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EDITORIAL

Of Pandemics, Epidemics, and Outbreaks.

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It's been 1 year 4 months and 15 days since the world dealt with this pandemic head on. At the onset, we struggled with COVID-19 diagnosis, treatment and prevention. It was a tough process. We know better now as we continue to discover new things.

In this issue, we share interesting discoveries on COVID-19. 'Fulminant hepatic failure in a SARS-CoV-2 positive pediatric patient', and 'Outcomes of infants born to mothers with SARS-CoV-2 infection' are some of these. A rapid review on the sensitivity of SARS-CoV-2 RT-PCR done on different clinical specimens is an equally interesting read.

As if COVID-19 was not enough, HIV and MDRO outbreaks continue to slip in the background. An institutional experience on 'Outcomes of HIV exposed infants enrolled in the prevention of mother to child transmission of HIV (PMTCT) at the Philippine General Hospital' is presented. 'Use of polymyxins against multidrug resistant gram-negative bacteria' also provide a timely review on MDR infections.

Leptospirosis a seasonal cause of outbreaks in the local setting is revisited in 'Clinical profile of pediatric patients with leptospirosis.'

We bring at the forefront sequela from immune dysregulation as a result of COVID-19 and other viral infections --- MIS-C and HLH. 'Multisystem inflammatory syndrome in children (MIS-C): a case series' and 'Etiology, treatment and outcome of children diagnosed with secondary Hemophagocytic lymphohistiocytosis' are highlighted.

'Fever of unknown origin among children in two private, urban, tertiary hospitals: a 27-year retrospective study' also looks into FUO clusters.

To cap this issue, principles relevant to this pandemic are featured. 'Interim Guidelines on Screening, Assessment and Clinical Management of pediatric patients with suspected or confirmed coronavirus disease 2019' and 'Childhood immunization schedule 2021' are put into focus.

As we continue to live in the present, I can't help but look forward to the future and recount events of the past. Reality commands though that here and now, we should let sound scientific principles and correct consistent practices be our armor. I encourage the same for all. We will end our duel someday soon with COVID-19.

REVIEW ARTICLE

Rational Use of Polymyxins Against Multi-Drug Resistant Gram-Negative Bacteria

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ABSTRACT

The current strategy in treating multi-drug resistant gram-negative bacterial (MDR-GNB) infections is salvage therapy by using polymyxins. However, the beginning emergence of polymyxin resistance should enforce strict antimicrobial stewardship programs to preserve polymyxin efficacy. Knowledge of structural characteristics, pharmacodynamic, and pharmacokinetic profiles of polymyxins, as well as consideration of efficacy, safety, suitability, and cost, will help in the choice of the appropriate polymyxin for therapy. Polymyxin B is the recommended polymyxin for systemic use, while colistin is recommended for lower urinary tract infections, intraventricular, and intrathecal use. Either polymyxin can be used for hospital-acquired and ventilator-associated pneumonia. Combination therapy over monotherapy remains to be advantageous due to synergism and decreased resistance development. The choice of the second drug to be used should be based on full susceptibility, or if unavailable, a drug with the least minimum inhibitory concentration relative to the breakpoint set by the Clinical and Laboratory Standards Institute. Using the mnemonic **ESCAPE** can also guide physicians in their polymyxin prescription process: (1) Checking if the pathogen is **E**xtensively resistant or multi-drug resistant; (2) checking the patient's clinical status if compatible with **S**ignificant infection; (3) using **C**ombination therapy; (4) ensuring **A**dequate dosing; (5) **P**roper preparation and administration of drug; and (6) keeping an **E**ye for response and adverse effects.

KEYWORDS: *Polymyxin B, Colistin, MDR-GNB, Polymyxins*

INTRODUCTION

Emergence of antimicrobial resistance

The emergence of multi-drug resistant gram-negative bacteria (MDR-GNB) has been raising clinical concerns due to swift and unprecedented transmission and spread, especially in health care settings.[1] In the Philippines, according to the Antimicrobial Resistance Surveillance Program (ARSP) in 2018, MDR rates continued to rise across clinically relevant gram-negative bacteria (GNB). MDR rates for *Escherichia coli* and *Klebsiella pneumoniae* blood isolates were at 46% and 59%, respectively. *E. coli* has notable carbapenem resistance rates at 5%, but *K. pneumoniae and Pseudomonas aeruginosa* have even higher rates at 16-19%. However, *Acinetobacter baumannii* exhibited an alarming carbapenem resistance at 56%. [2]

Current antimicrobial use

In relation to the current global situation, data from hospitals show that more than 90% in some cohorts are being treated with antibiotics to cure or protect against secondary infection during hospitalization.[3] Unfortunately, the patients at greatest risk for superbugs are the ones who are already more vulnerable to illnesses. Inappropriate use of antimicrobials (e.g., disregard for the spectrum of activity, inappropriate dosing, timing, and duration) led to the emergence of MDRs.

Use of salvage therapy

A further complication is that there has been a slow-down in the development of newer antimicrobials in the development pipeline, forcing clinicians to use "salvage" therapy from old but less studied drugs such as polymyxins.[4,5] However, there is still limited clinical experience with the use of these drugs in terms of appropriate dosing to limit adverse effects without sacrificing efficacy. This could potentially lead to misuse and resistance development of these last resort antimicrobials.[6]

Usage timeline of polymyxins

Polymyxins were initially discovered in 1947, derived from products of strains of *Bacillus polymyxa* (Polymyxin B) and *Bacillus colistinus* (Colistin). They were used parenterally but eventually lost their favor when anti-*Pseudomonas* aminoglycosides came into the picture. They subsequently fell into disuse by the 1980s due to safety concerns, including nephrotoxicity. The resurgence in the use of polymyxins in clinical practice was due to the recent development of multi-drug resistance. In the Philippines, polymyxin use was considered as the last therapeutic option for multi-MDR-GNB in the mid-2010s (see Fig. 1).

One of the main reasons behind the preferential use of colistin over polymyxin B was the anecdotal belief that colistin was the safer option with respect to nephrotoxicity. However, modern-day data suggests that polymyxin B might be the safer option with respect to kidneys, debunking this historical notion.[7]

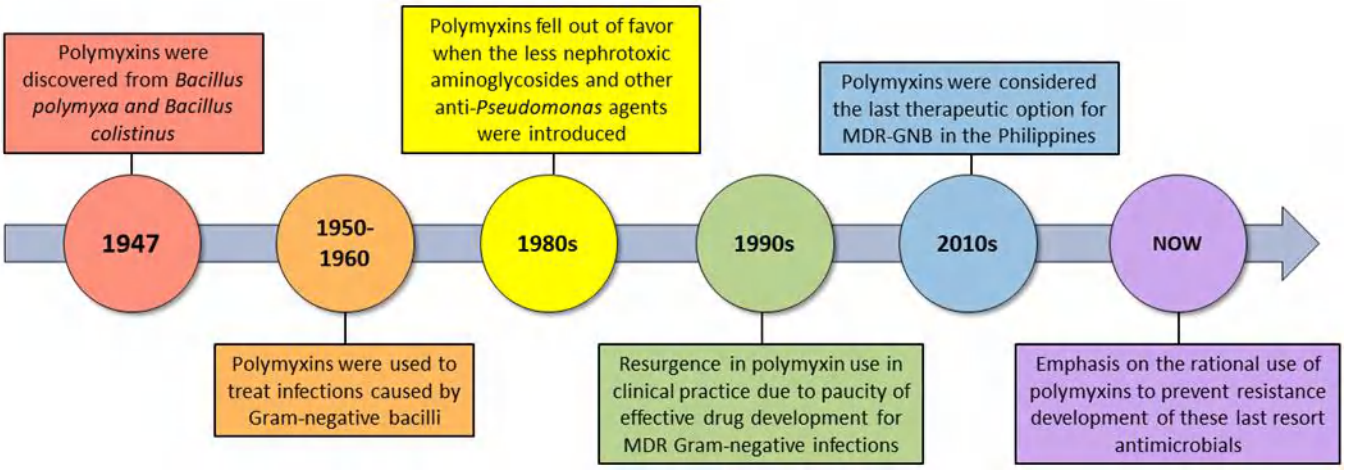

Figure 1. Development and usage timeline of polymyxins

Polymyxin resistance begins

There have been increasing reports of polymyxin resistance among carbapenem-resistant GNBs.[8–11] In the Philippines in 2018, there was actual documentation of the emergence of colistin-resistance gene *mcr-1* in *E. coli* clinical isolates. Both isolates came from patients admitted in a tertiary hospital in Quezon City, Philippines, with no prior colistin treatment nor travel history within 6 months prior to admission. The first isolate came from a diabetic foot wound of a 75-year-old female, while the second isolate came from a blood sample of a 61-year-old male with urinary tract infection. This may be indicative of local transmission of *mcr-1* from community settings within the Philippines. This implicates plasmid-mediated polymyxin resistance via the *mcr-1* gene.[12]

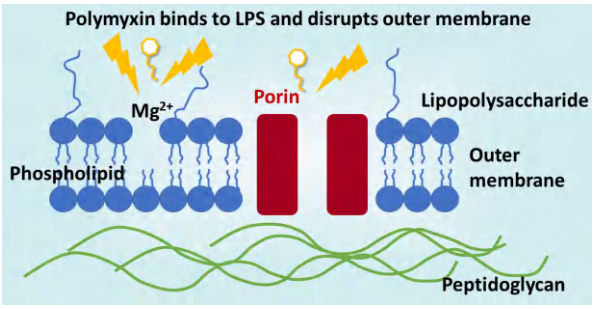

Figure 2. Interaction between polymyxin and gram-negative bacterial cell wall

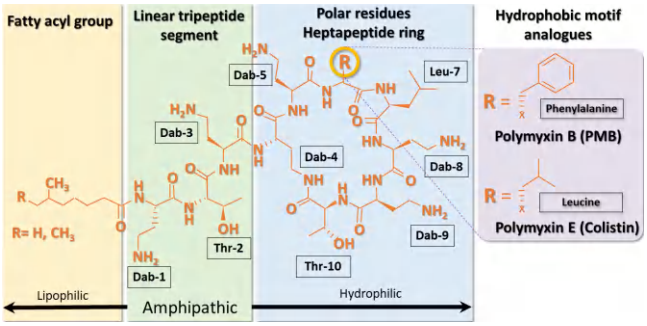

Figure 3. Chemical structure of Polymyxins.
Dab = diaminobutyric acid; *Thr* = threonine; *Leu* = leucine

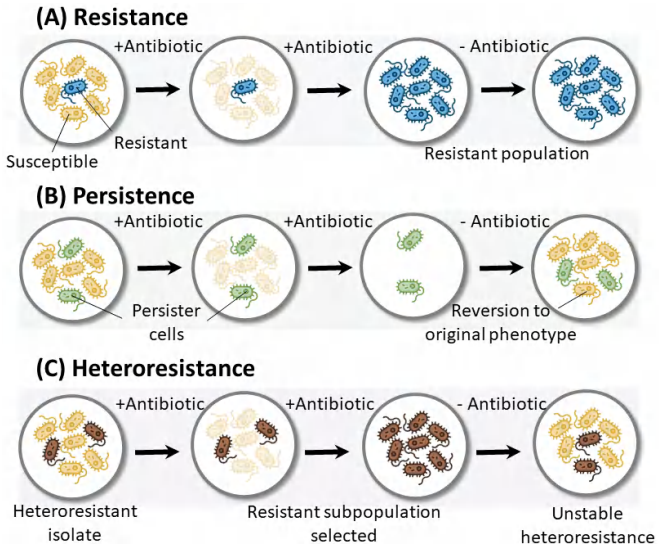

Figure 4. Bacterial heterogeneity and variance in behavior

Rational use of polymyxins

This leads us to signal the need to establish strict antimicrobial stewardship programs and strategies for the rational use of polymyxins to preserve their efficacy.[5,12] This article will (1) illustrate the structural characteristics, basic pharmacokinetics, and pharmacodynamics of polymyxins; (2) emphasize the importance of using combination therapies instead of monotherapy in using polymyxins; (3) present benefits and disadvantages in using polymyxin B or colistin depending on specific situations; and (4) formulate a simple guide in the use of polymyxin class of antibiotics in a healthcare setting using the ESCAPE mnemonic.

POLYMYXIN CLASS (B and E)

Chemistry and mechanism of action

Polymyxins are bactericidal antibiotics that are cationic, while GNB cell walls have anionic lipopolysaccharides (LPS). The interaction (see Fig. 2) between polymyxins and the gram-negative bacterial cell wall results in the displacement of calcium and magnesium from the phosphate group, leading to destabilization of the monolayer, reduction of the circulating endotoxin, and ultimately cell death.[13,14]

Polymyxin B and polymyxin E/colistin (see Fig. 3) share a common sequence, and the only difference is *R* at position 6, for which phenylalanine is the amino acid for polymyxin B and leucine for colistin.[5] Thus, these two polymyxins are basically similar: having the same structure with just one amino acid difference, but with the same mechanism of action. Like other peptide antibiotics, the presence of hydrophilic and lipophilic

groups makes them amphipathic, a property essential for its mechanism of action, as previously discussed.

Bacterial heterogeneity and resistance mechanisms

Figure 4A illustrates the concept of bacterial resistance. Applying antibiotic pressure would kill the bacteria, but a certain resistant subpopulation would remain despite the presence of the antibiotic. Resistant cells thereby give rise to a new population that is genetically distinct from the original one.[15]

Ongoing researches have been exploring polymyxin resistance mechanisms, and these include: (1) modification of bacterial LPD lipid A component; (2) halting of LPS production—once LPS is lost, there is nothing for polymyxins to target; (3) efflux pump production; and (4) plasmid-mediated resistance in which the resistance gene can be transferred to other bacteria.[16]

In contrast to resistant cells, there are bacterial subpopulations that exhibit a different kind of behavior, such as persistence (Figure 4B). Antibiotic pressure kills the bacteria but persister cells, which are phenotypic variants that can survive antibiotic treatment, remain. The difference is that they cannot grow in the presence of the antibiotic. When treatment ceases, persisters can switch back to the antibiotic-sensitive phenotype and give rise to a new population that is genetically identical to the original one.[15]

Another kind of behavior that proves to be one of the bigger problems in MDROs is heteroresistance (Figure 4C). Similarly, antibiotics kill bacteria, but heteroresistant cells survive and grow even in the presence of the antibiotic. Once antibiotic pressure drops, the cells revert to the antibiotic-sensitive state. Heteroresistant cells are persister cells that grow under antibiotic therapy.[15]

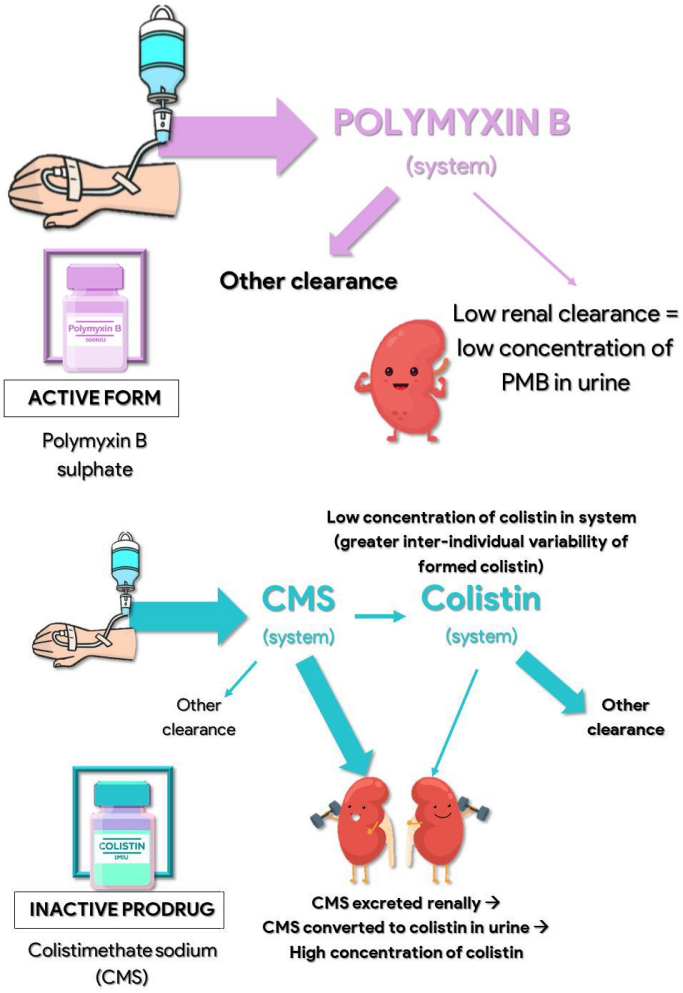

Figure 5. Pharmacokinetic pathways after intravenous polymyxin administration. *Note: Arrow thickness and font boldness indicate relative extent of clearance provided that renal function is normal*

Problem of Heteroresistance

Reaching optimum concentrations of an antibiotic can kill bacteria, but unfortunately, the presence of heteroresistant subpopulations can lead to bacterial regrowth. One of the proposed solutions to this problem is source control. It has been shown that polymyxins bactericidal activity is inhibited when exposed to a high initial inoculum. This may pose problems in treating infective endocarditis or deep-seated abscesses without prior adequate source reduction. With adequate source control, most of the initial inoculum will be removed, thus enabling antibiotics to eradicate the remaining bacterial population.[5]

Minimum inhibitory concentrations (MIC)

The Clinical and Laboratory Standards Institute (CLSI) has established recommended breakpoints for *P. aeruginosa* and *Acinetobacter* species for both colistin and polymyxin B. On the other hand, no breakpoints were made yet for *Enterobacteriaceae*, but epidemiologic cut-offs were defined (MIC ≤2µg/mL).[16,17] MIC breakpoints have already been determined for *Acinetobacter* (MIC ≤2µg/mL) and *Pseudomonas* (MIC ≤2µg/mL).[17] There are no major differences in breakpoints between colistin and polymyxin B because they are essentially similar.

Dosing and conversions

Conversion might be a little tedious when it comes to colistin because some practitioners variably use Colistin Base Activity (CBA) units, International Units (IU), or milligrams (mg). Approximately 1 CBA is equivalent to 30,000 IU per mg. On the other hand, polymyxin B conversion is easier, since 1 mg is equal to 10,000 IU. Either polymyxin requires loading doses to achieve desired antibiotic concentrations, followed by recommended maintenance doses:

1. Colistin loading dose is 150,000 IU/kg, followed by maintenance dose of 150,000 IU/kg/day divided q8 hours (for neonates) or 75,000 IU/kg/day divided q8 hours (for children); and
2. Polymyxin B loading dose is 2.5 mg/kg, followed by maintenance doses of 2.5-3 mg/kg/day divided q12 hours.

A relatively larger volume of diluent is required for polymyxin B (around 300-500 mL of D5 fluid for every 500,000 IU) compared to colistin (10 mL NSS to reconstitute 1M IU with 50 mL NSS to infuse).

Pharmacokinetics

The two polymyxins differ pharmacokinetically. Figure 5 shows the pharmacokinetic pathway following intravenous administration of polymyxin B and colistin.

Generally, polymyxin B has a superior pharmacokinetic profile because it is already formulated in its active antimicrobial form. After IV administration, the drug gets to the system already in its active form, achieving desired concentrations in plasma rapidly and reliably performing its killing duty.[7] Eventually, it is subjected to renal filtration and tubular reabsorption, with a low concentration of polymyxin B in urine due to low renal clearance. Most of the drug undergoes non-renal elimination.[5]

On the other hand, the pharmacokinetic pathway of colistin is rather complicated because it is administered in the form of an inactive prodrug, colistimethate sodium, or colistin methanosulphate (CMS). CMS is predominantly excreted by the kidney and is converted to colistin in urine; hence, a high urinary concentration of colistin is expected. Only about 20-25% of CMS are converted to colistin, and this conversion estimation has great inter-individual variability. Thus, to obtain sufficient plasma concentration of active colistin, about five times the amount of CMS is needed to be administered. This slow conversion of CMS also leads to a delay in bacterial killing. The rest of colistin undergoes non-renal elimination after.[5,14]

POLYMYXIN USE IN CHILDREN

There is lack of data in the use of polymyxins among the pediatric age group, especially in the critically ill. However, several studies regarding the use of colistin and polymyxin B in children have been made and are cited within this article.

Pharmacokinetic and pharmacodynamic data on polymyxin use are mostly derived from adult studies, as studies involving neonates and children are very limited. The first pharmacokinetic study involving intravenous CMS use in critically ill neonates was published by Nakwan *et al.* in 2016. It was found that approximately 150,000 IU/kg of CMS was well tolerated with no adverse effects, albeit with suboptimal plasma colistin concentrations. Further studies exploring higher daily doses and different dosing regimens were recommended.[18]

In terms of efficacy of polymyxin use in neonates, a case-control study involving forty-seven (47) neonates admitted in two centers in Turkey has shown that CMS was effective for treating MDR-GNB infections in neonates but was significantly associated with low magnesium and potassium, which led to its discontinuation.[19] On the other hand, two retrospective studies done in Turkey involving neonates have shown good recovery rates and effective MDR-GNB microbiologic clearance with the use of CMS. However, CMS use was associated with reversible acute kidney injury and electrolyte imbalances.[20,21] A similar retrospective study involving neonates was also done in the Philippines (see the section on *Choosing the Right Polymyxin: Safety*). Large prospective controlled studies

are needed to confirm CMS efficacy and safety in neonates.

In contrast, there are only sporadic published reports involving polymyxin B (PMB) use. There were no studies yet involving neonates, but there are some published involving children (see also section on *Monotherapy vs. Combination Therapy: Clinical outcomes in Polymyxin B monotherapy*). A retrospective study involving polymyxin use for bacterial meningitis in children showed successful results.[22] Similarly, a retrospective study involving the use of polymyxins (including PMB) for the treatment of intracranial infections in children after the neurosurgical operation has shown effectiveness with no noted serious adverse effects.[23]

No studies yet have been published that compared the efficacy of CMS and PMB in children or neonates. Randomized controlled trials are needed to meticulously outline the most effective and safest polymyxin regimen in pediatrics.

MONOTHERAPY VS COMBINATION THERAPY

Polymyxin B *in vitro* performance

A study by Tam et al. in 2011 measured the potency of polymyxin B components against three standard wild-type bacterial strains and three clinical MDR strains (*P. aeruginosa, A. baumannii,* and *K. pneumoniae*) using the broth dilution method, and they found out that there were no substantial differences in potency against wild-type and MDR strains. Another *in vitro* study measured the activity of polymyxin B against 217 strains of carbapenem-resistant *A. baumannii* from different patients, and they identified 98.2% of the strains being susceptible to polymyxin B.[24] A similar *in vitro* study done in Mexico measured susceptibility of highly lethal and biofilm-producing clones of MDR *A. baumannii* to polymyxin B, and results were promising at 100% susceptibility rate.[25]

Clinical outcomes of polymyxin B monotherapy

Although *in vitro* studies show satisfactory efficacy of polymyxin B against drug-resistant isolates, some clinical studies show guarded results. A retrospective study by Nelson *et al.* in 2011 examined the clinical outcomes of 151 patients receiving polymyxin B therapy for carbapenem-resistant GNB bloodstream infections (*K. pneumoniae* 60.9%, *A. baumannii* 21.2%, and *P. aeruginosa* 11.3%). They noted a 30-day mortality at 37.8% and clinical cure by 7th day at 63.6%. Another retrospective study involving pediatric cases in a developing country (critically ill children less than 15 years old) likewise measured clinical outcomes of children receiving polymyxin B against MDR-GNB infections showed only a modest survival of 8 out of 14 children—57.1%.[26]

Risk factors for monotherapy failure

A retrospective study conducted by Dubrovskaya *et al.* in 2013 investigated the risk factors for polymyxin B treatment failure among carbapenem-resistant *K. pneumoniae* (CRKP). The group found out that the only identified independent risk factor after the multivariable analysis is baseline renal insufficiency, for which it is associated with six (6) times greater chances of clinical failure. The study also showed relatively higher treatment success—clinical cure at 73% (29/40) and microbiologic cure at 28% (17/32)—as well as low 30-day mortality at 28%. However, what this study also found is that with monotherapy, 45% (18/40) had repeat CRKP infection and 7.5% (3/40) had breakthrough infections intrinsically resistant to polymyxin B. One of the recommendations of this study was to give it as a combination with other antibiotics to prevent emergence of resistance.[27]

Advantages of combination therapy

Combination therapy basically provides advantages in the treatment of MDR infections, namely: (1) effectively increasing bactericidal activity via synergism; and (2) reducing the development of resistance compared to monotherapy.[28]

Synergism in combination therapy

A study done in Australia illustrated via scanning electron microscopy the synergistic killing of MDR *K. pneumoniae* by using polymyxin B and chloramphenicol. Chloramphenicol monotherapy was shown to be ineffective (no significant cell wall change) since it is only bacteriostatic and is involved in protein synthesis inhibition. Polymyxin B monotherapy caused projections and blebs on the bacterial surface, which is consistent with its mechanism of action. However, there was also rapid regrowth and resistance emergence with monotherapy. Combination treatment showed denser projections and blebs than polymyxin B monotherapy, and there were no polymyxin-resistant isolates noted.[29]

Other combination treatment studies differ in treatment regimen used and the organisms they chose to target, but their results show polymyxin and beta-lactam/carbapenem combination most effective in

eradicating MDR / extremely drug-resistant (XDR) organisms and has lower mortality reports.[30,31] A study conducted by Teo *et al.* in 2015 identified bactericidal polymyxin B-based combinations against XDR *A. baumannii.* The clinical samples came from Thammasat University, Thailand, and the combination treatment regimen they used include polymyxin B plus imipenem, meropenem, doripenem, rifampicin, and tigecycline. Polymyxin B monotherapy against the XDR strain is satisfactory at 87.8%. However, whenever polymyxin B is combined with carbapenems, bactericidal activity rose to 100%. This supports the premise that combination therapy is superior to monotherapy.[32]

Combination therapy synergism was also well-described in a study done in Israel in which they meta-analytically pooled the synergy rates across 39 studies. They had found that even when the strains were carbapenem-resistant, synergy rates from polymyxin B and carbapenem combination against *Acinetobacter* were still acceptable (77% versus 71% for resistant strains) and even increased against *Klebsiella* (44% versus 55%) and *Pseudomonas* strains (50% versus 59%).[32]

Less resistance development in combination therapy

The meta-analysis of Zusman *et al.* also showed that polymyxin monotherapy led to resistance development in almost 100% of the strains *in vitro* after 24 hours. Resistance was found to appear earlier for monotherapy at 24 hours than with combination therapy at 72 hours (if at all). Combination therapy also successfully suppressed polymyxin-resistant populations,[33] further supporting its advantage against monotherapy.

CHOOSING THE RIGHT POLYMYXIN

International Consensus Guidelines

Recent international consensus guidelines on the use of polymyxins were released last 2019, as endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ECSMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). This guide in choosing the right polymyxin will heavily reference this consensus guideline[7] and will consider four (4) main factors: efficacy, safety, suitability, and cost, as summarized in Table 1.

Efficacy

Systemic use

In terms of efficacy, one should take into account the differences in pharmacokinetics between the two polymyxins. The preferred agent for invasive infections is polymyxin B due to its pharmacokinetic advantage in that it is already in its active form, which can reliably reach desired concentrations to perform its bactericidal function. Risk of acute kidney injury is also associated less with polymyxin B use.[5,7]

Lower urinary tract infections

Colistin has superior activity in the urinary system. It is the preferred agent for the treatment of lower urinary tract infections given that the prodrug CMS renal clearance is eventually converted to active colistin in the urinary tract.[5,7,14]

Hospital-acquired pneumonia

It is recommended by the guideline to use either polymyxin as an adjunctive treatment for XDR gram-negative hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP). No comparison yet between CMS and polymyxin B has been made in this regard. Since only about 9% of colistin reaches the lungs, the problem lies with the actual aerosol delivery of CMS.[7] Recommendations for the dosing varies among randomized controlled trials. In terms of outcomes, a meta-analysis done in Sweden has shown improved clinical response and lower mortality with the use of adjunctive aerosol CMS therapy. However, there was documentation of nephrotoxicity with its use, and analysis was shown to have outcome inconsistencies.[34] A retrospective cohort study done in Turkey involving children aged 1 month to 18 years with conducted culture-proven VAP due to colistin-only susceptible (COS) GNB showed that adjunctive aerosol CMS therapy in addition to IV colistin led to shorter median time to bacterial eradication but no significant difference in VAP outcomes.[35] Although ECSMID has released a position paper to avoid routine adjunctive inhaled antibiotics, the joint guidelines state that benefits may outweigh the risks in this case.

