touch screens, remote controls, and keyboards, remove visible contamination if present.

2. Follow the manufacturer's instructions for all cleaning and disinfection products.

3. Consider use of wipeable covers for electronics (e.g. cover computer keyboard and screen with plastic, put cellphones in Ziploc® bags).

4. If no manufacturer guidance is available, consider the use of alcohol-based wipes or sprays containing at least 70% alcohol to disinfect touch screens.

5. Dry surfaces thoroughly to avoid pooling of liquids.

H. General outpatient or ambulatory care wards include waiting areas, consultation areas, and minor procedural areas.

The following are the recommended frequency and method of cleaning for specific areas of patient care.

Recommendations for Outpatient Wards by Area, Frequency, Method, and Process.[3]

Area	Frequency	Method	Process
Waiting / Admission	At least once daily (e.g., per 24-hour period)	Clean	High-touch surfaces and floors
Consultation / Examination	At least twice daily	Clean	High-touch surfaces and floors
Procedural (minor operative procedures; e.g., suturing wounds, draining abscesses)	Before and after (i.e., between see Footnote) each procedure **Footnote:** If there is prolonged time between procedures or local conditions that create risk for dust generation/dispersal, re-wipe surfaces with disinfectant solution immediately before the subsequent procedure.	Clean and disinfect	High-touch surfaces and floors, with an emphasis on the patient zone, procedure table
Procedural (minor operative procedures; e.g., suturing wounds, draining abscesses)	End of the day (terminal clean)	Clean and disinfect	All surfaces and the entire floor Handwashing sinks, thoroughly clean (scrub) and disinfect Sluice areas/sinks or scrub areas
All	Scheduled basis (e.g., weekly, monthly) and when visibly soiled	Clean	Low-touch surfaces;

Recommended Material Cleaning and Disinfectant Compatibility Considerations by Disinfectant, Material Compatibility Considerations, and Best Practices.[3]

Disinfectant	Material compatibility considerations	Best practices for use on noncritical patient care equipment
Chlorine/ hypochlorite-based	Corrosive to metals	• Concentration should not exceed 1000 ppm or 0.1% • Rinse equipment with clean water after disinfection
Alcohols (60-80%)	Could deteriorate glues and cause damage to plastic tubing, silicone, and rubber	• Good for disinfecting small equipment or devices that can be immersed (e.g., stethoscopes, thermometers)

COLLECTING AND HANDLING LABORATORY SPECIMENS FROM PATIENTS WITH SUSPECTED COVID 19

When collecting diagnostic respiratory specimens (e.g., nasopharyngeal swab) from a patient with possible COVID-19, the following should occur:[1]

A. All specimens collected for laboratory investigations should be regarded as potentially infectious. HCWs who collect, handle, or transport clinical specimens should adhere rigorously to the following standard precaution measures and biosafety practices to minimize the possibility of exposure to pathogens.

B. Ensure that HCWs who collect specimens use appropriate PPE (i.e. eye protection, a medical mask, a long-sleeved gown, and gloves). If the specimen is collected during an aerosol-

generating procedure, personnel should wear a particulate respirator at least as protective as a NIOSH-certified N95, an EU standard FFP2, or the equivalent.

C. Specimen collection should be performed in a normal examination room with the door closed.

D. The number of HCP present during the procedure should be limited to only those essential for patient care and procedure support. Visitors should not be present for specimen collection.

E. Clean and disinfect procedure room surfaces promptly.

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INTERIM GUIDELINES ON THE SCREENING, ASSESSMENT AND CLINICAL MANAGEMENT OF PEDIATRIC PATIENTS WITH SUSPECTED OR CONFIRMED CORONAVIRUS DISEASE 2019 (COVID-19)

Version 2, 12 April 2020

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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.