Intraventricular/Intrathecal

Colistin remains to be the preferred agent for intraventricular (IVT) or intrathecal (ITH) use. Only 5% of IV colistin typically penetrates the cerebrospinal fluid.[7]

Drug combinations guide

Typically, for carbapenem-resistant *Enterobacteriaceae* and carbapenem-resistant

Pseudomonas aeruginosa, choose an appropriate polymyxin and combine it with a second drug with evidence of susceptibility. If the second drug is unavailable, use a non-susceptible drug with the lowest MIC relative to its breakpoint. The same rule applies to CRAB, but contentiously, the guidelines advise monotherapy if the second drug is unavailable. However, this is a weak recommendation with moderate quality of evidence due to study confounders and low sample size and has only won panel voting at 8-7. Monotherapy has limitations in terms of bacterial synergism and resistance development.[7]

Safety

The consensus guidelines recommend the preferential use of polymyxin B—especially for countries where both colistin and polymyxin B are available—due to its lesser rate of polymyxin-associated acute kidney injury. In addition, polymyxin B does not require renal adjustments. CMS requires renal adjustments depending on creatinine clearance.[7] A meta-analysis involving MDR-GNBs has shown that there was no significant difference in mortality between the use of colistin and polymyxin B, but colistin administration was found to be an independent risk factor for the development of nephrotoxicity, even if the relative colistin dose was lower than polymyxin B dose used.[36]

A recent retrospective study done in the Philippines involving neonates with MDR-GNB infections determined adverse effects (including acute kidney injury) of intravenous colistin. Nephrotoxicity was seen in only 4% of patients (n=175), although the clinical outcome of mortality was at 50.7%. Further studies involving neonates and children are recommended to elucidate further rate of nephrotoxicity of polymyxin use in this population.[37]

Suitability

Take note that concomitant use of other nephrotoxic agents should be avoided in patients receiving polymyxins. Checking for comorbidities and medication history (e.g., calcineurin inhibitors, loop diuretics, NSAIDs, ACEIs, vancomycin, rifampicin, aminoglycosides) will be helpful in the decision making of choosing antimicrobials. However, in cases where polymyxin + aminoglycosides are the needed combination for a specific MDR infection, this might be unavoidable and should still be considered for use.[7]

Table 1. Factor analyses in choosing the right Polymyxin.

	Polymyxin B	Colistin
Efficacy	For routine systemic use since it is already administered in its active form	Alternative for systemic use, given as a prodrug; Superior activity for lower urinary tract infections; preferred for IVT/IT use
Safety	Lesser rate of nephrotoxicity; no renal adjustments required	Associated with colistin-associated nephrotoxicity; needs renal adjustments for AKI
Suitability	Exert caution when given for patients with concomitant nephrotoxic agent use; administered as intravenous form	Exert caution when given for patients with concomitant nephrotoxic agent use; administered as intravenous form
Cost	Slightly more expensive than colistin	Slightly less expensive than polymyxin B

IVT = intraventricular; IT = intrathecal; AKI = acute kidney injury

Cost

The cost will matter in the choice of polymyxin, especially in resource-limited countries, and it will play a factor in ensuring commitment to therapy. The current average price for a CMS 2M IU vial is ₱ (Philippine Peso) 1,700.00 and for a polymyxin B 50 mg vial is ₱2,200.00. Thus, for a 5-kg child, the estimated cost for the first 72 hours is as follows: ₱1,500.00 for CMS and ₱2,200.00 for polymyxin B (this is assuming no wastage of the contents).

GUIDE TO PRESCRIBING POLYMYXINS

This guide uses the mnemonic ESCAPE (alluding to ESKAPE organisms) to summarize the steps in choosing polymyxins for the treatment of MDR/XDR infections (see Figure 6).

Step 1. *Extensively resistant or multi-drug resistant organisms*. Check if the pathogen implicated in the infection is culture-based. Keep in mind that even if the pathogen is drug-susceptible, there can be heteroresistant subpopulations present *in vivo*.

Step 2. *Significant infection.* Check the patient's clinical status and sepsis markers (if available)—do they depict colonization or infection? Although it is difficult to

differentiate colonization from infection in many instances, the decision to treat remains in the hands of the primary physician. Careful attention and interpretation must be given to culture material (sterile versus non-sterile) and utilization of sepsis markers (e.g., procalcitonin) to aid in decision making to treat infections.

Step 3. *Combination therapy* provides advantages in effectively increasing bactericidal activity via synergism and reducing resistance development versus monotherapy.

Step 4. *Adequate doses.* Check proper dosing, especially if adjustments are needed in the presence of acute kidney injury (in the case of CMS).

Step 5. *Proper preparation and administration* must be observed to maximize drug efficacy (pay attention to dilution and infusion rates).

Step 6. Keep an *Eye for response and check for adverse effects* such as renal function and neurologic status.

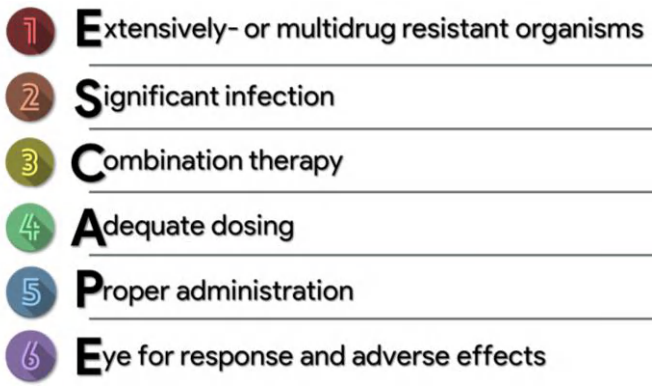

Figure 6. Prescribing Polymyxins using the ESCAPE mnemonic

CONCLUSION

In view of the emergence of multidrug-resistant and extremely drug-resistant gram-negative infections, the use of polymyxins as salvage therapy came to light. The beginning emergence of polymyxin resistance also signals the need to prescribe polymyxins for infections rationally. Knowledge of polymyxin similarities in structural characteristics and mechanism of action, as well as differences in their pharmacokinetics, will aid in choosing the right polymyxin for each situation. It should also be noted that the presence of heteroresistant bacterial subpopulations can lead to regrowth if not addressed. Combination therapy remains advantageous over monotherapy due to increased bactericidal activity through synergism and decreased resistance development. Efficacy, safety, suitability, and cost should always be considered in choosing one polymyxin over the other. Using the mnemonic ESCAPE can aid physicians in guiding their rational prescription process.

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CASE REPORT

Fulminant Hepatic Failure in a SARS-CoV-2 Positive Pediatric Patient: A Case Report

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ABSTRACT

Respiratory symptoms are the most common manifestation of COVID-19 across all age groups and it is most often associated with radiographical findings consistent with pneumonia.[2] A recent systematic review estimated that 16% of children with SARS-CoV-2 infection are asymptomatic,[3] or others may present with seizures, gastrointestinal bleeding or jaundice. This reports a 2-year old boy with no known co-morbidity who had a 2-week history of abdominal pain and jaundice then had a rapidly progressive course of neurological deterioration and eventual demise. He had markedly elevated liver enzymes and deranged bleeding parameters with elevated ammonia and ferritin levels. Hepatitis B and hepatitis A titers were non-reactive. He was managed as a case of hepatic encephalopathy secondary to cholestatic jaundice. His chest x-ray was normal but his SARS-CoV-2 RT PCR result was positive with a low cycle threshold. Locally, this is the first reported case of SARS-CoV-2 RT-PCR positive pediatric patient presenting as fulminant hepatic failure with no associated respiratory manifestations. Clinicians should be mindful that such presentation, however uncommon, is possible and a high index of suspicion should be maintained.

KEYWORDS: *COVID-19, SARS-CoV-2, hepatic failure, fulminant hepatitis, case report*

INTRODUCTION

According to the Philippines' Department of Health (DOH) data as of February 11, 2021, around 9.7% of COVID-19 cases are of the pediatric population.[1] Respiratory symptoms are the most common manifestation of COVID-19 across all age groups and it is most often associated with radiographical findings consistent with pneumonia.[2] A recent systematic review estimated that 16% of children with SARS-CoV-2 infection are asymptomatic,[3] or some may present with seizures, gastrointestinal bleeding or jaundice. Other typical manifestations since this disease emerged last December 2019 include fever, diarrhea, weakness and fatigue.[4] However, in our institution's experience, a tertiary pediatric referral center, the manifestations in children are varied. One rare manifestation we encountered is jaundice with a rapidly progressive course causing fulminant hepatic failure. Infected children are reported to have a milder disease course and a better prognosis than adults[5]. The incidence ranges from 5%-22% of pediatric patients with laboratory-confirmed COVID-19 exhibiting only mildly elevated liver enzymes[6,7] In this case though, we report a child with fulminant hepatic failure who tested positive for SARS-CoV-2.

CASE REPORT

This is a case of a 2-year-old boy presenting with irritability, abdominal pain, and jaundice of 2 weeks duration.

14 days prior to admission, he had intermittent generalized abdominal pain accompanied by development of icteric sclerae. He had no fever, changes in bowel habits, abdominal distention nor vomiting. His abdominal pain would be relieved spontaneously hence no medications were given.

12 days prior to admission, he was brought to a pediatrician due to the persistence of symptoms. He was assessed to have hepatitis A. Laboratories were requested which were not complied with. No medications were given.

7 days prior to admission, he still had persistence of abdominal pain and jaundice. Work-up was done revealing: elevated liver transaminases [ALT (3,378U/L), AST (4,010.05U/L)], and bilirubin levels: total bilirubin 11.62mg/dL, direct bilirubin 10.87mg/dL, indirect bilirubin 0.76mg/dL. Abdominal ultrasound showed minimal ascites, hepatosplenomegaly, and a thickened gallbladder wall. Telemedicine consult was done with the pediatrician and he was given unrecalled medications. In the interim, there was progression of jaundice and note of acholic stools and tea-colored urine. He remained afebrile and active with good appetite.

4 days prior to admission, with the progression of symptoms, he was brought to a hospital. The patient and his mother adhered to minimum infection control measures and wore masks and face shields during the entire time. HBsAg, anti-HBe, HBeAg, total anti-HBc, anti-HAV IgM results were nonreactive and anti-HBs was reactive. Protime was 23.9 sec, INR 1.68, percent activity 52%. Further work-up including serum ceruloplasmin, serum copper levels, ANA, anti-smooth muscle antibody, anti-LKMI, and liver biopsy were requested. The patient was assessed by a gastroenterologist to have viral hepatitis versus Wilson's disease. Ursodeoxycholate was started and they were advised admission but because of financial constraints, the patient was lost to follow-up. 3 days after, there was further progression of jaundice, persistence of abdominal pain and the patient became irritable, hence he was brought to our medical center and subsequently admitted.

He was born full term in a lying-in clinic with no feto-maternal complications and was discharged well after 24 hours of life. He was breastfed and given milk formula since birth and currently consumes table food prepared by his mother. His neurodevelopmental milestones were at par with age. He has completed his primary childhood immunizations from a health center that included BCG, 3 doses of hepatitis B vaccine, DPT, polio and Hib vaccines and a dose of measles vaccine. He had no known past illnesses, no previous hospitalizations and no heredo-familial diseases including liver diseases nor jaundice. There was no intake of paracetamol or other hepatotoxic drugs. He is the only child and his parents denies having any flu-like illness nor exposure to any COVID-confirmed case for the past 2 weeks. His father works as a private driver and his mother is a production operator. They use purified water for drinking and, due to the pandemic, buys food from a local supermarket while observing strict social distancing and wearing of masks.

At the Emergency Department, the patient was alert, irritable but consolable. He was afebrile, normotensive, with stable vital signs, no desaturations at

room air. There was generalized jaundice. No rashes, pruritus nor bleeding were noted. Cardio-pulmonary examination was essentially normal. The abdomen was flat, soft, with a palpable, non-tender liver at 4cm below right subcostal margin midclavicular line and a palpable non-tender spleen at 2-3cm on the left upper quadrant. The abdomen was negative for fluid wave. There were no palpable lymph nodes. He was managed as a case of hepatic encephalopathy secondary to cholestatic jaundice, to rule out Wilson's disease. Intravenous fluid was started. He was given vitamins A, D, E, K, zinc and ursodeoxycholate. Other laboratory tests including serum ceruloplasmin, alpha-1 anti-trypsin, urine toxicology screening were requested however were not done immediately due to financial constraints. A schedule for liver biopsy was requested. 2 units of fresh frozen plasma were secured. Twelve hours into admission, he was observed to be more irritable and agitated.

Other laboratory test results were: chest radiograph was normal, complete blood count: white blood cell 6.9 x 10^9/l, segmenters 0.55, lymphocyte 0.37, platelet count 216; ALT 4,320 (86x elevated), AST 7,282 (123x elevated), alkaline phosphatase 433 (3.4x elevated), total bilirubin 41.2 mg/dL, direct bilirubin 33.7 mg/dL, indirect bilirubin 7.6 mg/dL (3x elevated), protime 54.7 sec, INR 4.42, APTT 53.0 sec. Direct Coomb's test was negative and reticulocyte count was 13.1 (8x elevated). CRP <5mg/dl and procalcitonin was 0.463 ug/l. Blood culture was negative.

On the 36th hour after admission, he had decreased sensorium with a Glasgow Coma Scale (GCS) of 11 (E4V2M5) and developed fever (38.6-39°C). His ammonia level was at 105 umol/L (3.2x elevated) on admission and further elevated to 323 umol/L (10x elevated) hence metronidazole and cefotaxime were started.

On the 40th hour of admission, a repeat chest x-ray was done that still showed normal results. Due to persistent fever with changes in sensorium, SARS-CoV-2 real-time reverse transcriptase polymerase chain reaction (RT-PCR) nasopharyngeal and oropharyngeal swab samples were obtained. Serum ferritin was elevated at 3,957 ng/ml (9.8x) and LDH 1,583 U/L (6.4x elevated). IVIG was given at 1g/kg/dose x 1 dose. Despite medical and supportive measures, the patient's sensorium further decreased with development of bradycardia. He was transferred to the COVID-19 ward and required intubation but the patient eventually expired on the 48th hour of admission with a final diagnosis of indeterminate fulminant hepatic failure.

The RT-PCR for SARS-CoV-2 results came in 3 days after the patient's demise revealing a positive result for SARS-CoV-2 with a cycle threshold value of 15.59. Patients in the same room who were exposed to him were swabbed 5 days after exposure and all revealed negative results. His parents were referred to their regional epidemiologic surveillance unit and the mother also tested positive for SARS-CoV-2 on RT-PCR, but remained asymptomatic.

Parents did not consent to an autopsy. Consent to submit this case for publication was obtained from the parents.

DISCUSSION

We report a pediatric case of fulminant hepatic failure in a SARS-CoV-2 patient. ACE2 receptors are known to be found on type 2 alveolar cells, and up to 59.7% of cholangiocytes, and less commonly, hepatocytes (2.6%).[8] SARS-CoV-2, like SARS-CoV, bind to the angiotensin-converting enzyme 2 (ACE2) receptor to enter target cells,[9] where the virus replicates and subsequently infects other cells in the upper respiratory tract and lung tissue. It is reasonable to consider then that SARS-CoV-2 can bind to the ACE2 receptors of cholangiocytes inducing direct injury to bile ducts, acute liver injury, and even cause acute fulminant hepatitis. A loss of hepatocyte function sets in motion a multiorgan response, characterized by hepatic encephalopathy, a complex coagulopathy, derangements in intrahepatic metabolic pathways, rapid deterioration and hemodynamic disturbances.[9] All of which were reflected in our patient's clinical course. The patient's elevated liver profile may also reflect a direct virus-induced cytopathic effect and/or immune damage from the provoked inflammatory response. Because of the unusual manifestations of COVID-19, and it being a novel virus, it should be ruled out as one of the causes of acute hepatic failure especially in the pediatric age group.

Our patient was a previously well-child with no known co-morbid conditions. The initial presentation was not typical for COVID-19. Viral infections other than SARS-CoV-2, are the most common causes of acute hepatic failure.[10] Work-up for hepatitis A and B were

negative in this case but ideally further work-up to rule out other viruses such as-hepatitis C, E, Epstein-Barr Virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV 1), HSV 2, and human immunodeficiency virus (HIV) should be done. These were not done due to the patient's rapid deterioration. Clinically though, the patient didn't present with abdominal distention, lymphadenopathies, skin nor mucocutaneous lesions that are commonly seen in EBV, CMV, HSV. Considering the patient's age and rapid clinical course, these were also not consistent with the other viral organisms mentioned above.

Wilson's disease, an autosomal recessive disorder of copper metabolism, cannot be excluded in children presenting with hepatic involvement using commonly practiced clinical and laboratory parameters.[11] Due to limited resources and time, serum ceruloplasmin, copper level, slit-lamp exam to check for Kayser-Fleischer ring and liver scan were not performed. The absence of liver disease in both the maternal and paternal side makes the diagnosis of Wilson's disease less likely.

Adult patients with severe COVID-19 have a higher rate of liver dysfunction and infected children were reported to have a milder disease course and a better prognosis.[5] Qiu et al analysed 36 pediatric patients (aged 0-16 years) with laboratory-confirmed COVID-19 in three hospitals in Zhejiang and they recorded only 2 children with elevated liver enzymes.[6] Moreover, in a report involving 31 cases of SARS-CoV-2 infected children, only 22.2% of patients had elevated transaminases levels, being the highest value for ALT and AST were 68 U/L and 67 U/L respectively.[7] In contrast to our case, which revealed ALT at 4,320 U/L (86x elevated) and AST at 7,282 U/L (123x elevated). An autopsy would have helped in the definitive diagnosis; however, the relatives did not consent. Of note, is a study by Bangash et al of liver injury of COVID-19 patients which indicated that post-mortem liver biopsy of COVID-19 patients showed only steatosis, which is common in patients with sepsis.[12]

There have been two case reports on children treated for acute fulminant hepatic failure in the context of COVID-19 but these cases had respiratory symptoms and chest CT scan findings of pneumonia[13,14] in contrast to our patient who didn't present with any respiratory symptoms and had normal chest radiograph results.

Our patient tested positive for SARS-CoV-2 and the ORF1ab cycle threshold (Ct) value was 15.59. Ct values and culture positivity rates were reported to have a significant relationship. It was La Scola et al., who reported that culture positivity rate was shown to be inversely proportional with Ct values. The samples with Ct values of 13 to 17 all led to positive culture; whereas at Ct value of >34, no culture was obtained.[15] The data above may indicate that the lower Ct value of our patient may be associated with his worse course of illness and outcome. Likewise, the mother also testing positive for SARS-CoV-2 RT-PCR makes a false positive result for our patient less likely.

CONCLUSION

This is the first reported pediatric case of fulminant hepatic failure in a SARS-CoV-2 positive patient without respiratory manifestations. Clinicians should be mindful that such presentation, however uncommon, is possible and a high index of suspicion should be maintained. Although literature reports a good prognosis or outcome for children with COVID-19, unusual manifestations with poor prognosis can happen.

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CASE SERIES

Multisystem Inflammatory Syndrome In Children (MIS-C): A Case Series in a Tertiary Hospital

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ABSTRACT

The clinical course of COVID-19 in the pediatric population has been reported to be mild in the majority of affected patients. However, a condition referred to as multisystem inflammatory syndrome in children (MIS-C) can occur with SARS-CoV-2 infection where patients can become critically ill. In this series, we describe five pediatric patients with the spectrum of MIS-C associated with SARS-CoV-2 infection.

KEYWORDS: *MIS-C, COVID-19, SARS-CoV-2*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China and since then has spread throughout the world causing an unprecedented pandemic in March 2020. The clinical course of COVID-19 in the pediatric population has been mild, but some children infected with SARS-CoV-2 can be critically ill due to multisystem inflammatory syndrome in children (MIS-C).

The World Health Organization (WHO) has provided a case definition of MIS-C which must meet six criteria: (1) patients 0-19 years of age, (2) fever ≥3 days, (3) at least two clinical signs of multisystemic involvement (rash, conjunctivitis, hypotension, cardiac dysfunction, evidence of coagulopathy, gastrointestinal symptoms), (4) elevated inflammatory markers (eg, ESR, CRP or procalcitonin), (5) no other obvious cause of inflammation, and (6) evidence of SARS-CoV-2 infection either by exposure to a confirmed case or a positive SARS-CoV-2 RT PCR, serology or antigen test.[1]

In this case series, we describe five pediatric patients with the spectrum of MIS-C associated with SARS-CoV-2 infection.

PATIENTS' INFORMATION

Five children aged 17 months to 12 years with features of Kawasaki Disease (KD) and who are positive for SARS-CoV-2 are presented. All patients were previously healthy with no comorbidities.

CASE PRESENTATION

Case 1: A 12-year old male presented with a 9-day history of fever, bilateral eye redness, pruritic, erythematous rashes and vomiting. Dengue was ruled out and the patient was given an unrecalled antibiotic. Two days prior to admission, fever was accompanied by diarrhea with generalized, crampy abdominal pain, decreased appetite and activity. On the day of admission, there was persistence of symptoms with body malaise. He was brought to a local hospital where the following laboratory tests were done: CBC showed a WBC of 25.8 x10^9/L, segmenters of 86.2% and platelet count of 500x10^9/L. Urinalysis showed a WBC of 5-10/hpf. Serum sodium was 130 mmol/L and potassium was 2.9 mmol/L. The patient was subsequently transferred to our institution. There were no sick contacts nor exposure to COVID-19 confirmed cases.

The patient was seen weak-looking and dehydrated with the following vital signs: BP of 90/60 mmHg, HR 145 breaths/min, RR 30 breaths/min and temperature of 38.6°C. On physical examination, there was conjunctival injection, hyperpigmented macules on bilateral lower extremities with weak pulses, cold extremities, and capillary refill time (CRT) > 2 seconds. Assessment was compensated shock secondary to infectious diarrhea, to consider typhoid fever; COVID-19 suspect. Blood tests revealed a WBC of 28.4 x 10^9/L, segmenters at 89% and procalcitonin at 9.992ug/L (20x). Serum potassium was 2.9 mmol/L and calcium was 2.17 mmol/L. Blood, stool and urine cultures were negative. Ceftriaxone was given at 100 mg/kg/day IV once daily. SARS-CoV-2 RT-PCR nasopharyngeal and oropharyngeal swabs were positive for viral RNA with a Cycle threshold (Ct) value for N Gene of 36.94 and ORF1ab of 0.00 done.

Despite several courses of antibiotics, patient remained to have high grade fever, with loose stools, abdominal pain and anorexia. Inflammatory markers showed an ESR of 115 mm/hour (5x elevated), CRP of 110 mg/L (110x elevated) and ferritin of 772 ng/mL (2x elevated). A diagnosis of MIS-C was considered. IVIG 2 g/kg/dose for 12 hours and Aspirin 80 mg/kg/day orally every 6 hours were given on the 16th hospital day. Fever resolved after 36 hours of IVIG. ASA therapy at 5 mg/kg/dose once daily orally was continued. Repeat SARS-CoV-2 RT PCR result was negative after 14 days. There was diffuse coronary arteritis on 2D-echocardiogram which was done on the 17th hospital day. On the 22nd hospital day, he was sent home improved with home medication of aspirin at 5 mg/kg/dose once a day orally until follow up with the cardiologist.

Case 2: A 17-month-old female presented with a 9-day history of high-grade fever and decreased appetite and activity. She subsequently developed bilateral eye redness with periorbital edema, dry, red, cracked lips, intermittent episodes of vomiting, diarrhea, and productive cough.

On admission, impression was complete Kawasaki Disease, pneumonia, COVID-19 suspect. On physical exam, the patient had fever, bilateral conjunctival injection, erythematous, cracked lips, a unilateral 2-cm cervical lymphadenopathy, perineal desquamation, and bipedal edema. Chest radiograph showed mild pulmonary underinflation. CBC showed a

hemoglobin of 81 g/L, WBC of 12.3 x 10^9/L, neutrophils of 76%, and a platelet count of 297 x 10^9/L. Blood culture was negative. Serum AST was 46 U/L, with normal ALT, and albumin was 27.5 g/L. Inflammatory markers showed a CRP of 226 mg/dL, ESR of 65 mm/hr, procalcitonin of 11.57 ug/L, and ferritin of 1064 ng/mL. 1 dose of IVIG at 2 g/kg and aspirin at 90 mg/kg/day for 24 hours were given and fever immediately resolved within the 1st hour of IVIG infusion. SARS-CoV-2 RT-PCR nasopharyngeal and oropharyngeal swab done on the 9th day was positive with Ct values for N Gene of 37.78 and ORF1ab of 0.00. A 2d-echocardiogram was requested but was not done during the admission since the swab result was still pending. She was discharged on low-dose aspirin and was advised to do strict isolation. The caregiver and the local epidemiologic surveillance unit was informed when the SARS-CoV-2 RT-PCR nasopharyngeal and oropharyngeal swabs turned out positive.

Case 3: An 11-year-old female presented with a 6-day history of fever and nonpruritic, maculopapular rashes over the extremities. She was initially admitted at another hospital on the 3rd day of fever and laboratories showed a WBC count of 15.1 x 10^9/L with segmenters of 84%, lymphocytes of 7%, CRP of 49.5 mg/dL, and a positive serology for dengue IgG and IgM. Her chest radiograph was normal. Due to hypotension and persistence of fever, the patient was transferred to our institution.

At the triage, the patient had the following vital signs: BP 70/40 mmHg, HR 130 beats/min, RR 30 breaths/min and temperature of 36.7°C. She had non-blanching, urticarial rashes over the extremities with bilateral subconjunctival hemorrhages. Fluid resuscitation and inotropes were started. Chest radiograph showed right pleural effusion with intercurrent pneumonia. She was given oxygen support and was eventually intubated due to respiratory failure. Inflammatory markers were as follows: procalcitonin 1.708 ng/mL, serum ferritin 472 ng/mL, LDH 282 mg/dL and CRP 259 mg/dL.

SARS-CoV-2 RT-PCR nasopharyngeal and oropharyngeal swabs on the 8th day of illness was positive with a Ct value of N Gene: 30.63 and ORF1ab: 32.18. IVIG at 2g/kg over 12 hours and dexamethasone at 0.15mg/kg once daily were given. Piperacillin-tazobactam was started for hospital-acquired pneumonia. Nutritional support with 20mg elemental zinc 2x daily and 2,000 IU/day of vitamin D3 were given.

Despite aggressive supportive and medical management, she remained hemodynamically unstable, with episodes of hypotension, and fever (37.8-39.5°C). Her sensorium quickly deteriorated on the 5th hospital day. On the 6th hospital day (12th day of illness), laboratories were as follows: prothrombin time 104sec, INR 8.71, D-dimer 10 ng/dL, CRP 45.5 mg/dL, LDH 37,562 mg/dL, procalcitonin 2.35 ng/mL, and serum ferritin 89,390 ng/mL. Blood cultures were negative. Hemoperfusion was considered, however, patient remained unstable. On the 16th day of illness, pulse methylprednisolone was given at 0.8mg/kg IV once daily, but the patient succumbed on the 17th day of illness.

Case 4: A 9-year-old female presented with a 4-day history of fever, diarrhea, tender left cervical lymphadenopathy, hematuria, anorexia and nonsuppurative bilateral conjunctivitis with dyspnea.

At the triage, she was febrile and in compensated shock. She was immediately intubated and started on inotropes. On physical examination, she had red, moist lips, with a 1-cm left tender cervical lymphadenopathy and a 2-cm occipital lymphadenopathy. She had clear and equal breath sounds but had marked intercostal and subcostal retractions. Abdomen was soft, flat with direct epigastric tenderness. Her chest radiograph showed pneumonia. SARS-CoV-2 RT-PCR nasopharyngeal and oropharyngeal swabs on 2 different occasions taken 3 days apart were both negative. Ceftriaxone was started for pneumonia and IVIG at 2g/kg as a 12 hour infusion was given. Pertinent laboratories were as follows: WBC 19.8 x 10^9/L, segmenters 93%, lymphocytes 6%, platelet count 131 x 10^9/L, CRP 139mg/dL, and ferritin 2,907ng/mL.

Despite medical and supportive management, the patient did not tolerate weaning from mechanical ventilation. From the COVID-19 ward, she was eventually transferred to the Pediatric Intensive Care Unit on the 8th hospital day (12th day of illness). MIS-C was highly considered and SARS-CoV-2 antibody determination using electro-chemiluminescence immunoassays (ECLIA) was done. The result was positive for SARS-CoV-2 immunoglobulin G antibody. Nutritional support with zinc sulfate at 20mg elemental zinc 2x daily and vitamin D3 at 2,000 IU/day were given. Other supportive management were adequate fluids, titration of inotropes

and rapid weaning from mechanical ventilation. She was successfully extubated on the 12th hospital day. A 2D-echocardiogram was done on the 13th hospital day (18th day of illness) showing minimal pericardial effusion. She was eventually discharged improved on the 15th hospital day (20th day of illness).

Case 5: An 8-year-old female presented with a 4-day history of fever with dizziness, vague, generalized abdominal pain, conjunctival injection, headache and myalgia. She was diagnosed to have tonsillitis on two occasions by a pediatrician and was given antibiotics without improvement. Two days prior to her admission, she developed erythematous patches over the hands, feet, knees and abdomen associated with diarrhea.

At the triage, vital signs were BP 60/40 mmHg, RR 65 breaths/min, HR 139 beats/min, temperature 39.7°C, with an O_2 saturation of 97%. She had conjunctivitis with perilimbal sparing. Non-tender, bilateral cervical lymph nodes were palpated which measured <1 cm in size. Crackles were appreciated on auscultation. There were erythematous patches on the abdomen, knees, palms and soles.

Laboratory results were as follows: CBC: WBC 27,000/µL, segmenters 95%, CRP 508 mg/dL, procalcitonin 95.2 µg/L, and serum ferritin 959.3 ng/mL. Liver function tests were normal but the BUN was at 16.3 mmol/L and creatinine was at 143 µmol/L. The chest radiograph showed reticulonodular densities scattered throughout both lungs, predominantly in the bilateral inner lung zones suggestive of pneumonia. Ceftriaxone 100 mg/kg/day and vancomycin 60 mg/kg/day were started. SARS-CoV-2 RT PCR was negative. MIS-C was highly considered and IVIG dose was given.

SARS-CoV-2 antibody testing using ECLIA was requested on the 5th hospital day (9th day of illness) with positive titers for both for IgG and IgM titers. A 2D-echocardiogram showed biventricular dysfunction with an ejection fraction of 18%, moderate mitral regurgitation, tricuspid regurgitation, mild aortic regurgitation, and pulmonic regurgitation. She was discharged on the 20th hospital day after completing treatment for healthcare-associated pneumonia.

DISCUSSION

The United Kingdom reported the first case series of a mysterious disease in eight children who exhibited mild symptoms with Kawasaki-like features at a tertiary center in South East England[2] last April, 2020. This condition was later called Pediatric Multisystem Inflammatory Syndrome (PMIS). Since then, reports in a number of cases with hyperinflammatory shock with phenotypic presentation of KD emerged in other parts of the world, including South Africa, Canada and the United States[1,3-5]. When it was reported in the United States, it was subsequently termed as Multisystemic Inflammatory Syndrome in Children (MIS-C). In several case reports, there have been overlapping features of KD and MIS-C but unlike KD which is predominantly seen in children of Asian descent, reports of MIS-C is scarce from Asian countries during the early parts of the pandemic[5,6]. Although many children met the criteria of either classic or incomplete KD, the epidemiology of both diseases is different. MIS-C occurs in older children with a median age of 8 to 11 years (range 1-20 years old)[7] and those belonging to the younger age group presented with worse clinical outcomes. Recently, rare cases of multisystem inflammatory syndrome associated with SARS-CoV-2 have been reported in adults (MIS-A)[8].

MIS-C can be seen in both children and adolescents. All our patients, aged 17 months to 12 years, were previously healthy with no comorbidities but presented with Kawasaki-like features including conjunctivitis, rashes and mucositis. All presented with signs of shock upon admission. They all met the WHO criteria for MIS-C with all five cases presenting with fever of more than 3 days duration. In a case series by Feldstein, et al., which included 186 patients, 78% had fever of more than 5 days, 12% had fever of 4 days while the remaining had fever of 3 days duration.[5] Four of our patients presented with gastrointestinal symptoms like diarrhea, vomiting, anorexia and abdominal pain. Compared to COVID-19, gastrointestinal signs and symptoms appear as a more prominent feature of MIS-C. [9,10]

Like Kawasaki disease, MIS-C can also present with cardiac dysfunction. Patients 1, 4 and 5 had 2D-echocardiogram findings of arteritis, pericardial effusion and valvular regurgitation, respectively. These findings associated with MIS-C are not uncommon. In a large case report by Godfred-Cato, et al., [11] involving 203 patients with clinical course consistent with MIS-C, approximately 30-40% of children had depressed left ventricular function and 8-19% had coronary artery abnormalities. Since MIS-C is an emerging disease with unknown long-

term sequelae, the occurrence of coronary involvement in association to MIS-C remains to be elucidated.

Some of the laboratory features of MIS-C strongly resemble those of hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS). Majority of our MIS-C cases have markedly elevated inflammatory markers on admission, such as C-reactive protein, procalcitonin, ferritin, and LDH. Among the five cases, the third case with refractory shock had an extremely high ferritin value (89,390 ng/mL from baseline of 472ng/mL), high LDH (37,562 mg/dL from baseline of 282mg/dL), lower platelet count (130 x 10^9/L), and lower serum albumin compared with the other cases. Viral infections are well-known triggers of HLH or MAS.[12,13] It is characterized by a robust immune response leading to cellular activation and "cytokine storm" but with inability to eliminate the antigenic stimuli.[14,15] Whether the third case ultimately developed HLH is difficult to establish as it is a rare, but potentially fatal disorder that can mimic MIS-C.

The interval between infection and development of MIS-C is unclear. Belot et al., reported that MIS-C was seen 4-5 weeks after the peak of COVID-19 cases in the country.[16] All our patients presented in the emergency department from June to September, which also occurred more than 4 weeks from the peak of COVID-19 cases in the Philippines. All 5 patients had a 4 to 9-day history of fever and one was critical and unstable on admission. Whether the patient (case 3) was a case of MIS-C or severe COVID-19 is hard to tell based on clinical presentation. We reviewed the Cycle threshold (Ct) values for N Gene and ORF1ab since prolonged Ct values (range 30.8-41.7) may be correlated with less cultivable virus.[17,18] Her results were 30.63 and 32.18, respectively.

MIS-C is a life-threatening post-infectious complication occurring unpredictably weeks after mild or asymptomatic SARS-CoV2 infection in otherwise healthy children[19] although the pathogenesis of the syndrome remains largely unclear. Patients with MIS-C can either have a positive RT-PCR or serology. Patients 1, 2 and 3 tested positive for SARS-CoV-2 on RT-PCR between the 8th to 12th day of illness. Although SARS-CoV-2 RT-PCR was negative, patients 4 and 5 tested positive for SARS-CoV-2 IgG using ECLIA taken on the 5th and on the 14th day of illness, respectively. These tests are crucial to augment clinical diagnosis and guide treatment.

The rationale for the use of IVIG and systemic steroids in SARS-CoV-2 infection is modulation of inflammation. Four of our patients had good response with resolution of fever after being given one dose of intravenous immunoglobulin (IVIG) given at 2g/kg. Patient 3 showed poor response to a single dose of IVIG, thus, additional doses at 1g/kg/day was given for the next 4 days. Dexamethasone was given for severe pneumonia at 0.15mg/kg/dose to patients 3, 4 and 5. Patient 3 received an additional dose of pulse methylprednisolone, after completion of a 10-day course of dexamethasone, because of worsening symptoms.

During the hospital admission of these MIS-C cases, the role of aspirin in MIS-C was not yet clearly defined. Patients 1 and 2 were treated with the standard therapy used for Kawasaki Disease, such as IVIG and aspirin at a dose of 80 mg/kg/day divided every 6 hours orally until patient was afebrile for at least 48 hours. Aspirin was subsequently shifted to anti-thrombotic doses at 3-5 mg/kg/day once daily. Aspirin has anti-inflammatory and anti-platelet properties which are believed to be the result of peripheral inhibition of COX-1 and COX-2. In one institutional protocol, aspirin 20 to 25 mg/kg/dose every 6 hours (80-100 mg/kg/day) is recommended in patients with MIS-C with Kawasaki disease-like illness, evidence of excessive inflammation (ferritin >700 ng/ml, CRP >30 g/dL, or multisystem organ failure), or cardiac involvement.[20] According to the American Academy of Pediatrics Multisystem Inflammatory Syndrome in Children Interim Guidance, all patients with MIS-C, unless with contraindications (e.g., platelets <100,000 or active bleeding), should be started on low-dose aspirin for thromboprophylaxis.[21]

Managing MIS-C requires a multidisciplinary team hence timing of subspecialty referral is crucial. Majority of the cases upon admission, were immediately referred to a pediatric intensivist on the first episode of shock. Since most patients presented with KD-like illness, all patients were referred to cardiology service for evaluation. Due to unavailability of the 2D-echocardiogram machine inside the COVID-19 ward, echocardiography was done when patients were no longer considered infectious. Either way, management for MIS-C was ultimately based on both clinical and diagnostic results, and management did not change whether or not a 2D-echocardiogram was done earlier.

Except for patient 3, all patients were discharged improved. Consent for publication was obtained prior to writing this case series.

CONCLUSION

We observed five cases of multisystem inflammatory syndrome in children (MIS-C) in previously healthy patients with SARS-CoV-2 infection. Children with this condition decompensate quickly and most will require intensive care unit admission. It is important to emphasize the need for families to seek immediate medical care since early diagnosis and timely intervention is imperative.

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ORIGINAL ARTICLE

A Rapid Review on the sensitivity of SARS-CoV-2 RT-PCR done on different clinical specimens

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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: RT-PCR using respiratory tract specimens, most commonly nasopharyngeal swab (NPS), has been used to confirm the diagnosis of COVID-19. NPS is a relatively invasive procedure that causes patient discomfort and risks viral transmission. Other specimens are therefore being investigated for the detection of SARS-CoV-2 RNA.
Objective: To determine the sensitivity of non-respiratory tract specimens in detecting SARS-CoV-2 RNA in patients with COVID-19.
Methodology: This review summarized the results of eight studies obtained from a literature search done in May 2020 in PubMed MEDLINE, Cochrane Library and MedRxiv. Two independent investigators reviewed and appraised the studies that were included, and pooled estimates of sensitivity for each specimen were determined using Stata's Metaprop function.
Results: The sensitivity in detecting SARS-CoV-2 RNA in non-respiratory tract specimens of diagnosed COVID-19 patients are as follows: Saliva 77% (95% CI 71-83%), stool/rectal swab/anal swab 22% (95% CI 22-37%), blood/serum/plasma 2% (95% CI 1-3%), and urine 22% (95% CI 18-25%).
Conclusion: SARS-CoV-2 RNA is detected in saliva, stool/rectal swab/anal swab, blood/serum/plasma and urine. Among these, saliva has the highest estimated sensitivity. However, more studies are needed to correct the heterogeneity brought about by factors such as timing of specimen collection, disease severity and treatment.

KEYWORDS: *COVID-19, nasopharyngeal, oropharyngeal, swabs and respiratory sample*

INTRODUCTION

SARS-CoV-2 was first identified in Wuhan, Hubei Province China in December 2019 and since then has spread throughout the world. It is a coronavirus (CoV) that has an enveloped positive-sense single-stranded RNA virus. Circulating coronaviruses in humans include two α-CoVs and two β-CoVs that cause the common cold. The SARS-CoV-2 is a human β-CoV. Other highly pathogenic human β-CoV that emerged in the past two decades include SARS-CoV-1 and MERS-CoV. Bats are considered the natural hosts for progenitors of highly pathogenic CoVs and transmission to humans involved intermediate animal hosts. Human-to-human transmission is via direct or indirect contact and primarily through inhalation of infectious respiratory droplets.

The viral particles enter the human body through the respiratory system. The glycoprotein spikes present on the outer surface of the virus are mostly responsible for attachment and entry to the host cell's respiratory epithelium to cause infection. Viral replication begins in the upper respiratory tract and peaks at day 5 of infection. This process is mediated by cleavage of the S1 and S2 regions of the viral protein and a myriad of symptoms such as high fever, sore throat, myalgia and fatigue may set in. In the lower respiratory tract, ACE II receptors bind to viral capsid antigens which facilitate viral entry into the epithelial cells lining the alveoli. Viral particles in lower respiratory secretions are expelled by coughing, sneezing or talking.[1] The presence of viral particles in respiratory secretions is the basis for using respiratory tract specimens for diagnosis through RT-PCR or viral load detection.

According to WHO guidelines published on March 19, 2020, in the laboratory testing for COVID-19 in suspected human cases, the decision to test an individual should be based on clinical and epidemiological factors and linked to an assessment of the likelihood of infection. Specimens should be collected from the upper respiratory tract: nasopharyngeal (NPS) and oropharyngeal swab (OPS) or wash in ambulatory patients and/or lower respiratory tract: sputum and/or endotracheal aspirate (ETA) or bronchoalveolar lavage (BAL) in patients with more severe respiratory disease, and sent for real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) to confirm the diagnosis of COVID-19.[2] A meta-analysis by Mohammadi et al. demonstrated the pooled sensitivity of OPS, NPS and sputum which are 43% (95% CI 34-52%), 54% (95% CI 14-67%), and 71% (95% CI 61-80%), respectively.[3] However, only 27% of patients diagnosed with COVID-19 have sputum production.[4] NPS and OPS swabs cause discomfort and may cause bleeding especially in patients with thrombocytopenia.[5]

This review summarizes the available evidence on the sensitivity of SARS-CoV-2 RT-PCR done on non-respiratory tract specimens of patients with COVID-19.

METHODOLOGY

Articles were selected based on the following inclusion criteria:

- **Population:** Suspect individuals based on history of exposure, and presence of signs and symptoms
- **Intervention:** Application of RT-PCR testing to detect SARS-CoV-2 nucleic acid in non-respiratory tract specimens
- **Outcomes:** Determination of diagnostic sensitivity of SARS-CoV-2 RT-PCR in non-respiratory tract specimen using a positive SARS-CoV-2 RT-PCR in any of the following respiratory specimens: NPS, OPS or wash, sputum, BALF or ETA, as reference standard.
- **Study designs:** observational (prospective and retrospective) cohort and case-control studies

Literature search was done in PubMed MEDLINE, Cochrane Library and MedRxiv. Study titles that did not satisfy the inclusion criteria were excluded. Review of abstracts was done on the remaining studies. Studies that were likely to be relevant based on review of the abstracts underwent full review and appraisal by two independent reviewers.

We excluded studies that did not specify the following: what samples were taken, whether or not study participants were symptomatic, and those that did not clearly state the results.

Pooled estimates of sensitivity at 95% confidence interval (CI) for each specimen were obtained when possible using the Metaprop function of STATA®. In cases where there were no studies identified that included a prospective cohort of suspected patients with COVID-19, we just reviewed studies that included confirmed cases that reported the sensitivity of the different specimens.

RESULTS

Characteristics of Included Studies

The search keywords COVID-19, nasopharyngeal, oropharyngeal, swabs, and respiratory sample were used. A total of 130 search results were obtained from PubMed MEDLINE, Cochrane Library and MedRxiv last May 21, 2020. After title review, review of abstract was done on 35 articles. Subsequently, 20 articles remained for full paper review.

Majority of these studies investigated individuals with laboratory-confirmed COVID-19. With the presence of limited data, we pursued to analyze the diagnostic accuracy of SARS-CoV-2 RT-PCR on non-respiratory tract specimens in comparison to SARS-CoV-2 RT-PCR of a respiratory tract specimen in patients with laboratory-confirmed disease.

A total of 12 studies were excluded from the 20 studies reviewed. Three of the studies were excluded because they did not specify whether a respiratory tract specimen was used to confirm COVID-19 infection. Seven other studies were excluded because the presence or absence of symptoms were not clearly described. Two studies were excluded because the results were not clearly stated.

The studies included were five prospective and three retrospective observational studies. Five were done in China, and one study each in the United States, Japan, and Italy, between the months of January to March 2020.

The studies we found investigated individuals with laboratory-confirmed COVID-19 through a positive SARS-CoV-2 RT-PCR of a respiratory tract specimen (NPA, NPS, TS, and/or sputum). In these studies, the following specimen types were sent for SARS-CoV-2 RT-PCR: saliva, blood/serum/plasma, urine, and stool/rectal swab/anal swab. The diagnostic sensitivity for each specimen type was determined. Majority of these studies reported these sensitivities as positive rates.

The characteristics of the studies included is summarized in Appendix 1.

Outcomes

The pooled estimate of sensitivity of the different non-respiratory tract specimens are as follows:

1. saliva at 77% (95%CI 71-83%, n=4),
2. stool/rectal swab/anal swab at 22% (95%CI 22-37%, n=5),
3. blood/serum/plasma at 2% (95%CI 1-3%, n=4), and
4. urine at 22% (95%CI 18-25%, n=5).

There was significant heterogeneity in all the comparisons for the different specimen sites. See tables 1 and 2 in the Appendix for the summary of results.

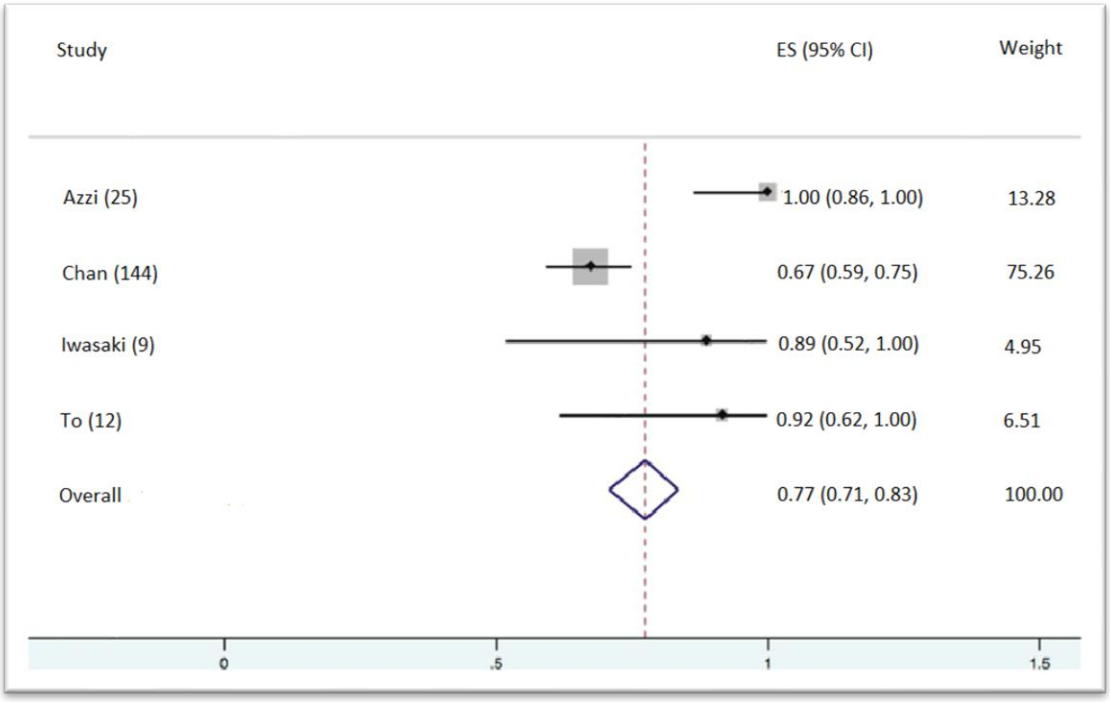

Figure 1: Pooled estimate of the sensitivity of saliva from four studies

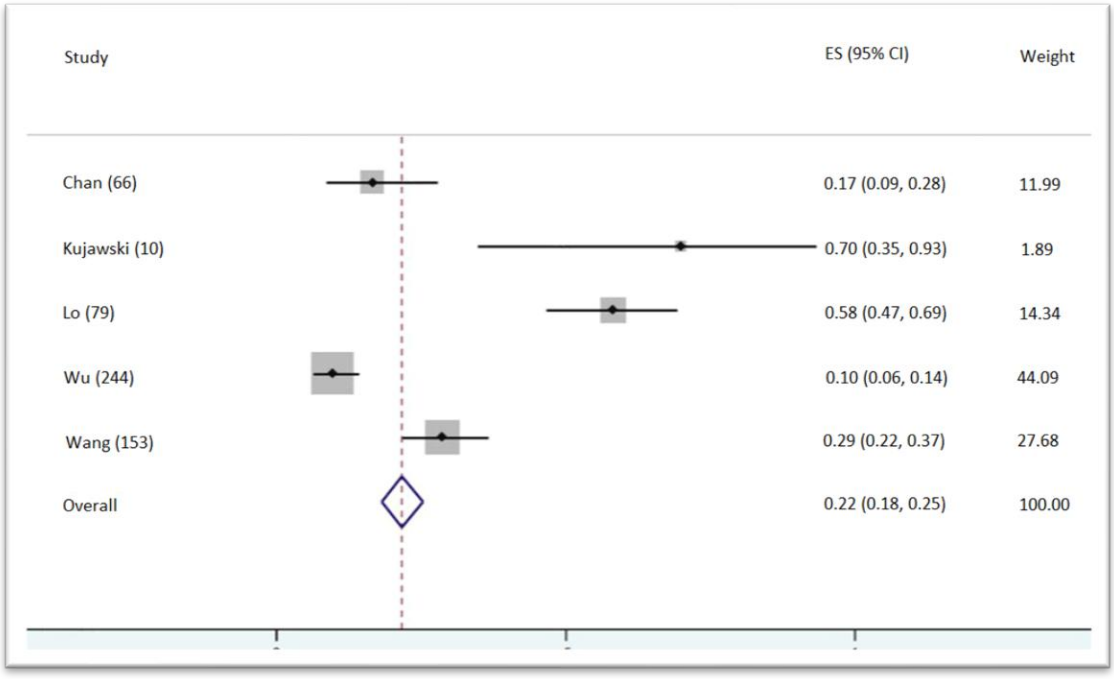

Figure 2: Pooled estimate of the sensitivity of stool/rectal swab/anal swab from five studies

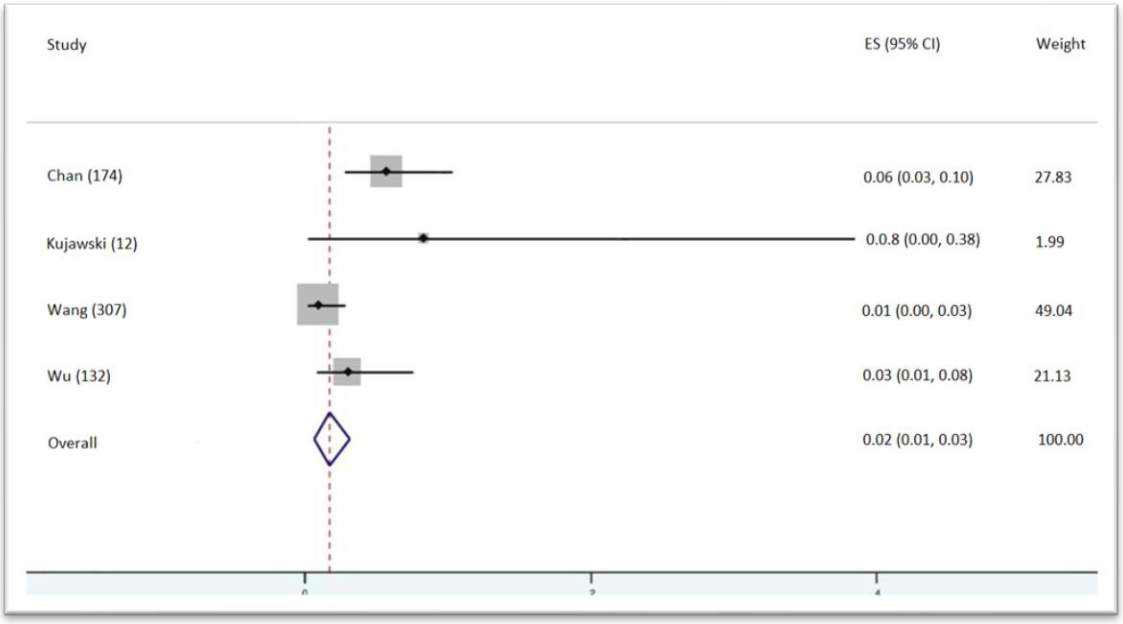

Figure 3: Pooled estimate of the sensitivity of blood/serum/plasma from four studies

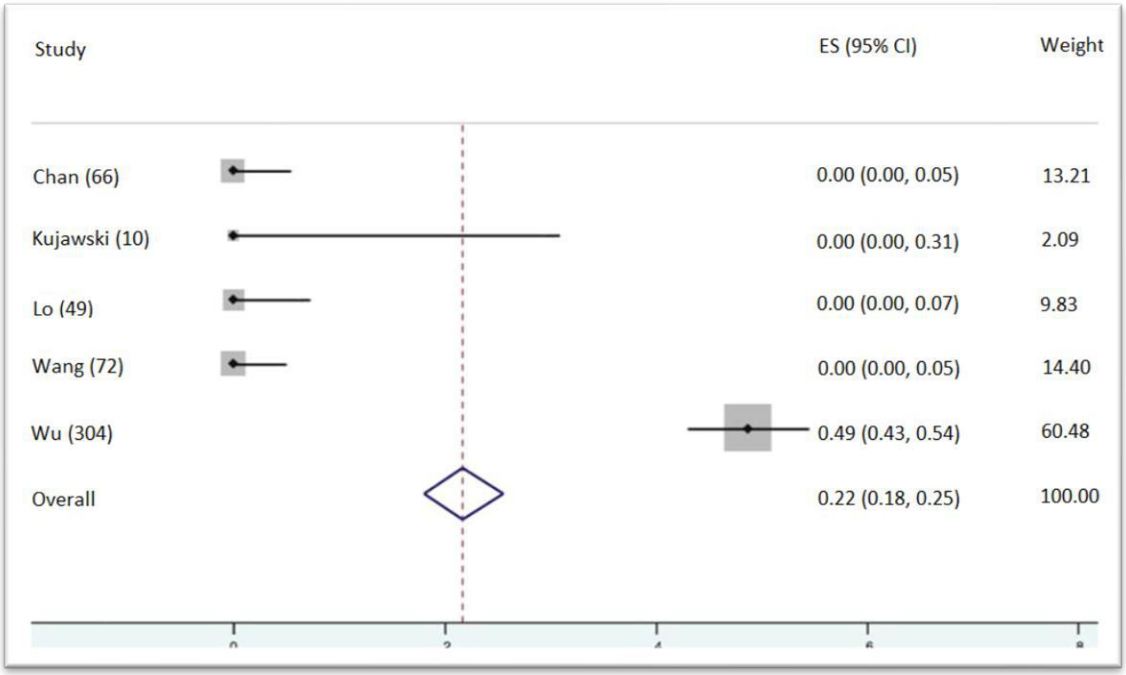

Figure 4: Pooled estimate of the sensitivity of urine specimen from five studies

Table 1: Summary of results of individual studies

Author	Saliva	Stool/Rectal swab/Anal swab	Blood/Serum/Plasma	Urine
Azzi	25/25			
Chan	97/144	11/66	10/174	0/66
Iwasaki	8/9			
Kujawski		7/10	1/12	0/10
Lo		46/79		0/49
To	11/12			
Wang		44/153	3/307	0/72
Wu		24/244	4/132	148/304

Critical Appraisal

Ideally, to examine the predictive value of RT-PCR on non-respiratory tract specimen to detect SARS-CoV-2 nucleic acid, the test should be performed on suspected cases. However, due to the urgency with which this test would need to be validated, majority of the studies used confirmed cases with a positive SARS-CoV-2 RT-PCR of a respiratory tract specimen – which at the onset of the pandemic, was considered to have the highest diagnostic yield, and pre-COVID samples which are the kind of samples utilized in phase IIC validation studies of diagnostic tests..

Although there was independent definition of the index and reference tests, blinding of independent comparison with the reference standard for study participants was not feasible since they were already patients with laboratory-confirmed disease. Specificity and likelihood ratios, therefore, could not be calculated. Some studies reported on the correlation of disease severity and timing of specimen collection with the diagnostic yield. However, this was not done with majority of the studies. Over-all, these studies are deemed to have a high risk for bias.

The methodologies of these studies are easily reproducible. All studies employed standardized methods of specimen storage, nucleic acid extraction and RT-PCR assays.

DISCUSSION

Pooled Sensitivity

Testing for COVID-19 currently makes use of NPS swab to detect for the presence of SARS-CoV-2 nucleic acid. This is based on previous experience with the MERS-CoV and SARS-CoV epidemics. However, this method of specimen collection has been a subject of discussion since it is uncomfortable to the patient and puts the health care worker collecting the specimen at an increased risk of exposure.

The pooled sensitivity of non-respiratory tract specimens of confirmed COVID-19 patients were as follows: Saliva 77%, stool/rectal swab/anal swab 22%, blood/serum/plasma 2% and urine 22%. However, there is significant heterogeneity in between studies which are expected in studies on diagnostic accuracy.

Saliva specimen

One of the most investigated specimens is saliva since patients can easily collect samples by themselves. Studies have shown that SARS-CoV-2 RT-PCR of saliva has been evaluated to have sensitivity comparable or higher than NPS.[5,6] Based on our review, we were able to get a pooled sensitivity of saliva at 77% (95% CI 71-83%) from four studies. The timing of specimen collection and severity of disease were heterogenous in these studies. Azzi et al. studied patients with severe disease. Majority of patients in the study of Chan et al. had stable medical condition. Iwasaki et al. included patients with mild to moderate disease treated with favipiravir, and while the disease status of the population studied by To et al. was not described, all patients were hospitalized.

Three of the four studies reported that saliva has a sensitivity of more than 90%, while only Chan showed a lower sensitivity of 67%. This can be attributed to Chan's methodology where they used two different RT-PCR assays – COVID-19-RdRp/Hel and RdRp-P2 probes – and where the study's results showed that there is significant difference between the two assays favoring COVID-19-RdRp/Hel assay ($p<0.001$). If Chan's study was excluded in the pooled estimation of sensitivity, we would yield an estimated sensitivity of 98% (95% CI 90-100%). More studies would be needed in order to correct

the heterogeneity brought about by this difference in methodology.

Stool/rectal swab/anal swab specimen

The pooled sensitivity of detecting SARS-CoV-2 from stool/rectal swab/anal swab specimens from five studies was determined to be 22% (95% CI 22-37%). In the study by Kujawski et al., only three out of 12 patients reported to have diarrhea, and two patients with vomiting. Lo et al. reported that 80% of patients had diarrhea and 50% with nausea. Like saliva, the timing of specimen collection, severity of illness and treatment given were factors that may be causes of heterogeneity. In the study by Wang et al., live SARS-CoV-2 virus was observed in the stool sample of two patients who did not have diarrhea. Transmission via exposure to fecal material is yet to be established. The utilization of stool SARS-CoV-2 RT-PCR as aide in the decision for hospital discharge or discontinuation of self-quarantine has not yet been evaluated.