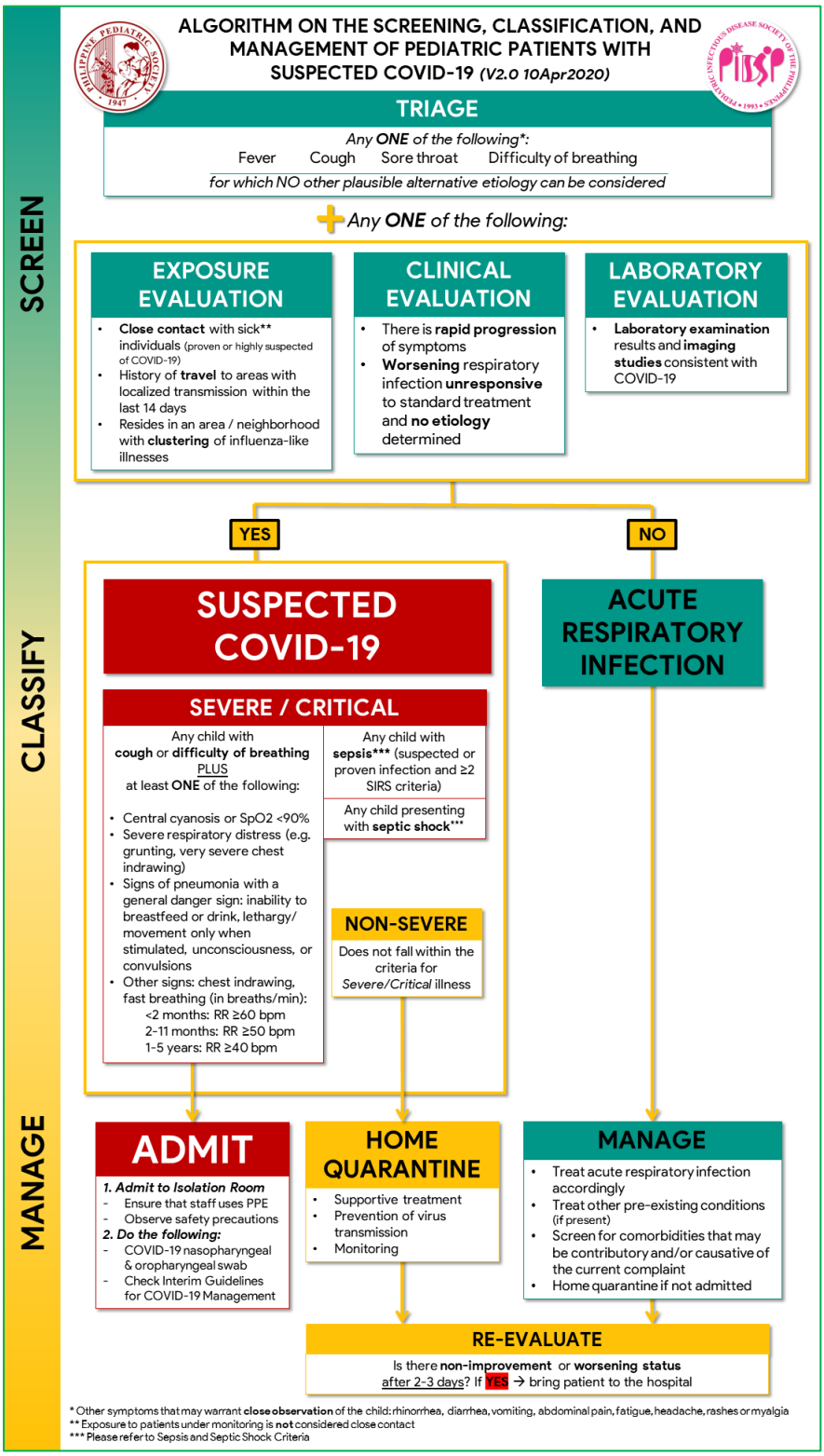
2. After discharge, ensure that the following considerations are kept in mind:

    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]***

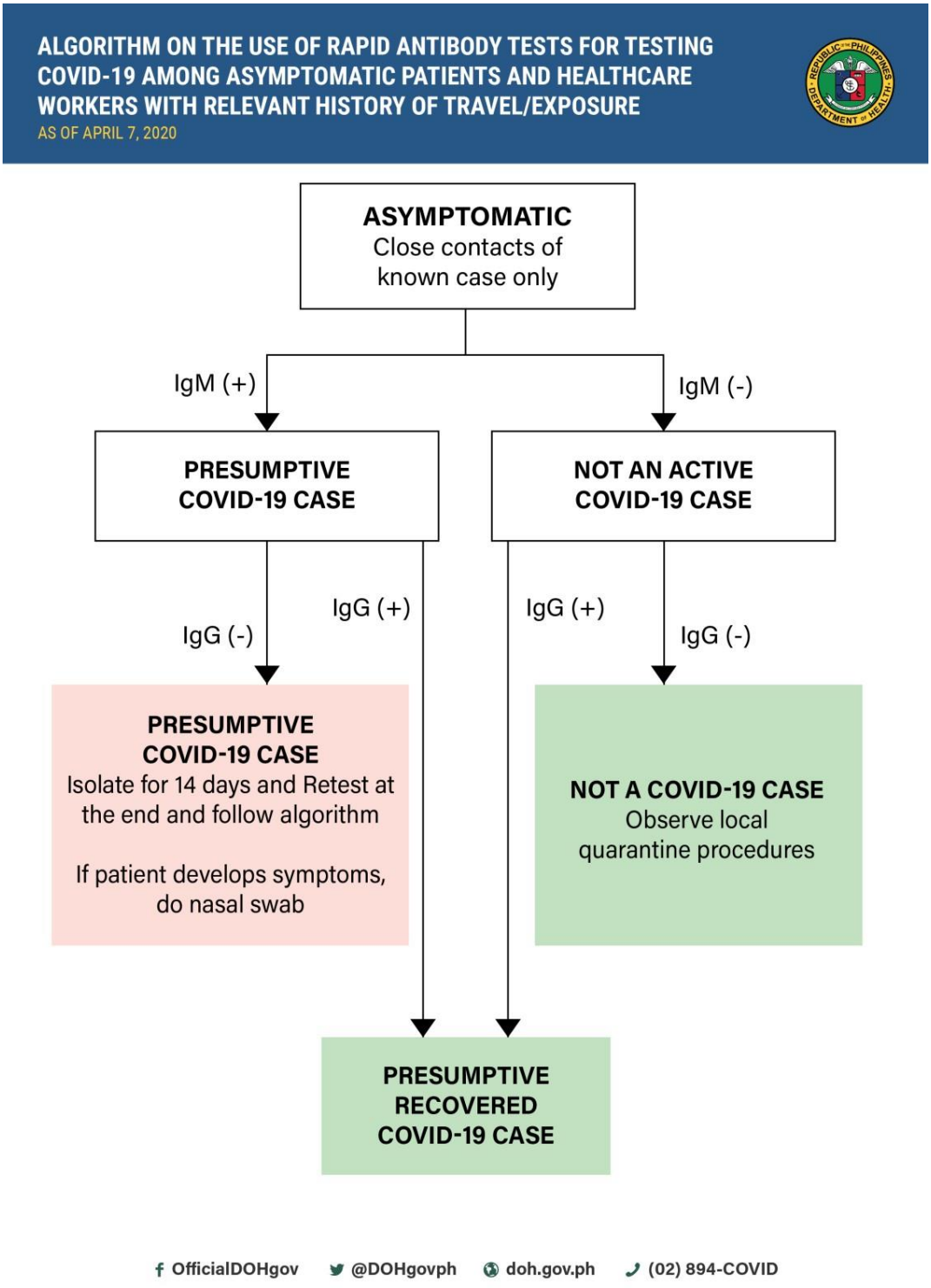
This treatment is subject to oversight by this hospital's Institutional Ethics/ Review Board/ Committee. If you have questions about your rights or any unresolved question, concerns, or complaints, talk to them at _____ ***[Insert contact information]***.