Blood/serum/plasma specimen

SARS-CoV-2 nucleic acid had also been detected in blood/serum/plasma specimen. However, this has not been correlated with viremia, severity of illness, and treatment given. From four studies, the pooled estimate of sensitivity is 2% (95% CI 1-3%) which was the lowest among the non-respiratory specimens. The samples taken were from stored blood of patients which may have affected the yield of the tests.

Urine specimen

Urine specimen had a pooled sensitivity of 22% (95% CI 18-25%) from five studies. However, it is only in the study by Wu et al. that SARS-CoV-2 nucleic acid was actually detected in urine specimens. In this study, 61% of the patients had non-severe (common type) disease, 33% had severe disease and 6% had critical illness. The detection of viral nucleic acid in urine was not correlated with the timing of specimen collection or the patients' disease course. There was also no explanation provided for the paradoxical results.

Correlation of timing of specimen collection and diagnostic yield

Azzi et al. reported that there was no significant difference of the Ct values of the initial saliva specimens sent for SARS-CoV-2 RT-PCR with regards to the period elapsed after the onset of symptoms. Iwasaki et al. reported a median day of sampling of 10 days (range 7-19 days) after onset of symptoms. In this study, when the viral load was correlated with the duration from onset of symptoms to timing of sampling, the viral load was seen to be equivalent between the NPS and saliva samples at earlier time points but declined in saliva at later time points. To et. al. reported that saliva specimens were collected at a median of two days after hospitalization (range 0-7 days). In their cohort of patients, six had viral load analysis of serial saliva specimens. It was seen that the viral load was highest in the earliest available schedule for five patients, and for one patient, viral load was slightly higher on day one after hospitalization than on the specimen taken on the day of admission.

In the study by Kujawski et al., serial testing to determine the duration of viral shedding was done and showed that SARS-CoV-2 nucleic acid was detected at a maximum of 26 days for NPS and OPS, 29 days in sputum, and 25 days in stool. It was reported that the duration of nucleic acid detection from the onset of symptoms did not differ by hospitalization status or supplemental oxygen requirement. All 12 patients in this study reported symptom resolution. The median duration of symptoms was 14 days (range 6-20 days). SARS-CoV-2 RNA was detected after reported symptom resolution in 11 patients who had cough as the last symptom, including six from NPS, two from OPS, one from sputum, and three from stool specimens. Lo et al. also did serial specimen collection in 10 patients to determine duration of viral shedding. Viral RNA was detected in the NPS and stool samples of these patients and the viral RNA conversion time in both NPS and stool were 18.2 days (SD 4.6) and 19.3 days (SD 3.4), respectively. No viral RNA was detected in the serial urine specimens of these patients. In the study by Wu et al, stool and anal swab were analyzed separately. Anal swab revealed a sensitivity of 10%.

Limitations of the study

The timing of specimen collection, severity of disease and treatment given to the study population were vastly heterogenous in these studies and would certainly affect the estimated sensitivity results. Some studies have reported the sensitivity of samples taken from a single person at different points in time from the onset of symptoms to monitor viral shedding in these sites, contributing also to the heterogeneity of the results.

Recommendation from Other Guidelines

The recommendation from the Centers for Disease Control and Prevention as of July 8, 2020 for collection and testing of specimens for SARS-CoV-2 include the following: (1) Nasopharyngeal specimen collected by a health care provider, (2) Oropharyngeal specimen collected by a health care provider, (3) Nasal mid-turbinate swab collected by a healthcare provider or a supervised onsite self-collection (using a flocked tapered swab) (4) Anterior nares (nasal swab) specimen collected by a healthcare provider or by onsite or home self-collection (using a flocked or spun polyester swab) (5) Nasopharyngeal wash/aspirate or nasal wash/ aspirate specimen collected by a health care provider.

CONCLUSION

The pooled sensitivity of detecting SARS-CoV-2 nucleic acid in non-respiratory tract specimens of patients was highest for saliva at 77% (95%CI 71-83%). However, the pooled sensitivity was unacceptably low for stool/rectal swab/anal swab 22% (95% CI 22-37%), blood/serum/plasma 2% (95% CI 1-3%), and urine 22% (95% CI 18-25%).

DECLARATION OF CONFLICT OF INTEREST

No conflict of interest.

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Appendix 1: Characteristics of included studies

First Author Article Title Month-Year Country	Study Design	Sample Population	Intervention	Outcome Measured	Population Characteristics	Study Results
Azzi, Lorenzo Saliva is a reliable tool to detect SARS-CoV-2 Apr-20 Italy	Prospective observational study	25 SARS-CoV-2 infected patients who underwent hospital admission after the diagnosis of COVID-19 provided by rRT-PCR on NPS	Saliva collected through the drooling or pipetting technique, analyzed by rRT-PCR.	Prevalence of positivity in saliva and association between clinical data and the cycle threshold as a semiquantitative indicator of viral load were considered	Male: female ratio 2.1:1; age range of 39-85 years (mean 61.5 years +/- 11.2 years); all were admitted in the ICU; included severe and very severe disease	Positive rate for saliva 25/25 (100%), Ct values (range 18.12–32.23, mean value 27.16 + / − 3.07); no differences in the Ct values with regards to the period elapsed after the onset of symptoms; inverse correlation between the LDH values recorded and the Ct values (p=0.04); no significant correlation between usRCT and the Ct values (p=0.07); Ct values were not influenced by the patient's age (p=0.34), sex (p=0.31) or comorbidities; Eight patients underwent a second salivary swab after 4 days and results were consistent with the initial analysis.
Chan, Jasper Fuk-Woo Improved Molecular Diagnosis of COVID-19 by the Novel, Highly Sensitive and Specific COVID-19-RdRp/Hel Real-Time Reverse Transcription-PCR Assay Validated In Vitro and with Clinical Specimens May-20 China	Prospective observational cohort study	15 patients with laboratory-confirmed COVID-19 in Hong Kong whose NPA/NPS/TS, and/or sputum specimens tested positive for SARS-CoV-2 RNA by the RdRp2 assay	120 respiratory tract (NPA/NPS, TS, saliva, and sputum) and 153 non-respiratory tract specimens (plasma, urine, feces/rectal swabs) were collected and sent for COVID-19-RdRp/Hel and RdRp-P2 assays	Comparison between the COVID-19-RdRp/Hel and RdRp-P2 real-time RT-PCR assays for the detection of SARS-CoV-2 RNA in different types of clinical specimens	Male:female ratio of 1:1.4; age range of 37-75 years (median 63 years); all had clinical features of acute community-acquired atypical pneumonia and radiological evidence of ground-glass lung opacities; 11 were in stable condition, 3 in critical condition, 1 expired	Among 273 specimens collected from these 15 patients, 77 (77/273, 28.2%) were positive by the RdRp-P2 assay; COVID-19-RdRp/Hel assay were positive for all these 77 patients, in addition to 42 other specimens including 29/120 (24.2%) respiratory tract specimens, and 13/153 (8.5%) non-respiratory tract specimens that were negative in the RdRp-P2 assay (119/273, 43.6%) (p < 0.001)
Iwasaki, Sumio Comparison of SARS-CoV-2 detection in nasopharyngeal swab and saliva	Prospective observational cohort study	9 COVID-19 patients diagnosed by a positive NPS SARS-CoV-2 RT-PCR	Paired nasopharyngeal swab and saliva samples were taken and sent for RT-qPCR	Comparison of the efficacy of PCR detection of SARS-CoV-2 between paired NPS and saliva samples	Median age 70.5years (range 30-97 years); most had mild to moderate disease; all patients received favipiravir	Specimens were sampled within 10 days (range, 7-19 days) after symptom onset. SARS-CoV-2 was detected in all 9 patients in nasopharyngeal samples and in 8/9 (89%) patients in

May-20 Japan			when symptoms were relieved to determine the timing of discharge			saliva samples. The mean ± SD of the CT values were 24.2 ± 4.4 and 30.4 ± 4.9 in nasopharyngeal and saliva samples, respectively, and significantly higher in saliva samples (P=0.018). The CT values were equivalent between the two samples at earlier time points but higher in saliva at later time points; All 11 samples taken within 2 weeks from the onset of symptoms were positive in both NPS and saliva. After 2 weeks, some samples tested negative.
Kujawski, Stephanie A First 12 patients with coronavirus disease 2019 (COVID-19) in the United States Mar-20 USA	Prospective observational study	12 patients diagnosed with COVID-19 who were confirmed by CDC during Jan 20- Feb 5,2020 by a positive SARS-CoV-2 rRT-PCR in >/= 1 respiratory tract specimen (NP, OP or sputum)	Respiratory, stool, serum, and urine specimens were submitted for SARS-CoV-2 rRT-PCR testing every 2-3 days for the first 17 days of illness for SARS-CoV-2 virologic testing	Report the epidemiology, clinical course, clinical management and virologic characteristics of the first 12 patients with COVID-19 diagnosed in the US	5 patients received only out-patient care and were isolated at home, 7 were hospitalized; male: female ratio of 1.5:1; median age 53 years (range 21-68 years); 4/5 patients with >/= 1 underlying medical conditions were hospitalized; 10 patients travelled to mainland China 2 weeks before onset of illness, 2 other patients reported exposure with a previously infected patient with COVID-19; Over the course of illness, patients reported cough (n=12), subjective or measured fever (n=9), diarrhea (n=3), and vomiting (n=2). Three patients who did not report fever were never hospitalized and remained on home isolation.	398 specimens were collected and tested from the 12 patients throughout the course of illness. All 12 patients had SARS-CoV-2 RNA detected in at least one NP swab, 11/12 in an OP swab, 6/6 in sputum, 1/12 in serum, 7/10 in stool, and 0/10 in urine (Figure 3). Among 98 pairs of simultaneous NP and OP specimens, 58 (59%) had concordant results. Among 27 discordant pairs with one positive specimen, the NP specimen was positive in 70%; the remaining 13 discordant pairs had one negative and one inconclusive specimen. Two patients provided sputum specimens when NP and/or OP specimens tested negative, and sputum continued to be positive in both patients. In Patient 7, viral RNA was detected in sputum 17 days after the last positive OP specimen and ≥2 weeks after reported symptom resolution. In seven patients who had SARS-CoV-2 RNA detected in stool, most detections occurred when viral RNA was still detectable in the respiratory tract. Among three patients who reported diarrhea, all had viral RNA detected in stool. Mean Ct

						values in positive specimens were 17.0–39.0 for NP, 22.1–39.7 for OP, and 24.1–39.4 for stool. Ct values were lower in the first week of illness than the second in most patients; in some patients, low Ct values continued into the 2nd and 3rd week of illness. There was no apparent relationship between Ct values in the upper respiratory tract and disease progression. SARS-CoV-2 rRT-PCR results turned positive in serum of Patient 9 in the second week of illness at the time of rapid clinical deterioration; Serial testing to determine duration of RNA detection and viral shedding. SARS-CoV-2 RNA has been detected at a maximum of day 26 in NP specimens, day 26 in OP, day 29 in sputum, and day 25 in stool. The duration of viral RNA detection did not differ by hospitalization status or supplemental oxygen requirement.
Lo, Iek Long Evaluation of SARS-CoV-2 RNA shedding in clinical specimens and clinical characteristics of 10 patients with COVID-19 in Macau Feb-20 China	Retrospective observational study	Ten COVID-19 patients enrolled in the Centro Hospitalar Conde de São Januário (CHCSJ) between Jan 21-Feb 16, 20, who were diagnosed through detected RNA signals in NPS and sputum specimen	Serial qRT-PCR for SARS-CoV-2 were performed for different specimens, including NPS, urine, and stool	Evaluation of SARS-CoV-2 RNA shedding in clinical specimens and clinical characteristics	Male: female ratio 1: 2.3; median age 54 years (range 27-64 years); 5 patients had comorbid medical conditions; 2 had mild disease, 4 had moderate and another 4 had severe disease; all patients received treatment with lopinavir and ritonavir	There were positive SARS-CoV-2 RNA signals in all patients' NPS (100%) and stool specimens (100%) but negative in all urine specimens (0%). The average viral RNA conversion time in both NPS and feces were 18.2 days (SD:4.6) and 19.3 days (SD:3.4), respectively.
To, Kelvin Kai-Wang Consistent Detection of 2019 Novel Coronavirus in Saliva	Prospective observational study	12 patients with laboratory-confirmed 2019-nCoV infection by a positive NPS or sputum SARS-	Saliva were collected for SARS-CoV-2 RT-PCR	Detection of SARS-CoV-2 nucleic acid in saliva	Male: female ratio of 1.4:1 ; median age of 62.5 years (range 37-75 years); all were hospitalized	Saliva specimens were collected at a median of 2 days after hospitalization (range 0-7 days); SARS-CoV-2 nucleic acid was detected in the initial saliva specimens of 11 patients (91.7%)

Feb-20 China		CoV-2 RT-PCR, in Hong Kong				
Wang, Wenling Detection of SARS-CoV-2 in Different Types of Clinical Specimens Mar-20 China	Retrospective observational study	205 patients with COVID-19 diagnosed based on symptoms and radiology and confirmed by SARS-CoV-2 detection in NPS	Pharyngeal swabs were collected from most patients 1 -3 days after hospital admission. Blood, sputum, feces, urine, and nasal samples were collected throughout the illness. Bronchoalveolar lavage fluid and fibrobronchoscope brush biopsy were sampled from patients with severe illness or undergoing mechanical ventilation. Specimens were sent for SARS-CoV-2 RT-PCR	Detection of SARS-CoV-2 in different types of clinical specimens	68% were male; mean age 44 years (range 5-67 years); 19% had severe illness	Bronchoalveolar lavage fluid specimens showed the highest positive rates (14 of 15;93%), followed by sputum (72 of 104; 72%), nasal swabs (5 of 8; 63%), fibrobronchoscope brush biopsy (6 of 13; 46%), pharyngeal swabs (126 of 398; 32%), feces (44 of 153; 29%), and blood (3 of 307; 1%). None of the 72 urine specimens tested positive
Wu, Jianguo Detection and analysis of nucleic acid in various biological samples of COVID-19 patients Apr-20 China	Retrospective observational cohort study	132 patients diagnosed with COVID-19 in East Section of Renmin Hospital of Wuhan University from Jan 31-Feb 29, 20, in accordance with relevant epidemiological and clinical manifestations and a positive SARS-CoV-2 RT-PCR	Nasopharyngeal swabs, sputum, blood, feces and anal swabs were sent for 2019-nCoV nucleic acid detection	Detection and analysis of nucleic acid in various biological samples of COVID-19 patients	Male: female ratio of 1.2:1; mean age of 66.7 years +/- 9.1 years; 33% had severe disease, 6% had were critical cases	Positive rate of 2019-nCoV nucleic acid test of oropharyngeal swab is 38.13% (180/472 times), the positive rate of 2019-nCoV nucleic acid test of sputum is 48.68% (148/304 times), the positive rate of blood 2019-nCoV nucleic acid test is 3.03% (4/132 times), and the positive rate of 2019-nCoV nucleic acid test of feces is 0.83% (24/244 times) The positive rate of 2019-nCoV nucleic acid detection in anal swabs is 10.00%（12/120 times) Positive rates of 2019-nCoV nucleic acid test were determined from all specimen types

Appendix 2:

Table 1: Summary of results of individual studies

Author	Saliva	Stool/Rectal swab/Anal swab	Blood/Serum/Plasma	Urine
Azzi	25/25			
Chan	97/144	11/66	10/174	0/66
Iwasaki	8/9			
Kujawski		7/10	1/12	0/10
Lo		46/79		0/49
To	11/12			
Wang		44/153	3/307	0/72
Wu		24/244	4/132	148/304

Table 2: Summary of pooled sensitivity

Specimen	Sensitivity	95% CI	Number of studies	Number of participants
Saliva	77%	71-83%	4	190
Stool/Rectal swab/Anal swab	22%	22-37%	5	552
Blood/Serum/Plasma	2%	1-3%	4	625
Urine	22%	18-25%	5	501

Appendix 3:

Literature search

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	Search (("Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2)) AND nasopharyngeal AND oropharyngeal AND swabs AND respiratory sample	May 21,2020 21:00:00	24 (23 observational studies, 1 meta-analysis)	6
Cochrane Library	COVID-19 AND nasopharyngeal AND oropharyngeal AND swabs AND respiratory sample	May 22, 2020 14:00:00	1	0
MedRixv	COVID-19 AND nasopharyngeal AND oropharyngeal AND swabs AND respiratory sample	May 21, 2020 22:00:00	105 including 2 meta-analysis	2

ORIGINAL ARTICLE

Outcomes of Infants Born to Mothers with SARS-CoV-2 Infection in a Tertiary Hospital

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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

Introduction: Pregnant women are a susceptible population to emerging infections. Recent published data have shown evidence of possible transplacental transmission of SARS-CoV-2. However, at present there are not enough data to determine its effect on the fetus. This study aims to determine the outcomes of infants born to mothers with SARS-CoV-2 infection.

Methods: A retrospective descriptive institution-based study using data collected from medical records of infants born to confirmed COVID-19 mothers delivered from April to June 2020.

Results: Of the 47 neonates, none of them were positive for SARS-CoV-2 RT-PCR. Majority were born full-term, mean gestational age of 37 weeks, weight of 2867 grams, appropriate for gestational age, good APGAR score, and delivered through cesarean section. Symptomatic neonates (27.7%) had tachypnea and vomiting as the most common manifestation, 13.3% had lymphopenia while pneumonia was the predominant radiologic finding. There was a significant association between the presence or absence of symptoms among mothers and neonates (p=0.037).

Conclusion: The neonatal outcome in this study was good with 98% survival at 2 weeks of life. There was note of 2.1% morbidity and mortality. Given that the clinical data in newborns are very limited and the possibility of a vertical transmission is still uncertain, it is crucial to closely monitor neonates with increased risk of COVID-19 infection.

KEYWORDS: *COVID-19, Neonates, Vertical transmission*

INTRODUCTION

Emerging infections have been shown to have an important impact on pregnant women and their fetuses, with increased risk of complications.[1] Human coronaviruses (CoV) are among the most common pathogens that cause respiratory infection. Among these are the Severe Acute Respiratory Syndrome (SARS) caused by SARS-CoV and Middle East Respiratory Syndrome (MERS) caused by MERS-CoV that appeared in 2003 and 2012, respectively. There are sparse data on the effects of SARS and MERS on pregnancy. For SARS, among 7 first-trimester infections, 4 ended in spontaneous abortion. Four of 5 women with SARS after 24 weeks' gestation delivered preterm. For MERS, there were 13 case reports in pregnant women, 2 pregnancies ended in fetal demise and 2 were born preterm. There was no evidence of in utero transmission seen in both coronaviruses.[1]

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was first recognized in Wuhan, China in December 2019.[2,3] While most people with COVID-19 develop mild or uncomplicated illness, approximately 14% develop severe disease requiring hospitalization and oxygen support and 5% require admission to an intensive care unit.[3,4] Pregnant women are a susceptible population of SARS-CoV-2 and are more likely to have complications and even progress to severe illness.[5] In the accumulating data, it is already clear that COVID-19 is less severe in pregnancy than the 2 previous coronavirus infections.[5]
SARS-CoV-2 is mainly transmitted through respiratory droplets, but other transmission routes have been hypothesized.[6] Recent published data have shown evidence of possible transplacental transmission of SARS-CoV-2 from mother to infant,[6,7,8,9] despite prior claims that vertical transmission does not occur. In Paris and Italy, SARS-CoV-2 RNA was found on the fetal side of the placenta in a few mothers who received a diagnosis of COVID-19, with the neonates also testing positive for COVID-19 on nasopharyngeal[6,9] and rectal swab RT-PCR,[6] suggesting that vertical transmission is possible.

At present, there aren't enough data to determine the effect of COVID-19 infection on the fetus. Whether COVID-19 has mother-to-child vertical transmission, and its short and long-term harm to the offspring is still unclear.[2] In the Philippines, outcomes of newborns born to COVID-19 positive mothers have not yet been evaluated. Thus, this study aims to determine the clinicodemographic profile, laboratory, radiologic findings and treatment of infants born to mothers with confirmed COVID-19 and to associate maternal features with neonatal outcomes.

METHODOLOGY

Study Design

A retrospective, descriptive institution-based study design was used to describe the outcome of all neonates born to confirmed COVID-19 mothers at the Philippine General Hospital (PGH).

Study Population and Setting

All neonates born to confirmed COVID-19 mothers from April 1, 2020 to June 31, 2020 delivered at the Philippine General Hospital were included in this study. Mothers with inconclusive RT-PCR results had swab tests repeated and if positive, infants were included in this study. Those with negative results on repeat swab test were considered non-COVID thus infants were not included in this study.

Definition of terms[10,11]

1. Close contact – person who has experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms:
   a. Face-to-face contact with a probable or confirmed case within 1 meter and for at least 15 minutes;
   b. Direct physical contact with a probable or confirmed case;
   c. Direct care for a patient with probable or confirmed COVID-19 disease without using recommended personal protective equipment; OR
   d. Other situations as indicated by local risk assessments
2. Cluster – is an unusual aggregation, real or perceived, of health events that are grouped together as to time and space and that is reported to a public health department.
3. Exposure – if the child has been in close contact with sick individuals or suspect, probable or positive COVID-19 patients, whether from home or during travel to areas with localized

transmission or local communities under quarantine.

4. COVID-19 Confirmed – any individual, with or without symptoms, who has laboratory-confirmed COVID-19 reverse transcription polymerase chain reaction (RT-PCR) test result from an accredited laboratory.
5. Survived – patient who is alive and well during the first 14 days of life.
6. Expired – patient who for any reason, died within 14 days from delivery.
7. Morbidity – patients who were sent home but had a new onset infection or illness within 14 days of life.
8. Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) – is the method used for the nucleic acid amplification testing, which is the preferred diagnostic tool for diagnosing SARS-CoV-2 infection.
9. Feeding intolerance – inability to digest enteral feedings presenting as residual volume of more than 50%, abdominal distention or emesis or both and the disruption of the patient's feeding plan.[12]

Data Collection and Procedure

All infants born to confirmed COVID-19 mothers who were delivered at PGH from April 1, 2020 to June 30, 2020 and subsequently referred to the INTROP (Infectious and Tropical Diseases in Pediatrics) service were identified. All corresponding neonatal and maternal charts were retrieved, reviewed and had all the necessary data needed for the study.

The following maternal data were recorded: (1) age, (2) gravida (parity), (3) pregnancy-related complications, (4) co-morbidities, (5) mode of delivery, (6) presenting signs and symptoms, (7) close contact with individuals proven or highly suspected of COVID-19, (8) history of travel to areas with localized transmission within the last 14 days, and (9) resides in an area or neighborhood with clustering of influenza-like illnesses.

The following neonatal data were recorded: (1) gender, (2) age of gestation in weeks, (3) birthweight, (4) size for gestational age, (5) APGAR score, (6) signs and symptoms, (7) underlying disease and complications, (8) laboratory results, (9) treatment, and (10) outcome.

Upon review, all infants of mothers with COVID-19 infection were delivered under contact, droplet and airborne transmission precautions. Neonates were immediately dried, transferred and isolated in the COVID NICU. As a precaution, NO early skin to skin contact, delayed cord clamping and non-separation from the mother were done and the mother wore a surgical mask during delivery. Nasopharyngeal swab (NPS) or Oropharyngeal (OPS) specimens and/or Endotracheal aspirate (ETA) specimens if the patient is intubated, were obtained from all neonates at 24 to 48 hours of life. The samples were placed in a viral transport medium and were sent to the Medical Research Laboratory (MRL) of PGH for processing via RT-PCR for COVID.

Study Outcome

The demographics, clinical features, laboratory, radiologic findings and treatment of infants born to confirmed COVID-19 mothers were described. The neonates were classified as survived, expired or morbidity depending on their outcome within the first 14 days of life.

Data Processing and Analysis

Descriptive statistics was employed. Univariate analysis was done by generating the frequency and percentage distribution for all categorical variables. Bivariate analysis was performed using Fisher's exact test or Chi square test, whichever is available, to determine the association between maternal and neonatal variables.

Ethical Considerations

This study was submitted and approved by the Philippine General Hospital Expanded Hospital Research Office (EHRO) Technical Review Panel and the University of the Philippines Manila Research Ethics Board (UPMREB) prior to data collection. This was conducted in accordance with the principles that have their origin in the Declaration of Helsinki and is consistent with the International Conference on Harmonization Tripartite Guidelines and the Good Clinical Practice Guidelines (ICH-GCP).

A waiver of informed consent was requested from the Ethical Panel since the research presents no more than minimal risk, the waiver or alteration will not severely affect the rights and welfare of the participants. In accordance with the National Ethical Guidelines of Health and Health-related Research 2017, the research cannot be carried out without the waiver and the review

of medical records and its anonymity will be maintained. Data was solely collected by the primary investigator. All patient information were anonymized via identification codes and kept confidential. Soft copy of the files utilized password encryption saved in a USB storage device. This and the data collection forms will be kept in filing cabinets under lock and key, accessed only by the investigators. The data will be securely stored for at least ten years from the date of final publication and will be destroyed thereafter. The risk to privacy is minimal in this study, however in case of a breach, matter will be forwarded immediately to the PGH data privacy officer.

The investigators declare that there was no conflict of interest in the conduct of this study. There was no funding received from any individual nor institution.

RESULTS

Of the 109 deliveries at PGH from April to June 2020, forty-five pregnant women had confirmed COVID-19. Forty-three mothers had singleton delivery, while 2 had twin pregnancy. Twenty-seven (60%) out of the forty-five were multi-gravid with a mean age of 29 years old (15 to 39 years). Sixty four percent (64.4%) were asymptomatic, while 35.6% had symptoms of the disease which most commonly presented with cough (62.5%). Only seven (15.6%) had an identified significant exposure. Twenty-two mothers (48.9%) had co-morbidities, majority of which was gestational diabetes mellitus (40.9%), while 6 (13.3%) had pregnancy-related complications such as intrauterine fetal distress (66.7%) and premature rupture of membranes (33.3%). The summary of the maternal clinical features is presented in Table 1.

Table 1: Clinical Demographic Profile of Mothers with SARS-CoV2 Infection

Variables	N (45)	%
Age		
<21 years old	2	4.4%
21-30 years old	21	46.7%
>30 years old	22	48.9%
Mean age	29.7 year old (15 to 39 year old)	
Obstetric score		
Primigravid	18	40%
Multigravid	27	60%
No co-morbidities	23	51.1%
With Co-morbidities	22	48.9%
Gestational diabetes mellitus	9	40.9%
Gestational hypertension	5	22.7%
Pre-eclampsia	4	18.2%
Chronic hypertension	4	18.2%
Bronchial asthma	3	13.6%
Diabetes mellitus type II	2	9.1%
Hypothyroidism	2	9.1%
Multiple myoma	2	9.1%
Multinodular toxic goiter	1	4.5%
Hepatitis B	1	4.5%
ADHD	1	4.5%
Pregnancy-related Complications	6	13.3%
Intrauterine fetal distress	4	66.7%
Premature rupture of membranes (PROM)	2	33.3%
Mode of delivery		
Cesarean Section	32	71.1%
Spontaneous Vaginal Delivery	13	28.9%
Asymptomatic	29	64.4%
Symptomatic	16	35.6%
Cough	10	62.5%
Fever	5	31.2%
Dyspnea	3	18.7%
Coryza	3	18.7%
Sore throat	1	6.2%
Diarrhea	1	6.2%
Body malaise	1	6.2%
Anosmia	1	6.2%
With Exposure	7	15.6%
Close contacts	6	85.7%
Travel history	1	14.3%
Clustering	0	0%

There was a total of 47 neonates born to confirmed COVID-19 mothers. As shown in Table 2, 53.2% were males, while 46.8% were females. Majority was born full-term (91.5%), with a mean age of gestation of 37 weeks (29 to 40 weeks) and average weight of 2867 grams (615-3860 grams), appropriate for gestational age (95.7%), with good APGAR score (95.7%). The predominant mode of delivery was cesarean section (71.1%), primarily due to a previously scarred uterus.

Table 2: Demographics of Infants born to Mothers with SARS-CoV 2 Infection

Variables	N (47)	%
Gender		
Male	25	53.2%
Female	22	46.8%
Age of gestation (AOG)		
Full term	43	91.5%
Preterm	4	8.5%
Mean AOG	37 weeks (29 to 40 weeks)	
Birth weight		
≥2500 grams	40	85.1%
1500-2499 grams	5	10.7%
1000-1499 grams	1	2.1%
<1000 grams	1	2.1%
Mean Birthweight	2867 grams (615-3860 grams)	
Size for gestational age		
AGA	45	95.7%
SGA	2	4.3%
LGA	0	0%
APGAR score		
≥7	45	95.7%
<7	2	4.3%

All live births were swabbed at 24 to 48 hours of life and showed a negative SARS-CoV-2 PCR result. Thirty-four neonates (72.3%) had no symptoms and were sent home immediately with a reliable caregiver. Of the 27.7% who were symptomatic, the predominant underlying cause were feeding intolerance (30.8%), neonatal pneumonia (23.1%) and transient tachypnea of the newborn (23.1%) with clinical manifestations as presented in table 3. Vomiting (38.5%), tachypnea (38.5%) and apnea (23.1%) were the most common presentation.

Table 3: Clinical Manifestations of Infants born to Mothers with SARS-CoV2

Signs and Symptoms	N=47	%
Asymptomatic	34	72.3%
Symptomatic	13	27.7%
Tachypnea	5	38.5%
Vomiting	5	38.5%
Apnea	3	23.1%
Poor activity	2	15.4%
Cyanosis	2	15.4%
Abdominal distention	1	7.7%
Regurgitation	1	7.7%
Hypotension	1	7.7%
Underlying Disease		
Feeding intolerance	4	30.8%
Pneumonia	3	23.1%
Transient tachypnea of the newborn	3	23.1%
Respiratory distress syndrome	2	15.4%
Pneumothorax	2	15.4%
Early onset sepsis	1	7.7%
Pulmonary insufficiency of prematurity	1	7.7%
Necrotizing enterocolitis	1	7.7%
Septic ileus	1	7.7%

The neonates in this study who were symptomatic or had risk factors for sepsis were worked up and none had with leukopenia nor thrombocytopenia. Two or 13.3% had a lymphocyte count of less than 20%, and 55.6% had elevated procalcitonin levels. The most common radiologic finding was pneumonia (55.6%). Details of the laboratory and radiologic findings are seen in tables 4, 5 and 6. A second RT-PCR was sent in one neonate who was intubated on the second day of life due to pneumothorax, that still turned out negative.

Table 4: Laboratory findings of Symptomatic Infants born to Mothers with SARS-CoV2

Test	N	%
CBC	(N = 15)	
WBC		
<4 x10^9 cells/L	0	0%
Normal	14	93.3%
>30 x10^9 cells/L	1	6.7%
Lymphocytes		
<20%	2	13.3%
Normal	10	66.7%
>40%	3	20%
PLT <100,000 x10^9 cells/L		
Yes	0	0%
No	15	100%
CRP	(N = 9)	
≤6	9	100%
>6	0	0%
Procalcitonin	(N = 9)	
≤0.5	5	55.6%
>0.5	4	44.4%
Blood Culture	(N = 11)	
No growth	11	100%
With growth	0	0%

**WBC-white blood cell; CRP-C-reactive protein*

Table 5: Radiologic findings of Symptomatic Infants born to Mothers with SARS-CoV2

Findings	N=9	%
Pneumonia	5	55.6%
Ileus	3	33.3%
Reticulogranular ground glass appearance w/ air bronchogram	2	22.2%
Pneumothorax	2	22.2%
Normal	2	22.2%

Table 6: SARS-CoV-2 RT-PCR results of Infants born to Mothers with SARS-CoV2

SARS CoV-2 RT-PCT	N=48	%
Result		
Negative	48	100%
Positive	0	0%
Specimen		
NPS	41	85.4%
OPS	5	10.4%
ETA	2	4.2%

Six (12.8%) out of the 47 newborns needed respiratory support (Table 7) upon delivery. One (16.7%) was placed on non-invasive positive pressure ventilation (NIPPV), while the other 5 (83.3%) were intubated and hooked to a mechanical ventilator for an average of 9.4 days (2 to 21 days).

Table 7: Treatment instituted to Infants born to Mothers with SARS-CoV2

Treatment	N=47	%
Respiratory Support		12.8%
Intubated	5	83.3%
Average days intubated	9.4 days (2 to 21 days)	
NIPPV	1	16.7%
None	41	87.2%
Antibiotics		
No	36	76.6%
Yes	11	23.4%
IVIG		
No	47	100%
Yes	0	0%

As shown in table 7, antibiotic therapy was given to 11 patients (23.4%). None were given investigational drugs for management of COVID-19 such as intravenous immunoglobulin. The average length of hospital stay for all infants was 7 days, where 95.8% were discharged with good outcome (Table 8). There was noted one mortality, preterm, 33 weeks, low birthweight, who expired due to severe respiratory distress syndrome and pneumothorax. The said neonate was intubated due to tachypnea associated with progressing respiratory distress, desaturation and hemodynamic instability. Patient was given surfactant therapy and was started on empiric antibiotics. However, patient expired on the 30th hour of life. One morbidity was also noted, full term, 39 weeks, who was discharged on the 2nd day of life. However, on the 3rd day, patient developed jaundice and fever, was readmitted and managed as a case of neonatal pneumonia, started on Ceftazidime and Amikacin with noted clinical improvement. Other than the radiologic finding and elevated C-reactive protein and procalcitonin, the rest of the laboratory work-ups were unremarkable. A repeat NP swab was also done upon readmission, which was still negative for SARS-CoV-2. Patient was eventually sent home after 10 days.

Table 8: Outcome Infants born to Mothers with SARS-CoV2

Outcome	N=47	%
Survived	45	95.8%
Expired	1	2.1%
Morbidity	1	2.1%

Further statistical analyses using the Fisher's exact test was done to check for association between the maternal features and neonatal outcomes, infant's weight, gestational age and APGAR score. It revealed that there were no significant associations observed except for mother having symptoms. The presence or absence of symptoms among mothers was noted to be significantly associated with the presence or absence of symptoms among neonates (p=0.037).

Table 9: Test of Association of Maternal Features to Infant's Signs and Symptoms

Variables	Signs and Symptoms N (%)		*p*-value
MATERNAL	**Asymptomatic**	**Symptomatic**	
Comorbidities	17 (50%)	5 (38.5%)	0.140
No Co-morbidities	17 (50%)	8 (61.5%)	
Pregnancy-related Complications	4 (11.8%)	2 (15.4%)	0.131
No complications	30 (88.2%)	11 (84.6%)	
Mode of delivery			0.749
Cesarean Section	24 (70.6%)	10 (76.9%)	
Spontaneous Vaginal Delivery	10 (29.4%)	3 (23.1%)	
Symptomatic	10 (29.4%)	8 (61.5%)	**0.037**
Asymptomatic	24 (70.6%)	5 (38.5%)	

DISCUSSION

When pregnant women become infected with viral pneumonia, they are more likely to have obstetrical complications and may progress to severe disease.[2,13,14,15,16] The severity of viral pneumonia in pregnancy is evidently related to physiological and immunological changes that result in a shift from cell-mediated to humoral-mediated immunity.[2,11]

Several systematic reviews on pregnant women with SARS-CoV-2 infection have been done, mostly from China, and showed that majority of the infected mothers were noted to be in their third trimester of pregnancy,[17] underwent cesarean section where several authors cited fetal distress as the reason behind the decision[18] and preterm birth, PROM and pre-eclampsia were the identified sequela.[19]

Like in literatures, majority or 71.1% of the mothers in our study delivered via cesarean section. However, it was primarily due to a previously scarred uterus. Only 6 (13.3%) out of the 45 mothers had pregnancy-related complications with intrauterine fetal distress as the most common. Twenty-two mothers (48.9%) had co-morbidities. In contrast to what was observed in the above studies in China, majority of mothers in our study had gestational diabetes mellitus (40.9%), with lower rates of pre-eclampsia (18.2%).

The Philippine Society of Newborn Medicine (PSNBM) reviewed five journals on the clinicodemographic profile of infants born to COVID-19 suspect or confirmed mothers and found that despite being born to a mother with SARS-CoV-2 infection, most neonates were born term, with a birthweight of more than 2500 grams, appropriate for gestational age and an APGAR score of more than 7.[20] Similar to our study, 91.5% of the infants were born full term with normal birthweight (85.1%), appropriate for gestational age (95.7%) and a good APGAR score (95.7%).

One of the difficult questions about COVID-19 in neonates is whether perinatal transmission of SARS-CoV-2 exists. Vertical transmission of many microorganisms from an infected mother to her fetus can lead to devastating results.[21] Transmission usually occurs during intrauterine life through the placenta, or during delivery by ingestion or aspiration of cervicovaginal secretions, and in the postpartum period by breastfeeding. To prove the possibility of an intrauterine viral infection, RT-PCR assay on multiple tissue samples deriving from placenta, amniotic fluid, cord blood, and neonatal nasopharyngeal swab has been recommended.[22] However in this study only NP swab was done due to the limited availability of test kits and constraints on finances.

In February 2020, Wang et al. reported the first case of neonatal SARS-CoV-2 infection admitted at the Tongji Hospital in Wuhan, China where the mother was confirmed with COVID-19. The clinical manifestations of

the mother and the baby were both mild and the baby's prognosis was good. The male infant in the case reported was delivered via emergency cesarean under contact, droplet, and airborne transmission precautions. Early cord clamping was done and patient was transferred to an isolation room in the neonatal nursery shortly after delivery. The newborn's pharyngeal swab was done at 36 hours of life and showed a positive result. However, the nucleic acid detection tests done on the cord blood and placenta in this case turned out to be negative, which do not support the diagnosis of intrauterine transmission.[2] This was followed by a cohort study on 33 neonates born to mothers with COVID-19 from Wuhan Children's Hospital. Three of the 33 infants (9%) presented with early onset SARS-CoV-2 infection. The most common symptom was shortness of breath with findings of pneumonia. Consistent with previous studies, these infants also had a favorable outcome. Strict infection control was implemented during delivery increasing the likelihood that the SARS-CoV-2 in these neonates were maternal in origin.[23]

Another case from Peru was reported on a neonate born to a mother with severe presentation of COVID-19 in pregnancy. A major finding in this case is the positive testing on RT-PCR of the neonatal nasopharyngeal swab as soon as 16 hours after delivery, repeated at 48 hours of life for confirmation which also turned out to be positive. Ventilatory support was required for 12 hours only with favorable outcome and not requiring antibiotic treatment. In utero transmission was strongly suspected due to sterility of the procedure and isolation measures implemented immediately after birth.[24] However for both studies,[23,24] testing of other tissues samples were not done.

In our study, none of the infants had positive result for SARS-CoV-2 PCR. Furthermore, majority were sent home after 24-48 hours and those with symptoms improved after they were managed accordingly.

The timing of sampling and contact with the infected mother may be pivotal to ascertaining when transmission occurs.[25] On the latest guidelines released by the Center for Disease Control and Prevention (CDC) on the Care for Newborns (3 August 2020), neonates born to mothers with suspected or confirmed COVID-19, regardless of mother's symptoms, should have testing performed at approximately 24 hours of age. If initial test results are negative, CDC recommends repeating the test at 48 hours. But for asymptomatic neonates expected to be discharged early, a single test can be performed between 24-48 hours of age.[26] This was similar to what was done to our study population where the swab was performed on day 1 to day 2 of life. However, for those who stayed at the hospital beyond 48 hours, the swab was repeated only on one neonate who had pneumothorax, result still turned out to be negative.

Despite recent reports on a few neonates turning out to be positive for SARS-CoV-2, there have also been studies on newborns of COVID confirmed mothers who had negative PCR results but were symptomatic upon birth. In the clinical analysis report by Zhu et al., nine of ten neonates born to COVID-19 infected mothers were symptomatic (respiratory distress in 6, gastrointestinal symptoms in 4, fever in 2, thrombocytopenia in 2 accompanied by abnormal liver function and 1 baby died of multiple organ failure and DIC).[27] Fan et al reported two neonates with mild lymphocytopenia and radiological findings of pneumonia, although both appeared clinically well and eventually made a full recovery.[28] Similarly, Peng and colleagues also reported on a newborn whose mother was positive for SARS-CoV-2, who presented with tachypnea, moaning, and periodic breath immediately after birth and was hooked to a nasal continuous positive airway pressure.[29] Notably, none of these neonates tested positive for SARS-CoV-2. Evidence of intrauterine transmission was also assessed by testing the amniotic fluid, cord blood, neonatal throat swab and breastmilk samples [28,30] even including vaginal secretions, placenta, venous blood from mother, and anal swab, sputum, venous blood, urine samples from the newborn,[28] which all tested negative for SARS-CoV-2.

Clinical features of COVID-19 in infected newborns, especially preterm infants, might be non-specific and include acute respiratory distress syndrome, temperature instability, gastrointestinal, cardiovascular dysfunction and lethargy.[31,32] Laboratory findings were not distinct and may show a normal or decreased leukocyte count, lymphopenia and mild thrombocytopenia. Radiologic findings were commonly pneumonia and ileus.[20]

In our study, while a greater number of the delivered neonates were asymptomatic (72.3%), 27.7% had symptoms commonly presenting as tachypnea (38.5%), vomiting (38.5%) and apnea (23.1%). None had

leukopenia and thrombocytopenia, only 2 (13.3%) had a lymphocyte count of less than 20%, which subsequently improved in the succeeding complete blood counts. Similar in the literatures mentioned earlier, although non-specific, the most common radiologic findings were pneumonia (55.6%) and ileus (33.3%). Six (12.8%) out of the 47 newborns needed respiratory support upon delivery, majority of which were preterms with respiratory distress syndrome and pulmonary insufficiency. Eleven (23.4%) of the neonates were given antibiotics with good clinical response. Comparably, the neonates in our study also showed a favorable outcome (95.8%).

Further statistical analyses showed that there was a significant association between the presence or absence of symptoms among mothers and neonates (p=0.037). From this, clinicians can anticipate that symptomatic mothers during delivery will most likely have symptomatic infants thus making a clinician more prepared in the management of these newborns.

At present, there have been recent published data showing evidence of possible transplacental transmission.[6,7,8,9] Although these findings may serve as a confirmation of placental infection, definitive evidence of congenital infection has not yet been proven and needs further studies. These suggest that infections in the placenta may not always equate with vertical transmission, although its possibility cannot be fully excluded at this time.[7]

CONCLUSION AND RECOMMENDATIONS

This is the first study in the Philippines to assess the outcomes of infants born to mothers with SARS-CoV-2 infection. Although the results of this study did not support the possibility of an intrauterine vertical transmission, there was a noted significant association between the presence or absence of symptoms among mothers and neonates. The fetal and neonatal outcomes appear very good, with 2.1% morbidity and mortality. These outcomes were achieved with intensive, active management which might be the best practice in absence of more robust data. Standard, droplet, contact and airborne precautions should be maintained with immediate separation of the newborn from the mother upon delivery until further evidence. Given that the clinical data on COVID-19 in pregnant women and their newborns are still very limited, with its ill-defined short and long-term harm to the offspring due to the uncertainty of a possible vertical transmission, it is therefore crucial to screen pregnant women and implement strict infection control measures, and closely monitor neonates with increased risk of COVID-19 infection.

Since this is a retrospective review, this study was dependent on medical records/charts. Hence, we recommend prospective studies with a larger sample size and longer study period. To help assess evidence of vertical transmission, testing for the SARS-CoV-2 virus should be done on multiple sites (placenta, amniotic fluid, cord blood, breastmilk, etc.) which may improve the detection rate and reduce false negative diagnoses. Repeating the swab at 48 hours of life for neonates who required a longer stay at the hospital as recommended by CDC should also be considered.

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ORIGINAL ARTICLE

Outcomes of HIV-Exposed Infants enrolled in the Prevention of Mother to Child Transmission of HIV (PMTCT) Program in Philippine General Hospital: An 8-year Retrospective Study

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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: Our country has the fastest growing number of HIV cases in the Asia-Pacific region with a 203% increase from 2010 to 2018. MTCT represents 6% of infections in children and interventions such as the PMTCT program are essential to help reduce new infant infections.
Objective: To determine the outcomes of HIV-exposed infants born in PGH from 2010 to 2018 enrolled in the PMTCT program. To analyze the association of maternal and neonatal clinicodemographic factors to MTCT of HIV.
Methods: A retrospective cohort study using data collected from medical records of HIV exposed infants enrolled in the program.
Results: Out of 117 mother-infant pairs, only 70 met the eligibility criteria. Maternal factors showed that majority have: timely antenatal visit (56/70), maternal HIV diagnosis (70/70) and ART initiation (67/70) prior to delivery, triple lifelong maternal ART (69/70), CD4 >200 prior to delivery (52/70) and cesarean delivery (67/70). Amongst the infant factors-early infant prophylaxis (60/62), >4weeks prophylaxis duration (62/70) and replacement feeding (62/70) were noted in the majority. 2/70 infants were HIV positive. Mortality rate was 1.4% and 50% for HIV infected infants. Overall LTFU rate was 33.3%. Logistic regression showed that maternal co-infection with Hepatitis B(p=0.0275) was a possible determinant of MTCT. Infant HIV prophylaxis duration of >4 weeks had higher survival proportion(p=.0001).
Conclusion: The HIV MTCT rate was 2.86% upon implementation of our PMTCT program, meeting the <5% goal of WHO, suggesting that the program was an effective health intervention strategy. The high LTFU rate though should be considered in the evaluation of the program effectiveness.

KEYWORDS: *PMTCT, HIV-Exposed Infant, ARV prophylaxis, HIV Philippines*

INTRODUCTION

Global statistics as of 2018 reported 37.9 million people living with Human Immunodeficiency Virus (HIV), 1.7 million of which are children less than 15 years old and a total of 1.7 million new infections were recorded.[1] While the prevalence of HIV and Acquired Immunodeficiency Syndrome (AIDS) in the Philippines is still low, our country has the fastest growing number of cases in the Asia-Pacific region with a 203% increase from 2010 to 2018.[1] Mother to child transmission (MTCT) represents 6% of acquired infection in children and adolescents.[2] MTCT of HIV refers to vertical transmission of HIV from an HIV-positive mother to her baby at one or more of the following stages: pregnancy, labor, delivery or breastfeeding. The following are integral components of Prevention of Maternal to Child Transmission (PMTCT): primary prevention of HIV, especially among women of childbearing age; preventing unintended pregnancies among women living with HIV; preventing HIV transmission from a mother to her infant; and providing appropriate treatment, care, and support to women living with HIV and their children.[3] Locally, the applicability and effectiveness of these programs are not known and there is limited information on maternal and infant outcomes.

In the absence of any intervention, MTCT rates range from 15% to 45%.[3,4] This rate can be reduced to below 5% in breastfeeding populations and below 2% in non-breastfeeding populations[5] with interventions such as the PMTCT program. "Elimination" of pediatric HIV is the ultimate goal, defined as 90% reduction of new infant infections and a decrease of MTCT to <5%.[6] Antiretroviral therapy (ART) has been proven effective in reducing rates of MTCT of HIV. In resource-limited countries, about 35% and 52% of HIV infected infants without any therapeutic intervention die by age one and two respectively.[7] Variability in prophylactic regimens remains and consistency with guideline implementation has not been evaluated in the Philippines. Several studies reported on the effectiveness and outcomes of the PMTCT program in other countries;[4,6,8-11] currently there are no published data in the Philippines. It is important to monitor the efficacy and uptake of the PMTCT program as HIV cases; along with the number of HIV exposed infants are increasing every day.

This study aims to determine the outcomes of the PMTCT program among HIV-exposed infants born in the Philippine General Hospital (PGH) from 2010 to 2018 and determine association of maternal and neonatal clinic-demographic factors to MTCT. Specifically, this study will evaluate the following outcomes of women-infant dyads enrolled in PMTCT: HIV transmission rate, infant survival and other morbidities. Likewise, to determine the association of maternal and neonatal factors with HIV infection among exposed infants. Factors to be analyzed are: maternal demographics, timing of maternal diagnosis and initiation of treatment, maternal ARV treatment and duration, maternal viral load and CD4+ lymphocyte count, manner of delivery, maternal co-infections, pediatric age at birth, size for gestational age and birth weight, type of feeding, initiation, duration and type of infant ARV prophylaxis.

METHODOLOGY

Retrospective cohort design was used to investigate the outcomes of the PMTCT program. Total enumeration of cases was done. The study included all infants born to HIV-infected mothers who delivered at the Philippine General Hospital from January 1, 2010 to December 31, 2018 and subsequently referred to the Division of Infectious and Tropical Diseases in Pediatrics (INTROP), enrolled in the PMTCT program and seen on follow up at the STD/AIDS Guidance Intervention Prevention Unit (SAGIP) Clinic. HIV-exposed infants were excluded if they were not delivered/born in PGH, infants aged 18 months or above and infants who do not have two virological tests done.

HIV-exposed infants were identified using INTROP and SAGIP charts/case records. Corresponding neonatal and maternal charts were retrieved as needed from PGH Medical Records Section. Information on maternal and neonatal clinico-demographic factors were recorded. The primary endpoint of this study was the outcome of the program, specifically, HIV transmission rate, infant survival and other related co-morbidities. Maternal and neonatal factors were also evaluated in association with HIV transmission.

Operational Definitions

ARV prophylaxis: short term use of ARV drugs in the mother and/or infant to reduce MTCT.[12]

ART: the use of 3 or more ARVs drugs simultaneously to treat HIV infection.[12]

Mixed feeding: alternation of replacement feeding and breast milk in the first six months or by substitution of breastfeeding with formula before six completed months of life.

HIV Infected infant: if the infant has a positive RNA-PCR test,[13,14] if the first test is positive, we label as "HIV infected infant" pending 2nd PCR.

HIV-Exposed, Uninfected infant: if the infant has 2 negative RNA-PCR tests.[13-15]

Loss to Follow-up: a period of more than 3 months without a visit for children receiving ARV prophylaxis or a period of more than 6 months without a visit for those not receiving ARV prophylaxis.[16]

Data Analysis

For descriptive analysis, maternal and infant variables were summarized as frequency and percentage distributions. Since the sample size turned out to be smaller than expected, and certain cells had small counts, the Fisher's exact test was used to determine the association between HIV transmission and maternal and neonatal factors. Logistic regression analysis was used to show the individual and simultaneous effects of maternal and infant factors on the risk of MTCT of HIV. A 5% level of significance or a p value of <0.05 was used in testing the hypotheses. Infant survival was evaluated based on Kaplan Meier Estimate.

Ethical Considerations

The study was submitted to the University of the Philippines Manila Research Ethics Board for approval prior to data collection. A waiver of informed consent was requested from the ethical panel in accordance to the National Ethical Guidelines of Health and Health-related Research 2017. A written informed consent was obtained from the parents/guardians upon admission/birth of the patient and upon enrollment in SAGIP. The principal investigator solely collected the data. All data gathered were anonymized using numerical and alphabetical codes, kept strictly confidential and filed in a secured cabinet. Soft copy of the files utilized password encryption saved in a USB storage device. The data will be stored for at least ten years from the date of final publication and will be destroyed thereafter. In case of breach to data privacy, matter will be forwarded immediately to the PGH data privacy officer. The investigator declares that there is no conflict of interest in the pursuit of this study. Researchers are not associated with any sponsor nor received any incentive for doing the study.

RESULTS

A total of 117 mother-infant dyads were enrolled in the PMTCT program from January 2010 to December 2018 (Figure 1).

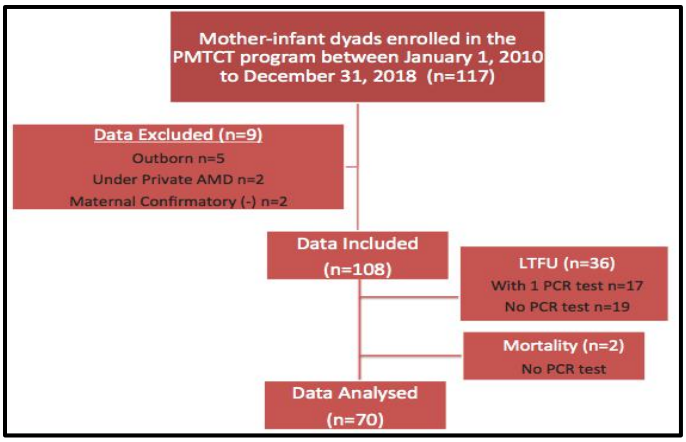

Figure 1. Population Flowchart/Process of Record

Considering the eligibility criteria, only 70 mother-infant pairs were included from the point of antenatal enrollment to birth until follow up visits. Maternal data (Table 1) showed that majority of mothers were between 18 to 35 years old, single, multi-gravid and finished secondary school. More than half 61.4% (43/70) were employed and 18.6% (13/70) were sex workers. The most common route of HIV transmission noted was through sexual contact, wherein 45.7% (32/70) of mothers had multiple partners and 40% (28/70) reported HIV positive partners in which 14.3% (10/28) of them were men having sex with men (MSM). Other modes of transmission included: domestic/sexual abuse (2.9%), having a high risk/promiscuous partner (4.3%) and blood transfusion (2.9%). Prenatal history revealed that majority had their first antenatal visit during the first trimester and were diagnosed and started on ART during pregnancy. 98.6% (69/70) of mothers were prescribed with lifelong ART with lamivudine (3TC), tenofovir (TDF) and efavirenz (EFV) being the most common choice, followed by 3TC, zidovidine (AZT) and lopinavir/ritonavir (LPV/r). Moreover, 18.6% (13/70) were classified as HIV Clinical Stage 3 and 4 and the most common co-infection was sexually transmitted infection (STI) / lower genital tract infection (18.6%). Diagnostic evaluation showed that 87.2% (61/70) had CD4 count (mean= 406.3 cells/mm^3) results prior to delivery, however, viral load determination was not routinely done. Intrapartum management showed majority delivered via cesarean section.

TABLE 1. Maternal Demographics

Variables	N=70 (%)
Age	
≤17 years old	0 (0.0)
18 to 35 years old	58 (82.9)
>35 years old	12 (17.1)
Marital Status*	
Single	44 (63.8)
Married	25 (36.2)
Obstetric Score	
Primigravid	20 (28.6)
Multigravid	50 (71.4)
Educational Attainment	
Primary	1 (1.4)
High School	41 (58.6)
College Level/Graduate	19 (27.1)
Vocational Course	9 (12.9)
Occupation	
Unemployed	27 (38.6)
Employed	43 (61.4)
Sex Worker	13 (18.6)
Reported Transmission Route	
Multiple Partners	32 (45.7)
Positive Partner	28 (40.0)
Men Having Sex with Men	10 (14.3)
IV drug user/Sharing needles	4 (5.7)
Unknown/No answer	15 (21.4)
Others	7 (10.0)
Domestic/Sexual Abuse	2 (2.9)
Having a high-risk partner	3 (4.3)
Blood Transfusion	2 (2.9)
HIV Status of Partner	
Positive	28 (40.0)
Negative	6 (8.6)
Unknown	36 (51.4)
First Antenatal Visit	
First trimester	56 (80)
Second trimester	14 (20)
Third trimester	0 (0.0)
Timing of HIV Diagnosis	
Before pregnancy	30 (42.9)
During pregnancy	40 (57.1)
First Trimester	9 (12.9)
Second Trimester	17 (24.3)
Third Trimester	14 (20.0)
After giving birth	0 (0.0)
Maternal ART Initiation	
Before pregnancy	20 (29.9)
During pregnancy	47 (67.1)
First trimester	8 (11.4)
Second trimester	18 (25.7)
Third trimester	21 (30.0)
After giving birth	3 (4.3)
Maternal ART given	
Single/Dual therapy	1 (1.4)
AZT + 3TC	1 (1.4)
Triple therapy	69 (98.6)
AZT + 3TC + LPV/r	10 (14.3)
AZT + 3TC + EFV	4 (5.7)
AZT + 3TC + NVP	3 (4.3)
TDF + 3TC + EFV	51 (72.9)
TDF + 3TC + NVP	1 (1.4)
None	0 (0.0)
WHO Clinical HIV Disease Stage	
Stage 1	56 (80.0)
Stage 2	1 (1.4)
Stage 3 and 4	13 (18.6)
Maternal Co-infections	
STIs/ Lower Genital Tract Infections	13 (18.6)
Pneumocystis jirovecii pneumonia	2 (2.9)
Tuberculosis	8 (11.4)
Hepatitis B	3 (4.2)
Candidiasis	4 (5.9)
Others	2 (2.9)
CD4 Count**	
< 200 cells/mm^3	9 (12.9)
200-499 cells/mm^3	32 (45.7)
>500 cells/mm^3	20 (28.6)
Not done/Unknown	9 (12.9)
Viral Load**	
< 50 copies/mL	15 (21.4)
50-1000 copies/mL	1 (1.4)
>1000 copies/mL	4 (5.7)
Not done/Unknown	50 (71.4)
Mode of Delivery	
Spontaneous Vaginal Delivery	3 (4.3)
Cesarean Section	67 (95.7)

**n=69, 1 maternal chart has no data*
***done during pregnancy*

Infant data (Table 2) showed that majority are male, delivered term and appropriate for gestational age with birth weight of ≥2500 grams. ARV prophylaxis was started within 12 hours of life in 96.8% (60/62) of infants. Duration of prophylaxis varied from 7 days, 4 to 6 weeks and more than 6 weeks. The antiretroviral/s prescribed was: single drug prophylaxis with nevirapine (NVP) or AZT, dual therapy with AZT and NVP and triple prophylaxis using 3TC+AZT+NVP. Majority of the infants were given replacement feeding. HIV PCR testing was done twice at 4 to 6 weeks and 4 to 6 months of life in most of the infants. Cotrimoxazole prophylaxis was given to all infants. Moreover, 11.4% (8/70) were given isoniazid prophylaxis due to exposure to tuberculosis in the household. Only 38.6% (27/70) of infants have completed vaccination up to 9 months. Majority of the infants had an unremarkable neonatal course. Neonatal comorbidities were prematurity (18.6% or 13/70), infection (20% or 14/70), specifically neonatal

pneumonia and sepsis and congenital anomalies (5.7% or 4/70). One infant had an allergic reaction to nevirapine.