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	

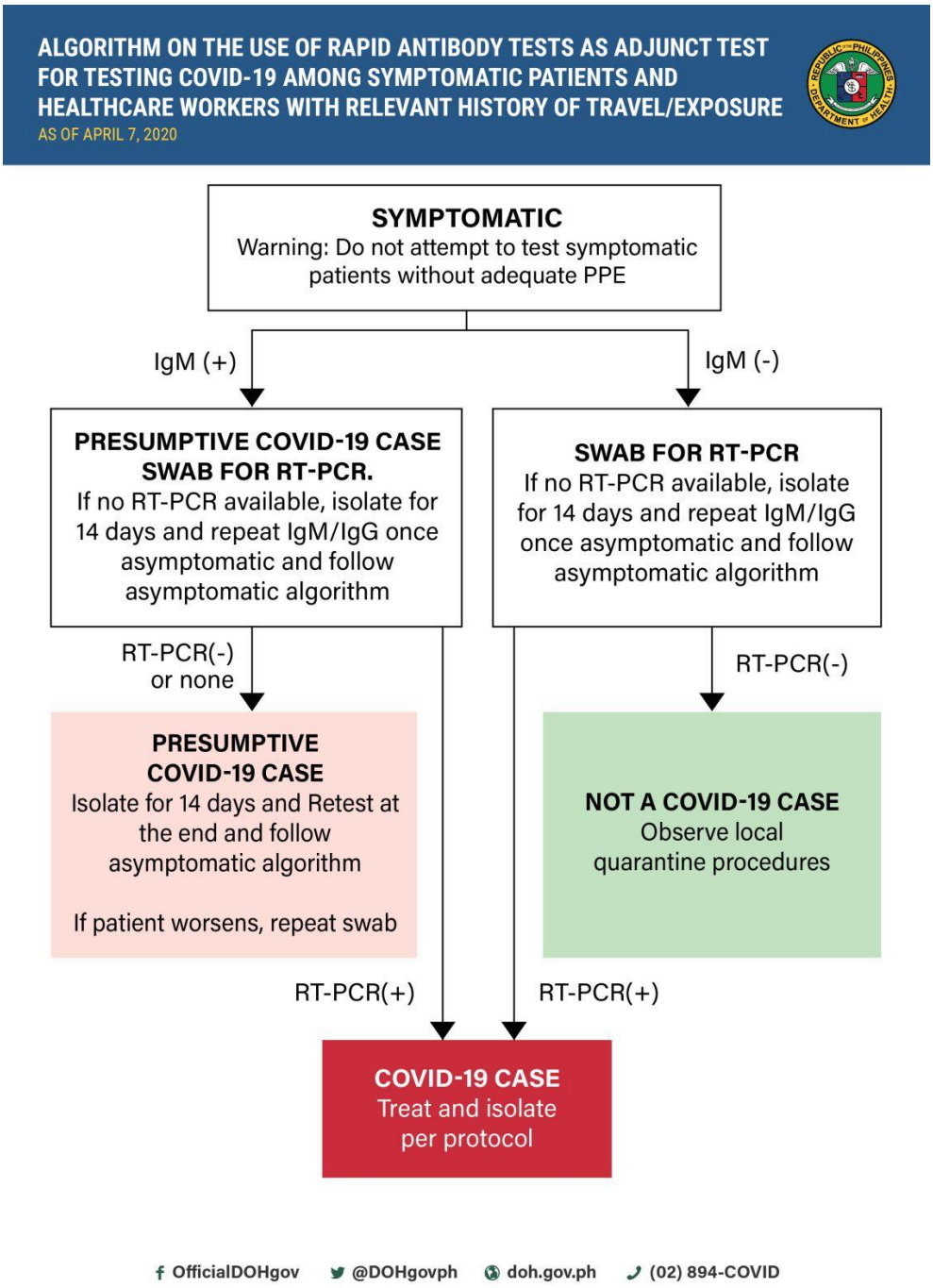
*Informed Consent Form replicated from Philippine Society for Microbiology and Infectious Diseases INTERIM GUIDELINES ON THE CLINICAL MANAGEMENT OF ADULT PATIENTS WITH SUSPECTED OR CONFIRMED COVID-19 INFECTION *Version 2.1, as of 31 March 2020*

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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