TABLE 2. Infant Demographics

Variables	N=70 (%)
Gender	
Male	43 (61.4)
Female	27 (38.6)
Pediatric Age at birth	
<28 weeks	0 (0.0)
28-32 weeks	0 (0.0)
33-36 weeks	13 (18.6)
≥ 37 weeks	57 (81.4)
Size for Gestational Age	
Small for Gestational Age	5 (7.1)
Appropriate for Gestational Age	65 (92.9)
Large for Gestational Age	0 (0.0)
Birth Weight	
< 1000 grams	0 (0.0)
< 1500 grams	0 (0.0)
1500-2499 grams	17 (24.3)
≥2500 grams	53 (75.7)
Prophylaxis Started*	
Within 12 hours of life	60 (96.8)
Within 24 hours of life	2 (3.2)
> 24 hours of life	0 (0.0)
Duration of Prophylaxis	
≤1 week	5 (7.1)
>1 weeks to ≤4 weeks	3 (4.3)
>4 weeks to ≤6 weeks	46 (65.7)
>6 weeks	16 (22.9)
Antiretroviral Prophylaxis	
Zidovudine alone	15 (21.4)
Nevirapine alone	36 (51.4)
NVP + AZT	6 (8.8)
NVP + AZT + 3TC	13 (19.1)
Feeding Practice	
Breastfeeding	2 (2.9)
Replacement Feeding	62 (88.6)
Mixed Feeding	6 (8.6)
HIV PCR Testing	
4 to 6 weeks and 4 to 6 months	56 (80)
Other Timing	14 (20)
With follow up Serological Test	
Yes	10 (14.3)
No	60 (85.7)
Cotrimoxazole Prophylaxis	
Yes	70 (100)
No	0 (0)
Isoniazid Prophylaxis	
Yes	8 (11.4)
No	62 (88.6)
Vaccination Status (up to 9 months)	
Complete	27 (38.6)
Incomplete	43 (61.4)
Neonatal Comorbidities	
Prematurity	13 (18.6)
Congenital Anomaly	4 (5.7)
Infection	14 (20)
Others	3 (4.3)
None	47 (67.1)

**n=62, 8 neonatal charts had no data on timing of prophylaxis initiation*

Results revealed that only 2 out of 70 subjects or 2.86% (95% CI 0.79% to 9.84%) had MTCT. All the above-mentioned variables were tested and did not show any significant association with MTCT but Hepatitis B infection in mothers was a potential factor (*p*=.0845). Table 3 highlights the maternal co-infection variables tested for association with MTCT.

TABLE 3. Fisher's Exact Test/Test of Association of Mother-Infant Profile to MTCT

Variables	HIV Positive N=2 (%)	HIV Negative N=30 (%)	*p*-value
Maternal Co-infections			
STIs/ Lower Genital Tract Infections	1 (50.0)	12 (17.6)	0.3391 ns
Pneumocystis jirovecii pneumonia	0 (0.0)	2 (2.9)	1.0000 ns
Tuberculosis	0 (0.0)	8 (11.8)	1.0000 ns
Hepatitis B	1 (50.0)	2 (2.9)	0.0845 ns
Candidiasis	0 (0.0)	4 (5.9)	1.0000 ns
Others	0 (0.0)	2 (2.9)	1.0000 ns

Univariate regression analysis revealed that coinfection with maternal Hepatitis B is a significant risk factor. Specifically, mothers with Hepatitis B were 33 times (95% CI 1.47 to 738.72; *p*=0.0275) more likely to transmit HIV infection to their infants as compared to those without Hepatitis B. (Table 4). On the other hand, none of the factors turned out to be significant in the multivariate regression run.

TABLE 4. Logistic Regression – Univariate and Multivariate Regression of Maternal and Neonatal factors associated with MTCT

			Univariate Analysis		Multivariate Analysis	
Variables	**HIV Positive n (%)**	**HIV Negative n (%)**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
MATERNAL						
Maternal Co-infections						
STIs/ Lower Genital Tract Infections	1 (50.0)	12 (17.6)	4.67 (0.27 to 79.96)	0.2879	1.94 (0.03 to 131.86)	0.7590^{ns}
PCP pneumonia	0 (0.0)	2 (2.9)	-	-	-	-
Tuberculosis	0 (0.0)	8 (11.8)	-	-	-	-
Hepatitis B	1 (50.0)	2 (2.9)	33 (1.47 to 738.72)	0.0275	29.98 (0.35 to 2548.9)	0.1336^{ns}
Candidiasis	0 (0.0)	4 (5.9)	-	-	-	-
Others	0 (0.0)	2 (2.9)	-	-	-	-

In terms of infant prophylaxis (Single- 98.08% Survival, Dual-83.33% Survival and Triple-92.86% Survival), figure 2 denotes that the survival rate across the different treatment regimens was not significantly different (Logrank *p* value=0.1816) while length of prophylaxis (Figure 3), that is-- duration of more than 4 weeks had significantly higher survival proportion than those given less than 4 weeks prophylaxis (Logrank *p* value=.0001).

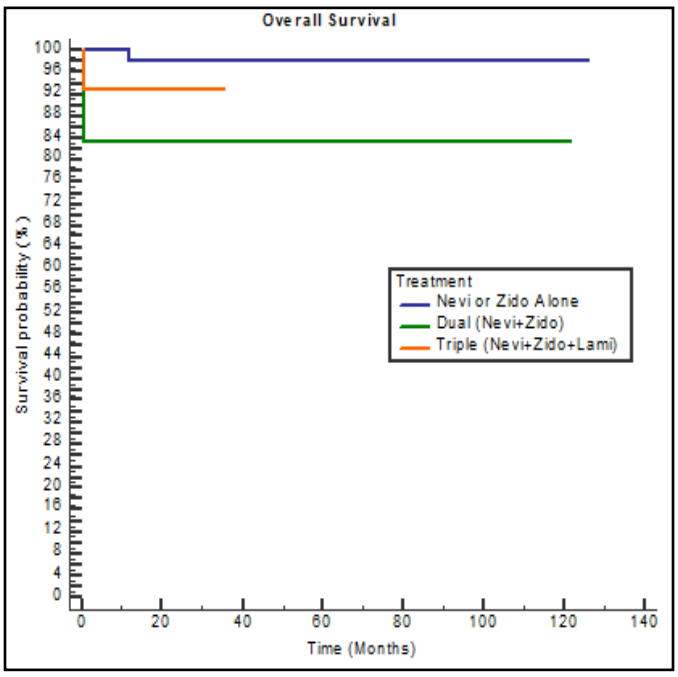

Figure 2. Kaplan-Meier Curve for Infant survival with single vs. dual vs. triple ARV prophylaxis

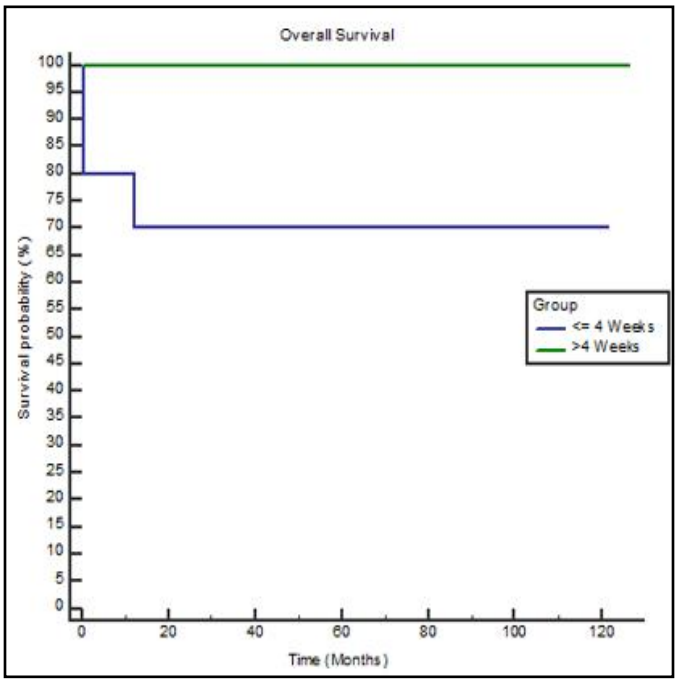

Figure 3. Kaplan-Meier Curves for Infant survival with ≤ 4 weeks vs. > 4 weeks duration of infant ARV prophylaxis

DISCUSSION

An effective PMTCT program is essential to eradicate MTCT of HIV in resource-limited countries such as the Philippines. The vital first step is early identification of mothers with HIV, which serves as the entry point to the program. We noted that majority of cases were enrolled during the later years (2016-2018) representing 65.7% of included pairs. Around this time, our institution was able to procure HIV Rapid Test kits and the DOH began to offer free HIV testing in health centers for pregnant women. These factors may have influenced a higher rate of maternal HIV detection and enrollment during 2016-2018 resulting in an increase in the number of HIV exposed infants.

The MTCT rate of HIV infection among exposed infants in this study was 2.86%. There is no available data on the national rate of MTCT, but according to the DOH 2020 HIV Registry,[2] 196 out of 3,349 pediatric cases from 1984-2020 acquired HIV through vertical transmission. Theoretically, the rate is estimated to be 15% to 45% without PMTCT intervention.[4] Regional rate for Asia and the Pacific is 21%.[1] Hence, a rate of 2.86% demonstrates that our interventions were probably effective. However, if we account for LTFU infants including the 2 mortalities with no virological test, worst-case scenario MTCT rate would be 37% (40/108). Thus, our rate might not be a true reflection of MTCT. There were 36 infants classified as LTFU, 52.8% (19/36) had at most 1 consult after discharge translating to a missed opportunity for virological testing. Overall LTFU rate was at 33.3% (95% CI 25.7% to 42.7%). In our setting, financial constraints and hospital proximity were some of the problems encountered. Thailand became the first Asian country to achieve WHO's target for the elimination of MTCT. In a study by Thisyakorn, MTCT rate was reduced from 20-40% to 1.9% in 2015 due to a pragmatic multi-sector response. Key factors that contributed to MTCT elimination were: an effective monthly monitoring system to improve missed opportunities for prevention; primary prevention of HIV in women of childbearing age through family planning programs, counseling and voluntary HIV testing; prevention of unintended pregnancies in women living with HIV by recommending dual methods of contraception for HIV-infected women and their partners; prevention of HIV transmission from a woman living with HIV to her infant by receiving free WHO Option B + through the national PMTCT programme; and provision of appropriate treatment, care and support to women and children living with HIV through HIV testing, CD4 testing and clinical staging to determine eligibility for ART in both pregnant women and infants.[17]

For better understanding of how the PMTCT evolved in our setting, Figure 4 shows a timeline of our PMTCT program. Changes were based on data from international guidelines. Our PMTCT program was adapted from two major guidelines, WHO[14] and the Aidsinfo U.S. guidelines.[15,18] Therefore, interventions varied among patients. We roughly assessed the protocol uptake and discovered that 91.2% (62/68, excluding 2 HIV infected infants) were given guideline-compliant management. This may have contributed to the low MTCT rate, although adherence studies should be done to support this notion. Reasons identified for non-adherence included: incorrect risk stratification, delayed initiation of prophylaxis beyond 12 hours and lack of maternal ART prior to delivery.

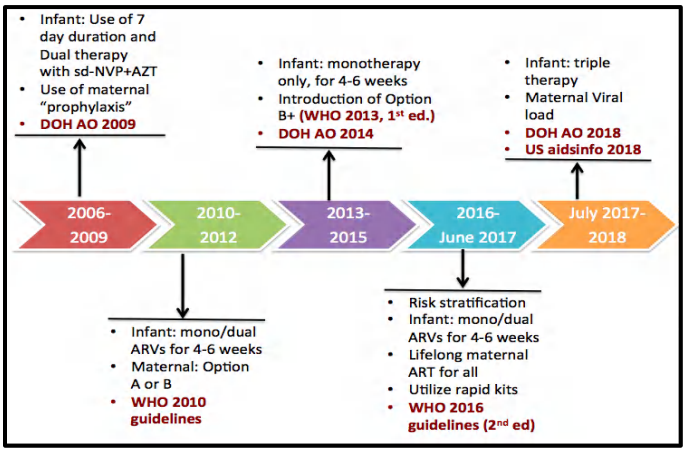

Figure 4. Evolution of PMTCT program in PGH

The PMTCT program is comprised of several components that must be approached comprehensively. Upon reviewing several PMTCT studies done globally,[4,8,9,11,19-25] the following program components have been implicated in vertical transmission of HIV: timely antenatal visit, HIV diagnosis and maternal ART initiation prior to delivery, CD4 count of >200 prior to delivery, life-long triple ART, delivery via cesarean section, infant prophylaxis initiated within 12 hours of life and lasting >4weeks and replacement feeding.

Early antenatal visit translates to an early opportunity for HIV testing resulting in early diagnosis and timely initiation of ART. PMTCT studies in Nigeria and Vietnam found that mothers who enrolled late into

the program had higher odds of transmission due to late initiation of ART.[11,19] Aziz et al. reported that pregnant women with ≥50% adherence, whether ARV-naive or -experienced, achieve a viral load of <1000 copies/ml within a median of 14 days of upon ART initiation.[20] In our institution, mothers are encouraged to undergo HIV screening at the earliest opportunity. Once diagnosed, they are enrolled into care and treatment is immediately started after obtaining baseline diagnostics.

The percentage of HIV positive pregnant women in the Philippines who have access to ART increased from 13% in 2010 to 18% in 2018.[1] In 2010-2013, the WHO recommended Option A and B as maternal prophylaxis. In option A, the regimen will depend on the stage of pregnancy: Antepartum: AZT as early as 14 weeks of pregnancy; Intrapartum: AZT and 3TC plus single dose NVP (sD-NVP) and Postpartum: AZT and 3TC for seven days. In option B, triple ARTs are prescribed but duration will depend on the mother's status. Mothers with CD4 count ≤500 cells/mm^3 or diagnosed with HIV clinical stage 3 or 4 at the time of ART initiation are eligible for lifelong therapy; otherwise, ARTs are discontinued after delivery unless the mother chooses to breastfeed.[26,27] Option B+ was introduced in the 2013 WHO guidelines wherein lifelong ART with TDF + 3TC + EFV were recommended for all HIV positive pregnant and breastfeeding women regardless of clinical stage or CD4 count.[27] Our local guidelines adapted this in 2014.[13] Out of 70 mothers in this study, only 1 (1.4%) was advised Option A, the rest were on Option B (18/70) or B+ (51/70) lifelong regimens. According to Muyunda et al., mothers on Option B+ had 50% reduced risk for MTCT compared to option A or B.[21] Having incorporated this intervention in our program probably contributed to better HIV prevention.

CD4 cells are destroyed by HIV infection, and a lower number correlates with increasing risk of morbidity and mortality. In analyses done in Ethiopia, South Africa, and Uganda, they reported that mothers with CD4 count <200 are at increased risk of transmitting HIV to their infants.[10,12,22] In our study, 85.2% had CD4 counts >200, postulating that this result may have a causal effect on transmission reduction.

Elective cesarean delivery is recommended at 38 weeks of gestation for all HIV-infected pregnant women with HIV RNA levels >1000 copies/mL near the time of delivery (or who have unknown viral load), regardless of the type of maternal ART being received.[18] In our program, 71.4% of mothers have no viral load determination, therefore majority of them delivered via cesarean section. In a study by Warszawski et al., elective cesarean section was inversely associated with MTCT but there was no significant difference in transmission risk among those with viral load of <400 copies/ml.[23] In contrast, a study by Mark et al. found that mode of delivery was not associated with MTCT.[24]

Newborn ARV regimens should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery.[18,28] Initiation of post exposure prophylaxis after 2 days of age is not likely to be efficacious in preventing transmission.[28] Our study showed that 96.8% (60/62) were given prophylaxis within 12 hours suggesting timely drug intervention as a factor in preventing MTCT but additional evaluation found no significant association. The reason for delayed initiation for the 2 patients was not written in the chart. One patient received prophylaxis on the 14th HOL, one on the 18th HOL, both though were not HIV infected.

According to WHO, HIV infected mothers should exclusively breastfeed for the first 6 months of life and may continue breastfeeding while being fully supported for ART adherence.[29] However, they also noted that an additional 5-20% of infants might become infected postnatally during breastfeeding without PMTCT interventions. In situations where breastfeeding cannot be avoided, extended infant prophylaxis would help reduce the risk of transmission.[30] Hence, upon entry into care, mothers are referred to our division for counseling on the choice of infant feeding. In our program, 88.6% opted to give replacement feeding, 2.9% decided to exclusively breastfeed for 6 months and 8.6% initially decided to breastfeed but switched to formula feeding within 6 months. Among those who were exclusively breastfed, prophylaxis was extended to ≥12 weeks. Several studies stated that exposure to breast milk had a higher MTCT rate than replacement feeding.[4,8,9] But other research suggested that breastfeeding was protective against MTCT.[31-33] Studies showed that mixed feeding is a significant determinant of transmission.[25,34] In our study, type of infant feeding was not significantly associated with HIV transmission. Similarly, a study in South Africa found out that morbidity and mortality were similar among HIV-exposed breast-fed and formula-fed infants.[35] These maternal and infant interventions, though not significant on statistical analyses when they were individually analyzed may have collectively

contributed to the low MTCT rate in this study. Additional studies are recommended to support this assumption.

Univariate regression analysis showed that mothers with hepatitis B are 33 times more likely to transmit HIV to their infants. One explanation could be: active co-infection stimulates the release of cytokines and inflammatory agents that enhance HIV replication systemically and weakens natural defenses to MTCT.[36] Persistent viremia and presence of co-infections in infants/mothers may further increase the load leading to immune activation resulting in immune dysregulation that exacerbate disease progression in a positive feedback loop.[37] While there are more studies tackling the reverse effect,[38-40] there were very few researches that investigated the effect on HIV MTCT.[36,41] A study done in India found out that maternal HIV-HBV coinfection did not increase HIV transmission.[41] In our study, 4.3% (3/70) had maternal co-infection with Hepatitis B. 1 out of 3 infants was HIV infected. After statistical analysis, it showed that Hepatitis B was a significant risk factor for MTCT of HIV. The reason for the discordant result remains to be elucidated. To date, this is one of the first researches to suggest this association. Constrained by the small sample size, further studies are needed to verify this information.

The impact of the PMTCT program could be measured in terms of lives saved or infections prevented. In our local registry,[2] a total of 26 deaths were recorded among those who acquired HIV through MTCT since 1984. Out of 117 mother-infant pairs included in the program during the study period, 3 infants expired, 2 out of 3 died within 7 to 10 days, hence, no virological test was done and thus, these infants were excluded. One out of three was HIV infected. The overall mortality rate was 1.4% (1/70) and 50% (1/2) for HIV infected infants. Again, due to the rate of LTFU, this number may be an underestimate. Assuming all LTFU infants expired, worst-case scenario mortality rate would be 36% (39/108). Mortalities in the program were included in the Survival Analysis. All were guideline compliant, delivered term via cesarean section, on replacement feeding, their mothers all had advanced disease (Clinical stage 3 and 4), no viral load testing and on combination lifelong ART (Option B and B+). Differences were seen in the choice of prophylaxis (single, dual, triple regimen) and infant survival was analyzed based on this. Survival rate across these regimens were not significantly different. Haile-Salassie et al. mentioned in a study, that because of selective use of triple prophylaxis for infants at higher risk, it is not appropriate to explore the association of type of prophylaxis and infection status.[42] Moreover, more than 4 weeks of prophylaxis was associated with a significantly higher survival proportion. This was an expected finding since recent guidelines[14,18,43] all recommend a minimum of 6 weeks duration for high-risk infants. This finding supports that the recommended duration is probably effective.

The greatest strength of this study is that it was conducted in the real world setting in one of the tertiary hospitals that caters to majority of HIV exposed infants. As a result, findings are more likely to reflect actual outcomes of PMTCT interventions in urban areas of the Philippines. Unlike other studies, we were able to look into the association of maternal co-infections like Hepatitis B with vertical transmission stressing the importance of antenatal screening and early initiation of maternal ART.

This is the first study in the Philippines to assess the outcomes of a PMTCT program. Our institutional program was well implemented with an uptake of 91.2%. The HIV MTCT rate was 2.86% upon application of our program, meeting the <5% goal of WHO. The rate was lower as compared to theoretical rates (15-45%) without PMTCT interventions. In conclusion, our local PMTCT program is a valuable health intervention strategy that can address the rising number of HIV cases in the Philippines and may be beneficial to other health facilities if adapted. Despite study limitations, in the absence of studies conducted in the Philippines to assess risk factors and effectiveness of PMTCT programs, our findings provide baseline and essential information on possible determinants of HIV transmission that can help improve prevention strategies for both the infant and mother.

RECOMMENDATIONS

This study has several limitations, which will be discussed with proposed recommendations for improvement. First, being a retrospective review, this study was dependent on medical charts with problems on data completeness. Because of this, adherence to medications and feeding practices were not assessed. Prospective studies may be able to control for these confounding variables. Second, we encountered a high rate of LTFU. Hence, the effectiveness of the program

may be overestimated. We recommend an integrated community approach and a unified record system for better inter-hub coordination, which can facilitate infant tracking, support and treatment uptake. It is also important to reinforce our vaccination program, which can increase the follow up rate of our patients. Third, because a number of infants were LTFU, the power of the study was limited due to the small sample size. Hence, we recommend a multicenter study among hospitals providing PMTCT measures. Lastly; maternal viral load determination prior to delivery was not routinely done.[44] We recommend baseline viral load testing to determine the mode of delivery, maternal response to ART and infant risk stratification.

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ORIGINAL ARTICLE

Fever of Unknown Origin Among Children in Two Private, Urban, Tertiary Hospitals: A 27-year Retrospective Study

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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

Introduction: Fever of unknown origin (FUO) is a problem commonly encountered by infectious disease specialists, and even general pediatricians, in spite of the improvement in diagnostic modalities. There is no local study on childhood FUO from a private hospital. Thus, there is a need to determine the etiology of FUO seen in private practice, which may be different from those encountered in government or teaching hospitals.

Objectives: The purpose of this study is to identify the etiologies of childhood FUO from two private, urban, tertiary hospitals, as evaluated by a single pediatric infectious disease physician; and to discuss epidemiologic, clinical and diagnostic clues for the most common etiologies.

Methods: Childhood FUO cases were compiled from 1993 to 2020. Each consecutive, inpatient, admission or referral of a patient, 18 years or younger, was logged into a personal computer, and the discharge diagnosis for the FUO was recorded. Clinical, epidemiologic, diagnostic and therapeutic data, relevant to the FUO diagnosis were likewise recorded. FUO was defined as daily fever of 38^0C for ten consecutive days, or more, with no etiology identified after being admitted for seven days.

Results: Of 171 cases of childhood FUO, the etiology was an infection in 68%, collagen-vascular disease in 13%, miscellaneous cause in 8%, malignancy in 6%, and no diagnosis in 5%. The most common infections were Epstein Barr Virus (EBV) mononucleosis, tuberculosis, enteric fever, sinusitis, pneumonia and incomplete Kawasaki disease. The most common collagen vascular diseases were juvenile idiopathic arthritis and systemic lupus erythematosus. Hemophagocytic lymphohistiocytosis was the most common miscellaneous cause. Lymphoma was the most common malignancy.

Conclusion: This study found EBV mononucleosis, sinusitis, pneumonia, incomplete Kawasaki disease, lymphoma, HLH and Kikuchi-Fujimoto disease to be FUO etiologies not reported previously in other local reports.

INTRODUCTION

Fever of unknown origin (FUO) is defined as fever of 8-21 days or more, according to different authors, with no diagnosis being evident after a careful history, physical examination and preliminary diagnostic evaluation.[1-6] This problem is encountered commonly by infectious disease specialists, and occasionally, by general pediatricians, in spite of improvement in diagnostic modalities. Locally, FUOs are due to infections in 44-54%, collagen-vascular disease in 6-39%, malignancies in 14-21%, histiocytosis in 0-7%, and are without a diagnosis in 4-18%.[4-6]

Studies from the Philippine General Hospital, Philippine Children's Medical Center and the University of the East-Ramon Magsaysay Medical Center showed that infections that most commonly cause FUO are enteric fever, tuberculosis (TB), and septicemia. The most common non-infectious causes are juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), leukemia, lymphoma and histiocytosis.[4-7] There are no reports from private, non-teaching institutions.

There is a need to be aware of the most common causes of FUO in private hospitals, where patients and hospital resources are less constrained by economic factors, so that clinicians who practice outside of urban centers, where diagnostic tests and radiographic imaging are not readily available, may be guided on the appropriate evaluation and treatment of FUO. When access to a good laboratory is hampered, even infectious disease specialists may not be able to provide the appropriate evaluation and treatment. Thus, there is a continuing need to identify the most common causes of FUO in both private and government hospitals, in order to provide efficient care and decrease morbidity and mortality.

The purpose of this study is to identify the etiologies of childhood FUO, as seen and evaluated by a single pediatric infectious disease physician, in two private, urban, tertiary hospitals, over a 27-year period. Secondarily, epidemiologic, clinical and diagnostic clues to the diagnosis of the most common causes of childhood FUO will be presented.

MATERIALS AND METHODS

Cases in this study of childhood FUO were compiled from 1993 to 2020. Each consecutive, inpatient admission or referral of a patient 18 years or younger, was logged into a personal computer and cases in which a discharge diagnosis of FUO, together with the eventual identified diagnosis to explain the FUO (if any such was arrived at), were included in this study. Clinical, epidemiologic, diagnostic and therapeutic data, relevant to the FUO diagnosis, were recorded in each patient's account. The inclusion criteria for FUO were: fever of 38^0C, or more, at any time during a 24-hour period, for ten consecutive days, or more, before the hospital admission, and during the hospital admission; with no etiology identified for the fever, after being admitted and evaluated as an inpatient for seven days, or more.

As the cases were compiled over 27 years, diagnostic tests to determine illness etiology evolved over time. The etiologic diagnosis was made, with the following criteria:

1. Epstein Barr Virus (EBV) mononucleosis: clinical findings, with a positive result for a serum heterophile antibody test; or EBV IgM and/or IgG; or/and an EBV polymerase chain reaction (PCR) test.
2. TB disease: clinical findings, a positive 5 TU PPD test or a serum TB Quantiferon result, characteristic radiographic findings, epidemiology, and laboratory findings (positive AFB smear, TB GeneXpert, and/or *Mycobacterium tuberculosis* culture). In addition, for TB lymphadenitis, pathologic findings of caseation necrosis, or a positive AFB smear, or *M. tuberculosis* culture of tissue; for TB meningitis, characteristic cerebrospinal (CSF) results and computerized tomography (CT) or magnetic resonance imaging (MRI) findings of hydrocephalus, basal cistern enhancement and/or presence of CNS tuberculomas; for vertebral TB osteomyelitis, typical radiographic findings of anterior vertebral body collapse, anterior paraspinal abscess, and disc narrowing between affected vertebrae.
3. Enteric fever: clinical findings, and a blood culture growth of *Salmonella typhi* or *Salmonella paratyphi*; or a positive Typhi IgM, if the child was previously treated with antimicrobials, and had no growth in a blood culture.
4. Paranasal sinusitis: clinical findings, confirmed by a paranasal sinus radiograph or a CT scan.
5. Pneumonia: clinical findings, confirmed with a chest radiograph or CT scan. Bacterial organisms were identified using standard laboratory methods; mycoplasma disease was identified using the

Immunocard Mycoplasma IgM test; *Pneumocystis jirovecii* was identified by a methenamine silver stain of Gomori, direct fluorescent antigen staining, or by PCR testing.

6. Herpes simplex virus (HSV) encephalitis: clinical findings, and a positive serology for HSV-1 or HSV-2 IgM or IgG, or a positive CSF HSV PCR result, and cranial CT or MRI findings compatible with the disease.
7. Anti-NMDA encephalitis: clinical findings, and a positive result for anti-NMDA receptor antibody.
8. Juvenile idiopathic arthritis (JIA): clinical findings, with the concurrence of the rheumatology service fulfilling the criteria for JIA.[8]
9. Kikuchi-Fujimoto disease: characteristic lymph node biopsy findings.[9-10]
10. Malignancies: based on biopsy, or bone marrow aspirate pathology, in conjunction with an oncology referral.
11. Hemophagocytic lymphohistiocytosis (HLH): based on standard criteria.[8-11]

Excluded were cases of patients who have chemotherapy-associated febrile neutropenia, HIV-related FUO, and infants born in the study institutions, who have not been discharged from the nursery after their neonatal stay.

This study was approved by each hospital's Institutional Review Board. As all the cases were obtained from the author's personal files in a password-protected, personal computer, no medical records were accessed from the hospitals' medical records department. The author declares no conflict of interest in the conduct of this study.

RESULTS

Table 1: FUO causes from two private, urban, tertiary hospitals, 1993-2020: (n=171)

Infections	**116 (68%)**
Mononucleosis	25
Tuberculosis	22
Enteric fever	16
Sinusitis	11
Pneumonia	7
Incomplete Kawasaki disease	5
Endocarditis	4
Rheumatic fever, with arthritis and no carditis	2
Clostridium difficile colitis	2
Urinary tract infection	2
Cervical lymphadenitis	2
HSV meningoencephalitis	2
Anti-NMDA encephalitis	2
Post-meningitic *Escherichia coli* frontal subdural abscess	1
Staphylococcus aureus bacteremia	1
Brevundimonas spp. sepsis	1
Pseudomonas aeroginosa tonsillitis	1
Retroperitoneal abscess secondary to a femoral vein perforated by a Broviac catheter	1
Multiple liver abscesses	1
Ruptured Appendicitis	1
Acute hemorrhagic pancreatitis	1
Ventriculo-peritoneal shunt infection	1
Leptospirosis	1
Bronchitis, cold-agglutinin-positive	1
Cryptococcal meningitis	1
HyperIgE eosinophilia syndrome with pneumonia and pyoderma	1
Systemic viral illness, clinical	1
Collagen Vascular Diseases	**23 (13%)**
Juvenile idiopathic arthritis	13
Systemic lupus erythematosus	5
Erythema nodosum	1
Henoch-Schonlein purpura	1
Takayasu's arteritis	1
Behcet's syndrome	1
Vasculitis, unspecified	1
Miscellaneous	**13 (8%)**
Hemophagocytic lymphohistiocytosis	7
Kikuchi-Fujimoto disease	3
Inflammatory bowel disease	3
Malignancies	**11 (6%)**
Lymphoma	7
Leukemia	2
Craniopharyngioma	1
Dysgerminoma	1
No diagnosis	**8 (5%)**
Total	**171**

Table 2: Epidemiologic, clinical and diagnostic clues to FUO etiology

1. Age:
   a. Under 3 years old: Kawasaki disease
   b. Over 3 years old: Enteric fever, *Mycoplasma pneumoniae*
   c. Over 6 years old: Collagen vascular diseases are equally prominent as infection; endocarditis
   d. Adolescents: EBV mononucleosis, Kikuchi-Fujimoto disease
2. Length of fever:
   a. Over 2 months: Collagen vascular diseases (JRA, SLE); malignancy (lymphoma, leukemia); TB; uncommon for bacterial causes
   b. 10 days to <2 months: EBV mononucleosis
3. Previous or current antibiotic use, but non-improving:
   a. With respiratory symptoms: *Mycoplasma pneumoniae*, TB, *Pneumocystis jirovecii*
   b. No respiratory symptoms: Enteric fever
   c. Broad spectrum intravenous: *Clostridium difficile* colitis
4. Toxicity:
   a. Absence of, or little signs of toxicity: Paranasal sinusitis
5. Cervical lymphadenopathy:
   a. With or without hepatosplenomegaly: EBV, lymphoma, TB
   b. Without hepatosplenomegaly: Kawasaki disease, Kikuchi-Fujimoto disease
6. Rash:
   a. Maculopapular, urticarial or erythema multiforme-like: Kawasaki disease
   b. Maculopapular: EBV
   c. Fleeting maculopapular: JIA
   d. Malar maculopapular: SLE
   e. Purpuric: Henoch-Schonlein purpura and leukemia
7. Transaminases (SGPT):
   a. Elevated SGPT = 60-200: Kawasaki disease, enteric fever, EBV
8. WBC count:
   a. Normal: Enteric fever, *Mycoplasma pneumoniae*
9. Platelet count:
   a. Increased: Kawasaki disease, deep organ abscess
   b. Decreased: Enteric fever, after the 7th day of fever; EBV, SLE, leukemia, HLH, Kikuchi-Fujimoto disease

DISCUSSION

This report identifies etiologies of childhood FUO among 171 inpatients seen by one pediatric infectious disease specialist over 27 years in two private, urban, tertiary hospitals. Fever of unknown origin had an infectious disease cause in 68%, with EBV, TB, enteric fever, sinusitis, pneumonia and incomplete Kawasaki disease being most commonly seen; collagen-vascular disease in 13%, malignancy in 5%, with lymphoma being most common; HLH in 4%; and no diagnosis in 5%.

Mononucleosis due to EBV was the most common infectious cause of FUO in this study. This finding has not been previously reported in four local studies of childhood FUO from three Metro Manila tertiary hospitals.[4-7] A recent local study of 23 childhood (mean age, 9 years) EBV cases from one of the hospitals in this study, showed a median fever length of nine days (range, 3-20 days); fever was seen in 100%, pharyngitis in 65%, cervical lymphadenopathy in 57%, a non-specific rash and exudates on tonsils.[12] Western studies and a Taiwanese study have reported EBV to be the most common infectious cause of FUO.[3,16-17] Disease due to EBV should be suspected in adolescents and pre-adolescents who have fever, pharyngitis and/or tonsillitis, neck lymphadenopathy, splenomegaly, elevated serum transaminases and leukocytosis, especially if such patients continue to be febrile in spite of being given a beta-lactam or macrolide antibiotic that would normally treat *Streptococcus pyogenes.*

Tuberculosis was the second most common infectious cause of FUO with 22 cases (13%). In the four other local studies on FUO, TB was among the top three infectious causes of FUO.[4-7] Among 174 inpatient cases of TB disease diagnosed in these two study hospitals between 1993-2020, illness was most commonly due to primary TB in 48%, TB cervical lymphadenitis in 16%, TB pneumonia in 14%, Pott's disease in 9% and TB meningitis in 6%; however, only 13% of the TB disease cases in this group presented as FUO (data not shown). Among the 22 that did cause FUO, 13 were due to either primary TB or TB pneumonia, while four had TB meningitis. Many cases with primary TB were admitted for fever, with no radiographic evidence of TB chest

infection initially, but because of non-defervescence, a repeat chest radiograph subsequently showed the findings of primary TB. Other cases presented with fever and clinico-radiographic evidence of a non-hypoxemic pneumonia, often, with a sub-acute course; after being treated with beta-lactam antimicrobials and/or macrolides, fever continued, and subsequent diagnostic procedures (5 TU PPD or serum TB quantiferon, repeat chest radiograph or chest CT, or sputum/gastric lavage for AFB smear, TB culture, and/or TB GeneXpert) showed that TB pneumonia was the cause of the prolonged fever, with defervescence occurring following the use of anti-tuberculous drugs. TB meningitis (TBM) caused four cases of FUO. In a report of 17 cases of TBM over 20 years from one of the hospitals in this study, fever (mean duration, 27 days) was seen in 100%.[10] For the four TBM cases which were FUO cases in this study, an initial cranial CT or MRI did not show the characteristic findings of TBM, but a subsequent imaging study showed the sought-out findings. Cerebrospinal fluid (CSF) tests may not be readily indicative of TBM, as CSF pleocytosis may not be revealing. One boy in this series had FUO for three months, and was found to have disseminated TB (intra-peritoneal TB, ascites, hepatosplenomegaly, pleural and pericardial effusion and pulmonary nodules). On the other hand, although TB lymphadenitis is the second most common form of TB disease, it is usually an afebrile illness, and should not cause FUO.[16-17] In a local report from one of the study hospitals, fever was only seen in 16% of cervical lymph node biopsy cases, for which TB lymphadenitis was the pathologic diagnosis.[18]

Enteric fever was the third most common infectious FUO cause in this study; in the other four local studies, it was the leading cause in three reports, and second most common in one.[4-7] In Metro Manila, *Salmonella typhi* or *Salmonella paratyphi* used to be the top two causes of community-acquired bacteremia but in 2001, the Metro Manila Water Supply System was sold by the national government to two private companies, and the cases of enteric fever noticeably dropped steadily over the past two decades, so that most of the cases in this report were seen in the 1990s and early 2000s. In the two hospitals in this study, the author saw 242 cases of community-acquired bacteremia during the study period, 173 (72%) of which were due to *S. typhi or S. paratyphi* (data not shown). Enteric fever causes prolonged fever, often without respiratory signs, accompanied by fatigue, anorexia and abdominal pain; a minority will have vomiting or diarrhea. Physical examination often only shows pallor and right upper quadrant tenderness. An epidemiologic history will often indicate a risk factor(s): eating street vendor food and/or shellfish, contact with chicken or turtles, and/or recent travel. Important clues in the laboratory results are a normal white blood cell count, unlike most other bacterial infections, in spite of a prolonged fever; a neutrophil predominance; and a mild to moderate elevation in the SGPT or SGOT levels. When the rapid test, Typhi IgM and IgG, became available in 1995, many cases of enteric fever were diagnosed earlier, and not labeled as FUO; previous to that, many such cases took some time to be diagnosed and treated, because blood cultures would yield no growth, often due to the previous outpatient use of antimicrobials like amoxicillin or cotrimoxazole before the hospital admission.

Sinusitis caused 11 FUOs. The usual findings in these children were prolonged low-grade fever with cough and prominent rhinorrhea, a history of allergic rhinitis, and absence of rales and/or wheezes, upon chest auscultation. Often, the child was admitted because of prolonged, intermittent fever, but not because the patient was ill-looking. The important hallmark noted in this study of children with prolonged fever and sinusitis was their non-toxic appearance.

Pneumonia was a cause of FUO in seven cases (4% of total). In two, mycoplasma was eventually diagnosed by serology; and in two cases, pneumonia occurred in children with congenital heart ailments. In one of the study hospitals, two previous studies found that 26% and 28% of children admitted for pneumonia tested positive for a serum mycoplasma IgM test; all such mycoplasma IgM-positive patients were febrile on admission, though fever, in general, was not prolonged. However, in the two studies, a frequent reason for the hospital admission was the child's continued fever in spite of receiving a beta-lactam antibacterial, which is not the suggested treatment for mycoplasma pneumonia.[19-20] This may explain why the two mycoplasma cases in this present study had prolonged fever, which resolved when a macrolide was given. One 18-year old, CD4-lymphocytopenic, HIV-negative, male, with pneumonia and fever for one month, was found to have *Pneumocystis jirovecii*.

There were five cases (3%) of incomplete KD as a cause of FUO. This number is 3% of the 160 KD cases seen by the author in the two study hospitals during the same time period (data not shown). Kawasaki disease may cause prolonged fever, especially when the physician is not familiar with the illness.[17] In these two institutions, 22% of KD cases were incomplete Kawasaki cases, which may have led to a longer time to diagnose. Patients with KD also had pneumonia (4%), sinusitis (3%), cellulitis over the cervical node (3%), jaundice (3%), and toxic shock syndrome (1%), all of which, required evaluation and treatment, because part of the diagnosis of KD is to rule out all other reasonable causes for the illness; the process of evaluating and treating these co-morbid illnesses can extend the length of fever, before intravenous immunoglobulin is finally given (data not shown). In other countries, KD was the FUO cause in 6% of 185 childhood FUO cases in Serbia, and was the top miscellaneous cause of FUO in a Taiwanese study.[3,14]

There was one case diagnosed to have a systemic viral infection. This occurred early during the study period, when many diagnostic tests (i.e., EBV, mycoplasma tests) were not yet available. The child eventually defervesced, without antimicrobial use.

Juvenile idiopathic arthritis (JIA) was the most common collagen-vascular disease cause of FUO, with 8% of the total. All cases were diagnosed using current criteria.[8] Among the twelve JIA cases, all presented as systemic-onset disease with prolonged fever, and joint manifestations only appeared at two to three weeks, or longer, after the onset of fever. Serum ferritin levels were elevated in all. In American FUO reports, JRA was the most common collagen-vascular disease cause of FUO.[2,13] In a classic childhood FUO article, Pizzo, et al, noted that when children are six years and older, connective tissue diseases are almost equal as infections, in frequency (32% vs. 38%), as the cause of FUO, as compared to children younger than six years, in whom infections are much more common causes, than collagen-vascular diseases (68% vs.8%).[2] Other than presenting as a systemic-onset illness, JIA cases become labeled as FUOs because, unlike infections and malignancies, there are no definitive diagnostic tests for JIA and a criterion for the diagnosis is that the illness has to have had a duration of six weeks, or more.

There were five cases (3%) of SLE as an FUO cause. Although an anti-nuclear antibody is frequently requested during an FUO work-up, the yield for a significant result has not been high (data not shown). In four local studies, including the present, JIA was a more common collagen-vascular disease to cause FUO, than SLE; only the PGH study found SLE to be more common. In foreign reports, SLE has also been found to be less common than JIA to cause childhood FUO. [2,13]

Hemophagocytic lymphohistiocytosis (HLH), which is not classified as an infection, collagen-vascular disease, or malignancy, was diagnosed in seven cases (4%). Four cases were post-EBV infection, two were post-salmonella bacteremia, and one was post-COVID-19 infection in a 13-year old boy, who also had COVID-associated MIS-C. Earlier studies had used the term histiocytosis. In the two institutions in this study, HLH has been increasingly diagnosed between 2010 to 2020, with 16 cases seen, 13 of which were secondary to an identified infection (EBV in six; dengue or cytomegalovirus in two, each; and *Klebsiella pneumoniae* sepsis, *Salmonella spp.* sepsis, and COVID-19 infection in one, each) and one being secondary to JIA. The illness is an infrequent, life-threatening disease of severe hyperinflammation; cytokines are secreted in large amounts and macrophages phagocytose blood cells. The diagnosis is made in the presence of five of the HLH-2004 criteria.[11] This diagnosis should be kept in mind especially in EBV cases, in which prolonged fever and splenomegaly are commonly present; if such fevers continue, and cytopenias evolve, checking serum ferritin, triglyceride and fibrinogen levels should be considered, to determine if the EBV infection is being complicated by a secondary HLH, which will entail additional therapy.

Kikuchi-Fujimoto disease (KFD) was seen in three cases (2%). This illness has only been reported once, locally, in a 12-year old child, though not as an FUO cause; another local report was of three adults.[19-20] This report's three cases were of a 10, 15 and 16 year-olds who had fever of 14, 18 and 42 days, respectively; non-specific symptoms were rash, myalgia, malaise, and night sweats. Two had an ANA of 1:80. As the only other physical examination findings were enlarged cervical lymph nodes in two, and a supraclavicular and axillary lymph node in one, biopsies were performed, due to a concern for malignancy. The biopsy subsequently showed pathologic findings of KFD.[9-10] This illness is a

cause of lymphadenitis, usually manifesting as painless, unilateral, cervical lymphadenopathy. Fever is seen in 33-40%, and the disease is a known cause of FUO.[21] There may be a rash in 16-40%, with nonspecific skin lesions; less commonly, there may be weight loss, malaise, chills, night sweats, vomiting and diarrhea.[24] Rarely, lymphadenopathy may be generalized, to involve the mediastinum and peritoneum. Laboratory tests may show neutropenia, atypical lymphocytosis, thrombocytopenia, and elevated ESR, transaminases, lactate dehydrogenase and ferritin.[25] The diagnosis is made only by finding the characteristic lymph node biopsy features of KFD.[24] Not all pathologists are familiar with the disease, so that the clinician has to alert the former, beforehand, to look for KFD. There is no treatment necessary, and symptoms usually resolve in one to four months, but recurrence may occur, and illness may last as long as one year.[25]

Inflammatory bowel disease (IBD) was seen in three cases (2%). All were suspected to have intestinal TB, but were eventually diagnosed with IBD, after colonoscopy and biopsies were performed.

Lymphoma was the most common malignancy, causing seven cases (4%). Due to the often, sub-acute growth of lymphomas in the neck, and the relative frequency of TB lymphadenitis locally, which similarly grows in a sub-acute manner, the diagnosis may be delayed because, as many Filipinos will have a positive PPD or TB Quantiferon test, many such cases of cervical lymph node enlargement will be treated for TB empirically, before it is realized that the mass is not diminishing in size, nor the fever breaking, if fever is prominent. An important clue against TB is that isolated TB of the lymph nodes is usually an afebrile illness;[16,18,26] however, in a local study of biopsied enlarged lymph nodes, 80% of children with a pathologic diagnosis of lymphoma were afebrile.[18] Lymphomas which are not found under cutaneous areas (intra-thoracic and intra-abdominal) may be even more difficult to diagnose because of the need for an invasive procedure, thereby causing prolonged fever.

Table 2 shows epidemiologic, clinical, and diagnostic clues to the etiology of FUO. The evaluation of childhood FUO should be individualized, based on a good history, epidemiology and physical examination. A complete blood count, cultures and serologic tests should be utilized, before more invasive tests are done. A big aid in the earlier diagnosis of TB, which is likely the top cause of FUO locally, is the TB GeneXpert, a PCR test that can detect the presence of minute amounts of TB organisms in a body fluid sample, with a result available on the same day. Acute-phase reactants like ESR and C-reactive protein (CRP). are useful when the results are negative or low, which predict for a benign or viral illness. Radiologic tests that are most commonly done, in decreasing order, are: chest and paranasal sinus radiographs, abdominal ultrasound, and, as indicated, 2-D echocardiogram, and abdominal CT scan, and a cranial CT scan or MRI. Biopsies are usually saved for last, particularly if malignancy cannot be ruled out. Among the FUO cases seen in this report, an abdominal ultrasound aided in the diagnosis of mononucleosis, HLH and lymphoma, when splenomegaly, with or without, hepatomegaly was seen; and an occult retroperitoneal abscess that resulted from a femoral vein being punctured by a Broviac catheter. An abdominal CT scan revealed a diagnosis of a peri-renal abscess in a one-year old girl with a two-month FUO, which was not seen in an abdominal ultrasound; multiple hepatic, splenic and pelvic Klebsiella abscesses, in a 10-year old child; and a post-appendectomy abscess. A cranial CT scan showed the characteristic findings of TB meningitis, although the findings were not seen in an earlier scan upon admission; a subdural abscess was seen as a complication of *Escherichia coli* meningitis. In a third case, an occult craniopharyngioma in a 12-year old girl with a four-month FUO, was unexpectedly seen in a cranial CT, which was done because the child had a first-time seizure; the child did not have symptoms of increased intra-cranial pressure. Cranial MRI helped in the diagnosis of encephalitis cases. Biopsies yielded the diagnosis of Kikuchi-Fujimoto cases, and, more importantly, ruled out a malignancy. Biopsies also made the diagnosis for extra-pulmonary TB cases (spine, peritoneum, bone, disseminated), malignancies and inflammatory bowel disease (IBD), while ruling out intestinal TB disease among the IBD cases.

CONCLUSION

This 27-year study of 171 cases of childhood FUO found the etiology to be infectious in two-thirds of cases, followed by collagen-vascular disease and malignancy. There was no diagnosis identified in 5%. The most common infections were EBV mononucleosis, TB, enteric fever, sinusitis, pneumonia and incomplete Kawasaki disease. The most common collagen vascular diseases were JIA and SLE. Hemophagocytic lymphohistiocytosis was the most common miscellaneous cause. Lymphoma was the most common malignancy. EBV mononucleosis, sinusitis, pneumonia, incomplete Kawasaki disease, HLH, Kikuchi-Fujimoto disease and lymphoma are childhood FUO etiologies that have not been often reported in previous local reports.

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ORIGINAL ARTICLE

Etiology, Treatment and Outcome of Children Diagnosed with Secondary Hemophagocytic Lymphohistiocytosis in A Tertiary Hospital

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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: Hemophagocytic lymphohistiocytosis (HLH) is a clinical syndrome that is associated with a variety of underlying conditions leading to the same characteristic hyperinflammatory phenotype.

Objectives: To describe the clinical profile of patients diagnosed with HLH admitted between January 1, 2010 to September 30, 2019 in a tertiary care hospital.

Methods: Retrospective descriptive study of pediatric patients diagnosed with HLH in a tertiary care hospital.

Results: Eleven subjects were included in the study. Age distribution showed a bimodal pattern: < 5 years old (5, 46%) and 10-15 years old (4, 36%). Male to female ratio is 4.5:1. All patients presented with fever (100%) followed by hepatomegaly (5, 45%) and splenomegaly (4, 36%) on physical examination. All eleven subjects fulfilled the following criteria for HLH such as fever, splenomegaly, and hyperferritinemia. Six out of eleven showed hypofibrinogemia (55%) and hypertriglyceridemia (55%). Among the eleven with two cell cytopenia, five presented with anemia (46%), six with neutropenia (55%), while all of them had thrombocytopenia (100%). Other laboratory findings noted were elevated ALT (5, 46%), CRP (4, 36%), AST (3, 27%), alkaline phosphatase (3, 27%), and hyponatremia (3, 27%). EBV and dengue (3, 27%) were the most common etiologies. Pneumonia (3, 27%) was the most common complication, followed by sepsis (2, 18%). All but one patient were responsive to either dexamethasone (7, 64%) and or IVIG (5, 45%) and chemotherapy (1, 9%). The antibiotic most commonly used was piperacillin tazobactam (3, 27%). The median hospital stay was 17 days. There was one mortality (9%).

Conclusion: HLH should be considered in children presenting with prolonged fever, hepatomegaly, and or splenomegaly, with hyperferritinemia, thrombocytopenia, anemia and neutropenia.

KEYWORDS: *Hemophagocytic lymphohistiocytosis, retrospective descriptive study*

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is an infrequently seen and diagnosed illness that is associated with significant morbidity and mortality. In the Philippines, there were only 232 cases recorded based on the PPS registry over a 10-year period (2009 to September 2019). The illness was loosely termed histiocytosis in the past, but was defined more in the 2004 diagnostic criteria for HLH.[1] Primary HLH is a familial genetic illness, often presenting within the first few months after birth, although 20% may manifest at more than 2 years of age.[2] Secondary HLH is that which occurs in the absence of a genetic predisposition and are due to infections, malignancies and autoimmune diseases.

The pathogenesis of primary HLH involves a malfunction of immunoregulation. When cells are infected by invading organisms, cytotoxic T-lymphocytes (CTL) act against infected cells and antigen-presenting cells (APCs). In HLH, CTLs are defective and ineffective, and APCs continuously stimulate CTLs, causing a continuing production of cytokines, especially interferon-gamma, which influence macrophage activation.[2]

Clinically, HLH manifests with prolonged fever, cytopenias and splenomegaly. Various infections may trigger secondary HLH, including Epstein Barr Virus (EBV), cytomegalovirus (CMV), dengue and other bacteria. Epstein Barr Virus has been reported as a frequent cause of HLH and EBV is also a common cause of fever of unknown origin (FUO). It is important to know that an FUO case that is found to be due to EBV may further lapse into, and be complicated by HLH, which has a high mortality rate.[3] It is thus important to be aware of the presence of HLH complicating viral and bacterial infections because treatment for this may entail more than just antimicrobials. It is important to profile pediatric cases with HLH, to improve clinical detection, treatment and to prevent complications associated with the illness.

There are a few studies related to pediatric HLH and published data are from the US and Europe. In the Philippines, there were only two published pediatric studies and both were case reports. With this knowledge gap, this study aimed to characterize the documented pediatric HLH cases admitted between January 1, 2010 to September 30, 2019 in a tertiary care hospital.

The Specific Objectives were as follows:

1. Describe the clinical profile of patients diagnosed with HLH as to Age distribution, sex ratio, clinical manifestations, ancillary work-up findings, medical complications, length of hospital stay, mortality, and
2. Describe the treatment and outcomes of patients diagnosed with HLH

METHODOLOGY

Study Design

This was a retrospective descriptive study of all pediatric patients up to 18 years old seen at a tertiary care hospital between January 1, 2010 to September 30, 2019 with a discharge diagnosis of HLH.

Population

A patient list was obtained from the medical records section by searching ICD 10 code of D76.1. Patient lists from pediatric department staff physicians (hematologist-oncologists, infectious disease specialists, intensivists and gastroenterologists) were likewise included. Electronic medical records (EMR) chart review was done subsequently by the primary investigator. The subjects included in the study fulfilled the five out of eight criteria as follows: fever, splenomegaly, two cell cytopenia (anemia, thrombocytopenia, neutropenia), hypertriglyceridemia and or hypofibrigonemia, hemophagocytosis in bone marrow or spleen or lymph nodes, low or absent NK-call activity, hyperferritinemia and elevated CD 25 level. Subjects who did not fulfill the HLH criteria were excluded. The medical records of eligible patients were subjected to further chart review and the following information were gathered: age distribution, sex ratio, clinical manifestations, ancillary work-up findings, treatment, length of hospital stay, complications, and mortalities.

As for the etiologies, the subjects were diagnosed to have Epstein Barr Virus (EBV) infection based on the clinical diagnosis of infectious mononucleosis characterized by fever, sore throat, petechial or exudative pharyngitis, cervical lymphadenopathy, hepatosplenomegaly, with or without atypical lymphocytosis, with either a normal or mild elevation in the white blood cell count with positive EBV IgM and or EBV PCR. Subjects with dengue fever were diagnosed based on the presence of fever, myalgia or arthralgia, rash, with minor or major hemorrhagic

manifestations, with laboratory findings of thrombocytopenia and an objective evidence of increased capillary permeability and a positive dengue NS1 or dengue IgM result. Cases of sepsis were diagnosed through clinical criteria with positive blood culture growths. Diagnosis of acute lymphoblastic leukemia was based on the bone marrow findings. Juvenile idiopathic arthritis was diagnosed by age of predilection of less than 16 years old with symptom onset of more than or equal to 6 weeks, with presence intraarticular swelling or presence of 2 or more of the following: limitation of movement, tenderness and pain on motion, and warmth on affected area in one or more joints and where infection has been ruled out. Probable drug reaction secondary to antibiotic use, was diagnosed based on clinical history, with appearance of wheals and maculopapular rash after use of the drug.[4]

Data Collection and Statistical Analysis

A standard case-study form was used for each medical chart where relevant data was entered. Descriptive statistics were used in the data analysis.

The variables of interest in the study were determined based on their clinical course as documented in the patient records. This study relied solely on data recorded on the patient's chart and in the instance where the information was not directly stated, the following operational definitions were applied to determine the variables of interest. (See Appendix A for operational definitions)

Ethical Considerations

This study was approved by the MMC Institutional Review Board (IRB) to access the required information needed to complete this research. Patient anonymity was strictly maintained throughout the duration of the study, in compliance with the Data Privacy Act of 2012 (Republic Act 10173). A unique numeric code was assigned to each patient to preserve the anonymity of each subject's personal information.

Patient confidentiality was further maintained by securing all information gathered in the researcher's personal computer that is password protected.

The authors report no disclosures. No potential conflicts of interest were identified. This study was initiated and funded wholly by the principal investigator.

RESULTS

Demographics

A total of 18 cases of pediatric HLH were screened from the data provided by the Medical Records department, combined with consultants' personal patient lists. Seven patients were excluded from the study for not fulfilling the inclusion criteria based on HLH-2004 guidelines, although these patients were diagnosed with Langerhans cell histiocytosis and probable HLH under ICD 10 code D76.1. Patients included in the study were not tested genetically, hence a diagnosis of primary HLH cannot be made.

A total of eleven subjects who were admitted between January 1, 2010 to September 30, 2019 fulfilled the HLH-2004 guidelines. The age, sex, clinical manifestations, laboratory findings, length of hospital stay, complications, and outcome were tabulated as follows:

Table 1: Age and sex profile of pediatric patients with HLH (n=11)

Age (years)	**Frequency (%)**
Less than 5	5 (46)
5 to 9	2 (19)
10-15	4 (36)
Sex	
Male	9 (82)
Female	2 (18)

HLH had a bimodal age distribution, with ages less than five years old (46%) and ten to fifteen years old (36%). It affected more males than females, with a M:F ratio of 4.5:1.

The most common chief complaint was fever (82%). All patients presented with fever, six of whom had fever of less than seven days, from the day of admission up to 2 weeks long; maximum temperature ranged from 38.8C to 40.5C. Other clinical manifestations were body weakness, cough, loss of appetite and loose watery stools.

One patient complained of seizure but had a history of head trauma secondary to fall. Another patient had right shoulder pain with multiple petechiae on the area, but without history of trauma.

Table 2.1: Symptoms of pediatric patients with HLH (n = 11)

	Frequency (%)
Fever	11 (100)
Body weakness	4 (36)
Cough	3 (27)
Loose watery stools	3 (27)
Sore throat	2 (18)
Loss of appetite	1 (9)
Rash	1 (9)
Abdominal pain	1 (9)
Seizure	1 (9)

Common physical examination findings were hepatomegaly followed by splenomegaly. Other findings were bilateral palpable lymphadenopathies on the cervical area and dry lips.

Table 2.2: Physical examination findings of pediatric patients with HLH (n = 11)

	Frequency (%)
Hepatomegaly	5 (45)
Splenomegaly	4 (36)
Lymphadenopathy	3 (27)
Dry lips	3 (27)
Pallor	2 (18)
Epigastric tenderness	1 (9)
Petechiae	1 (9)
Wheals	1 (9)

All subjects presented with splenomegaly, nine identified from ultrasound and two from CT scan. All had hypferritenemia and fulfilled 2 cell cytopenia with either anemia or neutropenia and thrombocytopenia. None were tested for hemophagocytosis in bone marrow or spleen, nor for NK cell activity and CD25 levels.

Table 3.1: Imaging studies and laboratory findings of pediatric patients with HLH

	Frequency (%)
Splenomegaly (Ultrasound or CT scan)	11 (100)
Hyperferritinemia (≥ 500 ug/ml)	11 (100)
Thrombocytopenia (<100000 uL)	11 (100)
Neutropenia (<1000/uL)	6 (55)
Hypertriglyceridemia (≥ 265 mg/dL)	6 (55)
Anemia (<90 g/L)	5 (46)
Hypofibrinogenemia (≤ 1.5 g/L)	3 (50)

The range of elevated ALT, CRP, AST and Alkaline phosphatase were 93 to >8522 mg/dl, 18.8 to 155 mg/L, 257 to 1362 mg/dl, and 105 to 236 u/L respectively. Hyponatremia ranged from 127 to 133 meq/L.

Table 3.2: Other ancillary work-up of pediatric patients with HLH (n = 11)

	Frequency (%)
ALT	
Elevated	5 (45)
Normal	2 (18)
Not done	4
CRP	
Elevated	4 (36)
Normal	0
Not done	6
AST	
Elevated	3 (27)
Normal	2 (18)
Not done	6
Alkaline Phosphatase	
Elevated	3 (27)
Normal	0
Not done	8
Sodium	
Elevated	0
Decreased	3 (27)
Normal	1 (9)
Not done	7
Potassium	
Elevated	0
Decreased	1 (9)
Normal	3 (27)
Not done	7

The most common etiologies for secondary hemophagocytic lymphohistiocytosis were EBV and dengue fever. Patients with EBV presented with fever, hepatosplenomegaly and cervical lymphadenopathy upon admission. The diagnosis was based on clinical manifestations of fever, sore throat, petechial or exudative pharyngitis, cervical lymphadenopathy, hepatosplenomegaly on physical examination and on ultrasound, with or without atypical lymphocytosis, with either a normal or mild elevation in the white blood cell count with positive EBV IgM and or EBV PCR. HLH was suspected due to progression of anemia and thrombocytopenia. Patients with dengue were worked up for HLH due to fever of more than seven days with splenomegaly which was not apparent upon admission. The sepsis cases (*Salmonella spp* and *Klebsiella spp*) both had culture growths but despite appropriate antibiotic treatment, fever persisted. In the cases of juvenile idiopathic arthritis and drug reaction the patients had prolonged fever with presence of persistent thrombocytopenia despite transfusion. The patient with hypersensitivity reaction secondary to antibiotic use also tested positive for EBV IgM; the patient had prolonged fever, splenomegaly, accompanied by neutropenia and thrombocytopenia. Patients had a median hospital stay of 17 days, ranging from 7 days to 28 days.

Table 4.1: Etiology and complications of pediatric patients with HLH (n = 11)

	Frequency (%)
EBV	3 (27)
Dengue	3 (27)
Sepsis (Klebsiella spp, Salmonella spp)	2 (18)
Pneumonia	1 (9)
Juvenile idiopathic arthritis (JIA)	1 (9)
Acute lymphoblastic leukemia (ALL)	1 (9)
Drug reaction	1 (9)

The most common complication was pneumonia. Three patients were diagnosed during the second to fifth hospital stay, and they presented with cough and tachypnea, with physical examination finding of rales during the course of admission. One patient had sepsis secondary to *Klebsiella pneumoniae* and one secondary to *Candida parapsilosis*. The patient with *Klebsiella pneumoniae* was still febrile after 16 days of hospitalization, with an epidural hematoma, status post craniotomy, and was persistently febrile despite antibiotic treatment. The patient with fungal sepsis was a case of aplastic anemia with pneumonia and had been febrile for 13 days prior to admission. The youngest patient at 5 months had uncontrolled sepsis secondary to Salmonella infection with anemia, hepatosplenomegaly and pericardial effusion. The patient died on the 11th hospital day from DIC and pulmonary hemorrhage while receiving IVIG infusion at the intensive care unit.

Table 4.2: Complications of pediatric patients with HLH (n = 11)

	Frequency
Pneumonia	3 (27)
Sepsis	2 (18)
Disseminated Intravascular Coagulopathy (DIC); Pulmonary Hemorrhage - Mortality	1(9)

Seven patients were treated with dexamethasone. Among three of seven patients on dexamethasone, one had EBV and two had dengue fever; all three improved with steroids alone with defervescence after one to five days of treatment. Three patients on steroids were cases of EBV, dengue and autoimmune arthritis, for whom dexamethasone was started after IVIG infusion. The patient with acute lymphoblastic leukemia defervesced after receiving dexamethasone, etoposide, cyclosporine, L-asparaginase and methotrexate.

Two patients were treated with IVIG. The first patient was a case of drug reaction secondary to cotrimoxazole who improved after one day of IVIG infusion. The other patient was an infant with sepsis secondary to Salmonella, who expired while receiving IVIG infusion, secondary to DIC and pulmonary hemorrhage.

All patients received antibiotic treatment prior to the diagnosis of HLH, except for one. They were treated for pneumonia, sepsis and other nosocomial infections due to prolonged hospital stay. The most frequent antibiotics used were piperacillin tazobactam, amikacin, cefuroxime, ceftriaxone and cotrimoxazole.

Table 5.1: Mode of treatment of pediatric patients with HLH (n = 11)

	Frequency
Dexamethasone	7 (64)
IVIG	5 (45)
Etoposide	1 (9)
Cyclosporine	1 (9)
Methotrexate	1 (9)
L-Asparaginase	1 (9)
Antibiotic	10 (91)
Antifungal	2 (18)

DISCUSSION

Hemophagocytic lymphohistiocytosis (HLH) is a clinical syndrome that is associated with a variety of underlying conditions leading to the same characteristic hyperinflammatory phenotype. It is a life-threatening hyperinflammatory syndrome.[5] Secondary HLH may develop as a result of a potent stimulus that activates the immune system. Virus-associated hemophagocytic syndrome has been described in immunocompromised hosts. It can occur in all age groups, however, there is no data regarding the incidence of acquired forms.[6] The pathophysiology involves excessive inflammation and tissue destruction due to abnormal immune activation. This dysregulation is thought to be caused by the absence of normal downregulation of activated macrophages and lymphocytes.[7] A study done by Zoller et al. demonstrated that the hemophagocytic macrophages have a pathologic role in the development of acute inflammation-induced anemia. They also determined that hemophagocytosis is triggered by interferon gamma and its direct action leads to development of severe consumptive anemia and other cytopenias.[8] The classic clinical picture of HLH is that of a prolonged fever unresponsive to antibiotics, with hepatosplenomegaly. Fever may be non-specific, and may be accompanied by signs of an upper respiratory or gastrointestinal infection. Less common are lymphadenopathy, icterus, and an uncharacteristic rash or edema. Neurologic signs such as seizures or cranial nerve palsies may be present in one third of patients. Anemia and thrombocytopenia are early signs.[6]

In our study, age distribution showed a bimodal pattern affecting children less than five years old (46%) and 10-15 years old (36%), a finding somewhat different from published data abroad. In a study done in Texas the mean age at diagnosis was at 2.1 years old with a slight female predominance (61%).[9] In a Chinese study, the median age at diagnosis was 2.2 years with a male:female ratio of 1.27:1.[10]

On physical examination, hepatomegaly and splenomegaly were present in 45% and 36% respectively. Clinical hallmarks of HLH are persistent fever, hepatosplenomegaly and neurological symptoms.[2] In our study, only one patient had seizure; this was attributed to an epidural hematoma secondary to trauma. Initial manifestations can resemble common infections, fever of unknown origin and other autoinflammatory disorders.[2] In a Chinese study, all subjects presented with fever upon diagnosis similar to our study. However, findings of hepatomegaly (86%) and splenomegaly (73.7%) were more common in non-active disease as compared to our study.[10]

A common finding in this study was splenomegaly by ultrasound or CT imaging. All subjects had thrombocytopenia with either anemia or neutropenia, hypertriglyceridemia, hypofibrinogemia, hyperferritinemia. Laboratory findings of HLH include two cell cytopenia, hypertriglyceridemia, hypofibrogenimia, hyperferritinemia, hemophagocytosis in bone marrow or spleen, low or absent NK cell activity and elevated CD25.[1] In a study done by George, M., laboratory findings upon diagnosis of secondary HLH were cytopenias (80%), hypertriglyceridemia (40%), hypofibrogenemia (40%), hyperferritinemia (95%), and decreased NK cell activity (30%).[11] A characteristic finding was a high percentage of hyperferritinemia in both studies. Serum ferritin is an easily available and valuable disease marker of HLH. A level above 10,000 ug/L in children is 90% sensitive and 96% specific.[12] Laboratory values in HLH include high ferritin, triglycerides, transaminases, bilirubin (mostly conjugated), and sCD25 (an α-chain of the soluble interleukin- 2 receptor), and decreased fibrinogen. Ferritin, may reach levels of 50,000 ng L^{-1} and more, and is an easily available and valuable disease marker of HLH. A level above 10,000 µg L^{-1} in children was 90% sensitive and 96% specific for HLH. An inflammatory hepatitis-like periportal infiltrate in the liver with lymphocytes and histiocytes, leading to obstructive jaundice is typical for HLH.[13]

Other abnormal ancillary findings noted in our study showed elevated ALT, AST, alkaline phosphatase, CRP and hyponatremia. These findings are consistent

with HLH-2004 diagnostic and therapeutic guidelines, which includes hepatic enzyme abnormalities, hypoproteinemia, hyponatremia, high VLDL, low HDL.[1]

Associated etiology in the study were, most commonly, EBV and dengue virus. Viruses are the predominant triggers in secondary HLH; protozoal, bacterial, and fungal infections have also been reported such as L*eishmania, Mycobacterium tuberculosis* and *Salmonella typhimurium.* Malignant disease such as malignant lymphoma and leukemia are less common in children than in adults. The major subtype of secondary HLH is induced most commonly by a primary EBV infection followed, by other infection or lymphoma associated HLH.[14,15] The incidence of EBV-HLH is high in Asian countries, suggesting an underlying genetic background. EBV infected B cells induce an increase in cytotoxic T cells, followed by macrophage activation having an uncontrolled immune response which brings about hypercytokinemia.[14] In a case series done by Pal, P. et al., all dengue patients presented with fever of more than 7 days, accompanied by persistent or progressive cytopenias, with unusual organomegaly with a negative blood culture.[16] As in our study, the cases of dengue, presented with fever longer than expected, with progressive cytopenia and splenomegaly which was absent on admission. Health care workers should be aware of dengue-induced HLH because it can be a potential cause of complications and death.

Complication reported in our study were pneumonia, followed by sepsis, DIC and pulmonary hemorrhage. In a similar study by Tsuge, M. et al., an 11 month old male was hospitalized for a 1 day history of fever where blood test revealed leukocytosis and an elevated CRP. Initial consideration was mild pneumonia, he was given a single dose of ceftriaxone and was discharged on ceftizoxime. However, fever persisted, blood tests showed progressive neutropenia and increased CRP, prompting readmission. Blood culture grew *S. pneumoniae* on blood culture. He was diagnosed with HLH based on prolonged fever, neutropenia, anemia, hepatosplenomegaly, hemophagocytosis on bone marrow and elevated triglycerides, ferrititin and sIL-2r. Pulse methylprednisolone, prednisolone and cyclosporin A were started. Thereafter, clinical status and blood tests started to improve.[17] A chest radiograph finding of interstitial pneumonia was also frequently seen in patients with EBV-HLH.[3] Many patients were admitted at the intensive care unit because of complications associated with a delay in diagnosis.[18]

All patients in the study were initially treated with antibiotics. Three patients were treated with dexamethasone alone. Three were treated with dexamethasone after IVIG infusion. Two were treated with IVIG alone, one of whom expired. The aim of treatment is to suppress the hyperinflammatory component of the disease by suppressing activated cytotoxic lymphocytes and macrophages.[2] Milder forms of HLH respond to corticosteroids with or without immunoglobulin, to suppress hyperinflammation. However, mild cases may rapidly worsen in a short period of time.[13] Early recognition of HLH with initial treatment of IVIG and or corticosteroids is important to prevent disease progression. The goal of treatment is to suppress the severe hyperinflammation. A second aim is to kill the pathogen-infected APCs to remove the stimulus for the ineffective activation of the cytotoxic cells. Hyperinflammation caused by hypercytokinemia can be suppressed by corticosteroids. Dexamethasone is preferred since it crosses the blood brain barrier better. Cyclosporin is used to inhibit activation of T-lymphocytes. Etoposide is highly active in monocytic and histiocytic disease. According to the HLH-2004 protocol, initial therapy from weeks 1-8 is based on etoposide, dexamethasone and cyclosporine and in cases of CNS-reactivation, intrathecal therapy with methotrexate and prednisolone is recommended. In cases of reactivation triggered by infections, broad-spectrum antibiotics, antiviral therapy, and antifungal therapy should be considered as supportive measures. Survival for patients have dramatically improved.[6] Long-term outcomes of patients treated with HLH-94 trial indicate a 50-60% complete response to therapy and approximately 20% mortality within 6 months of diagnosis, from inadequate disease control. About 54% will experience long term survival.[19]

Most patients in the study were discharged (91%), with one mortality (9%) while undergoing IVIG treatment secondary to uncontrolled sepsis, DIC and pulmonary hemorrhage. Patients dying from complications due to infection have been reported in 40-60%.[1] Sepsis-induced thrombocytopenia was related to peripheral consumption such as DIC.[18]

As our study could not document primary HLH, all our cases were labeled as secondary HLH. These were due to infections like EBV, dengue, sepsis, malignancy such as ALL, autoimmune disease like JIA, and hypersensitivity reaction. HLH should be considered when fever is continuing beyond expected, as in patients who continue to be febrile in spite of appropriate antibiotic use, or fever beyond the usual course of illness like dengue. HLH should be considered when cytopenia evolves during the hospital course or when splenomegaly appears, when none was present earlier. HLH may lead to morbid cytopenias and DIC, and treatment with IVIG and or dexamethasone is often only considered when the diagnosis has been made. It is important for clinicians to have a high index of suspicion as mild disease can evolve to a life threatening event. The results and analysis from this study have potential societal benefits, which will directly or indirectly benefit the participants through health systems delivery strengthening or improvements in implementation or policy change.

The limitation of this study was that other diagnostic tests were not available in our institution, such as CD 25, NK cell activity and hemophagocytosis in bone marrow, hence data for some patients may have been lacking.

CONCLUSION

During a ten year period, eleven children with HLH were seen with ages of less than five years old (46%) and ten to fifteen (36%), with a male to female ratio of 4.5:1. All presented with fever followed by hepatomegaly and splenomegaly on physical examination. All subjects fulfilled five criteria for HLH such as fever, splenomegaly, two cell cytopenia - either anemia, neutropenia, or thrombocytopenia; hyperferritinemia, hypofibrinogemia and or hypertriglyceridemia. Other laboratory findings were elevated ALT, CRP, AST, alkaline phosphatase, and hyponatremia. EBV and dengue were the most common etiologies, and the most common complications were pneumonia and sepsis. All but one patient was responsive to either dexamethasone and or IVIG and chemotherapy. The median hospital stay was 17 days with one mortality.

RECOMMENDATIONS

A larger sample is recommended for future researchers to compare clinical profile and outcomes of pediatric HLH. Future researchers may include ethnicity and race as a factor to examine if this plays a role in the outcome of the disease. A multi-institutional study is recommended as there may be variations in terms of recognition and management of the disease.

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APPENDIX A – OPERATIONAL DEFINITIONS

1. Hemophagocytic lymphohistiocytosis (HLH) – characterized by abnormal proliferation of macrophages associated with hypercytokinemia.[20]
   1a. Primary HLH – rare autosomal disorder, occurring before the first year of life reported up to age 8.[20]
   1b. Secondary HLH – there is an acquired cause, which is a result of a strong immunologic activation, commonly seen in an immunocompromised host. Common triggers are severe infection, malignancy and inflammatory disorders.[5]
2. Criteria for diagnosis of HLH (either 2a. or 2b. is fulfilled)[1]
   2a. Molecular diagnosis consistent with HLH
   2b. Diagnostic criteria for HLH (5 out of 8 criteria)
   i. Fever – temperature of 38C and above measured via rectal or axilla [21]
   ii. Splenomegaly – a palpable splenic edge more than 2cm below the left costal margin and on imaging with length above the upper limits of normal age, measured from the dome to tip on ultrasound [22]

Age	Measurement
12 months	7 cm
6 years old	9.5 cm
12 years old	11.5 cm
≥15 years old	Girls – 12 cm Boys – 13 cm

   iii. Cytopenias (affecting ≥2 lineages in the peripheral blood)
   Hemoglobin <90 g/L (infants <4 weeks, hemoglobin <100 g/L)
   Platelets < 100000/μl
   Neutrophils < 1000 /μl
   iv. Hypertryglyceridemia and/or hypofibrigonemia
   Fasting triglycerides ≥ 265 mg/dL
   Fibrinogen ≤ 1.5 g/L
   v. Hemophagocytosis in bone marrow or spleen or lymph nodes
   vi. Low or absent NK-cell activity
   vii. Ferritin ≥ 500 μg/L
   viii. Soluble CD25 ≥ 2400 U/L
3. Hepatomegaly – palpable liver edge more than 2 cm below the right costal margin.[4]
4. Laboratory Examinations
   4a. Alanine aminotransferase (ALT, SGPT) – reference for normal values according to age are as follows:[23]
   i. 1 to 12 months – 12 – 45 U/L
   ii. 1 to 19 years old – 5 – 45 U/L
   4b. Aspartate aminotransferase (AST, SGOT) – reference for normal values according to age are as follows:[23]
   i. 1 to 3 years old – 20 – 60 U/L
   ii. 3 to 9 years old – 15 – 50 U/L
   iii. 10 to 15 years old – 10 – 40 U/L
   iv. 16 to 18 years old (Male) – 15 – 45 U/L
   v. 16 to 18 years old (Female) – 5 – 30 U/L
   4c. Alkaline phosphatase – reference for normal values according to age are as follows:[23]
   i. 1 to 9 years old – 145-250 U/L
   ii. 10 to 11 years old – 140-560 U/L
   iii. 12 to 13 years old (Male) – 200-495 U/L
   iv. 12 to 13 years old (Female) – 105-420 U/L
   v. 14 to 15 years old (Male) – 130-525 U/L
   vi. 14 to 15 years old (Female) – 130-525 U/L
   vii. 16 to 19 years old (Male) – 65-260 U/L
   viii. 16 to 19 years old (Female) – 50-130 U/L
   4d. C-reactive protein - reference for normal values according to age are as follows:[23]
   i. 91 days to 12 months (Male) – 0.8-11.2 mg/L
   ii. 91 days to 12 months (Female) – 0.5-7.9 mg/L
   iii. 13 months to 3 years old (Male) – 0.8-11.2 mg/L
   iv. 13 months to 3 years old (Female) – 0.5-7.9 mg/L
   v. 4 to 10 years old (Male) – 0.6-7.9 mg/L
   vi. 4 to 10 years old (Female) – 0.5-10 mg/L
   vii. 11 to 14 years old (Male) – 0.8-7.6 mg/L
   viii. 11 to 14 years old (Female) – 0.6-8.1 mg/L
   ix. 15 to 18 years old (Male) – 0.4-7.9 mg/L
   x. 15 to 18 years old (Female) – 0.6-7.9 mg/L

ORIGINAL ARTICLE

Clinical Profile of Pediatric Patients with Leptospirosis admitted at a Tertiary Government Hospital

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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: In the Philippines, Leptospirosis is a seasonal but common and prevalent disease with an average of 680 cases and 40 deaths annually. Cases result from exposure to contaminated flood, water, or soil. Several studies showed that males are more commonly affected, who are believed to be more exposed to the outdoor environment. In terms of pediatric population, early diagnosis is based mainly on clinical and epidemiological factors.

Objective: This study was conducted to determine the clinical features and outcomes of pediatric leptospirosis, as well as determine the prognostic factors associated with mortality.

Methodology: A descriptive retrospective study was done in a tertiary hospital from January 2007 – December 2019. Review of all cases that satisfy the diagnosis of Leptospirosis by WHO Criteria (2003) was done. The data extracted from the chart were encoded using Microsoft Excel; processed and analyzed using STATA SE 15 to generate the required output.

Results & Conclusion: In this 12-year study, a total of 85 cases of leptospirosis in children, aged 0-18 years, were reported. Leptospirosis predominates in males in the adolescent age group. It is noted all year round but noted mostly during the rainy months which increases the risk to exposure to contaminated water through wading, especially in the cities of Navotas, Malabon and Tondo. The mean duration of symptoms was 3.6 days. The most common clinical findings noted in this study were fever, gastrointestinal symptoms, conjunctival suffusion, oliguria, calf tenderness and headache. Abnormal laboratory findings were leukocytosis, neutrophilia, thrombocytosis, elevated BUN and creatinine, hypokalemia and hyponatremia. Significant correlation with poor outcome was found in patients who have had pulmonary hemorrhage.

KEYWORDS: *Leptospirosis, leptospirosis in children, clinical profile*

INTRODUCTION

Leptospirosis is a common and widespread zoonosis caused by aerobic and motile spirochetes of the genus *Leptospira*. Ten out of the twenty-two identified species under this genus are considered pathogenic, the remaining seven are non-pathogenic, free-living saprophytes, and five are of unclear pathogenicity. It is a disease of global importance occurring both in rural and urban setting. It is highly prevalent in the Asia Pacific Region resulting in outbreaks in developing countries that are most frequently related to normal daily activities, overcrowding, poor sanitation and climatic conditions. In the Philippines, there is an average of 680 cases, and 40 deaths reported every year with a prevalence of 10/100,000.[1] It has a seasonal occurrence, with peak incidence occurring in the months of July to October.

Humans can become infected through mucous membranes or abraded skin or by ingestion of contaminated water. The spectrum of the disease ranges from asymptomatic to severe infection with multi-organ dysfunction and death. The disease manifestation depends on the infecting serogroup and the hosts, and symptoms range from mild flu-like illness to severe disease that may include jaundice, renal failure (Weil's disease), meningitis, myocarditis, hemorrhagic pneumonitis or hemodynamic collapse. Early diagnosis is essential since the progress of the disease to a severe state is rapid and may be irreversible, while early appropriate treatment results in cure.

In our country, several studies have shown the clinical features of leptospirosis; and based on the CPG guidelines of leptospirosis,[1] any individual presenting with acute febrile illness of at least 2 days and either residing in a flooded area or has high risk of exposure and presenting with at least two of the following symptoms: myalgia, calf tenderness, conjunctival suffusion, chills, abdominal pain, headache, jaundice, or oliguria should be considered a suspected leptospirosis case. This WHO criteria was established in 1980 when the WHO working group on the Formulation of Philippine Journal of Internal Medicine Leptospirosis Guidelines met in Manila. This is also being used in the new guideline released by the Department of Health (Philippines) entitled DOH Guidelines for Leptospirosis for Hospitals in 2019. The checklist consists of three main areas: clinical features (Part A), epidemiological factors (Part B) and laboratory findings (Part C).

The incubation period is generally 5 – 14 days with a range of 2 to 30 days. It presents in two (2) forms: anicteric (mild) or icteric (severe) leptospirosis. Anicteric leptospirosis is often characterized by abrupt onset of fever, headache, muscle aches, malaise and prostration. Icteric leptospirosis, on the other hand, may present with impaired renal and hepatic function, hemorrhage, vascular collapse and even severe alterations in consciousness. This is also called severe leptospirosis or Weil syndrome.[2]

Definitive diagnosis, based on the WHO criteria, requires isolation of leptospires in culture from any clinical specimen or demonstration by dark field microscopy. Culture and isolation still remains as the gold standard but due to the advent of serologic testing, diagnosis can be made with microscopic-agglutination test, a serogroup-specific assay using live antigen suspension of leptospiral serovars and dark-field microscopy for agglutination.

Results from this study can be used to guide clinicians in the early recognition and management of leptospirosis to prevent complications which can lead to severe morbidity and mortality.

RESEARCH OBJECTIVES

This study established the clinical profile and outcomes of pediatric patients diagnosed with leptospirosis in a tertiary hospital in Tondo from January 2007 to December 2019. It likewise determined the prognostic factors associated with mortality.

Specific Objectives were as follows:

1. To describe the demographic characteristics of pediatric patients diagnosed with leptospirosis based on WHO Criteria for Leptospirosis as to age, gender, locality.
2. To describe the clinical manifestations and laboratory features of leptospirosis among pediatric patients admitted at a tertiary hospital.
3. To determine the outcome of pediatric patients with confirmed leptospirosis, and

To identify the risk factors associated with mortality among pediatric patients.

OPERATIONAL DEFINITION OF TERMS AND VARIABLES

1. Albuminuria - is a pathological condition where more than +1 albumin/protein is present in the urine.
2. Anemia - laboratory findings of deficiency of hemoglobin (<13g/dL) in the blood
3. Confirmed Leptospirosis – refers to the patients/cases with suspected leptospirosis based on the clinical signs and symptoms and positive MAT.
4. Hematuria - the presence of red blood cells (>5 RBC/hpf) in the urine
5. LATS (Leptospira Antigen- Antibody Agglutination Test (Leptospira Serology Bio-Rad) detects Leptospira antibody in human serum through agglutination reaction which may persist for years. This is used as a screening test but is NOT sensitive. A positive result should be confirmed with MAT.
6. Leukocytosis – laboratory finding where there is a raised white blood cell count (the leukocyte count) above the normal range (WBC >10,000)
7. Microscopic agglutination test (MAT) – gold standard for the definitive diagnosis of leptospirosis. It determines agglutinating antibodies in the serum of a patient by mixing it in various dilutions with live or killed formalized leptospires. Antileptospiral antibodies present in the serum cause leptospires to stick together to form clumps. This clumping process is called agglutination and is observed using dark-field microscopy. Agglutinating antibodies can be of both IgM and IgG classes. Fourfold or greater rise in titer or seroconversion on paired samples obtained at least 2 weeks apart is diagnostic for leptospirosis
8. Pyuria - refers to urine which contains pus. Defined as the presence of >5 pus cells/hpf.
9. Presumptive diagnosis = 26 or more from Part A, or parts A and B scores OR 25 or more from the total of Parts A, B and C in the WHO criteria in the diagnosis of leptospirosis.
10. Risk Exposures – refers to the condition—occupational, environmental, recreational and behavioral which the patient has come in contact with 4 weeks before the onset of illness.
11. Thrombocytopenia – patient with a decreased platelet count (Normal = >150, 000 to 450, 000/µL)
12. Weil's disease – most severe form of leptospirosis, characterized by jaundice, renal dysfunction, and hemorrhagic diathesis with/ without pulmonary involvement.

METHODOLOGY

Research Design

Descriptive retrospective study.

Research Subject

All children, 1-18 years of age, admitted at a tertiary hospital from January 2007- December 2019 whose history and clinical manifestations satisfy the diagnosis of Leptospirosis as defined by the WHO Criteria (2003) were included in the study.

Exclusion Criteria

Patients who did not satisfy the WHO criteria in the diagnosis of Leptospirosis.

Study Procedure

The study was conducted in a tertiary government hospital. A 12-year retrospective descriptive study was made and all children admitted from January 2007 – December 2019, who satisfied the presumptive diagnosis of leptospirosis based on the WHO Criteria (Clinical and epidemiologic factors) were included. The list of names of all patients with leptospirosis were recovered in the medical records section and were reviewed individually. All charts with a discharge diagnosis of leptospirosis regardless of whether its admitting diagnosis was leptospirosis or not, were selected for review. Demographic data such as age, sex, residence address, and type of exposure were recorded. Chief complaint and clinical presentation during admission were noted. All available data in the charts were recorded. The complete blood count and platelet count, urinalysis, serum creatinine, Blood Urea Nitrogen (BUN), Prothrombin time (PT), Partial Thromboplastin time (PTT), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Microagglutination Test (MAT), and Leptospira Antigen-Antibody Agglutination Test (LATS) were tabulated. Outcomes among patients in the study were also determined.

Data Collection and Analysis

Frequency distribution and summary statistics were generated for descriptive analyses. Test of

association was done using Chi-square test of Independence or Fisher's exact test. Odds ratios were generated using Logistic regression. All were tested at 5% level of significance.

The data extracted from the charts were encoded in Microsoft Excel. The data were processed and analyzed using STATA SE 15 to generate the required output.

Ethical Consideration

Ethics approval was obtained by the investigator from the Ethics and Review Board prior to the conduct of the study. A waiver of informed consent was requested and granted by the Ethics Board since the study to be conducted is a chart review, and the feasibility of contacting all patients since 2007 will be difficult for the principal investigator.

RESULTS

A total of 90 patients were eligible to be included in this study but only 85 charts were retrieved from the Medical Records Section. All of these 85 charts were complete with a 100% retrieval rate. This study included 85 patients.

In this 12-year study, 29 leptospirosis cases (34.1%) were aged 13 to 16 years old with a mean age of 12.6 years. The majority of the subjects were boys (84.7%). Patients were mostly living in Navotas (35.3%), a highly urbanized city in Metro Manila and is known as the "Commercial Fishing Hub of the Philippines" (see Table 1).

TABLE 1. Frequency distribution of pediatric patients by Age, Sex, and Location

Characteristic	Freq	%
Age group (years)		
1-3	1	1.2
4-6	5	5.9
7-9	13	15.3
10-12	20	23.5
13-16	29	34.1
17-18	17	20.0
Sex		
Male	72	84.7
Female	13	15.3
Location		
Navotas	30	35.3
Malabon	24	28.2
Tondo	24	28.2
Caloocan	6	7.1
Samar	1	1.2
Total	85	100.0

It can be noted in our study that most frequent cases (40) have been observed in the year 2018 when Metro Manila experienced 24-hour non-stop torrential rains and with almost the same amount of rain as notorious Typhoon Ketsana (Ondoy) in 2009 (see Figure 1). No cases were reported from 2007 to 2010.

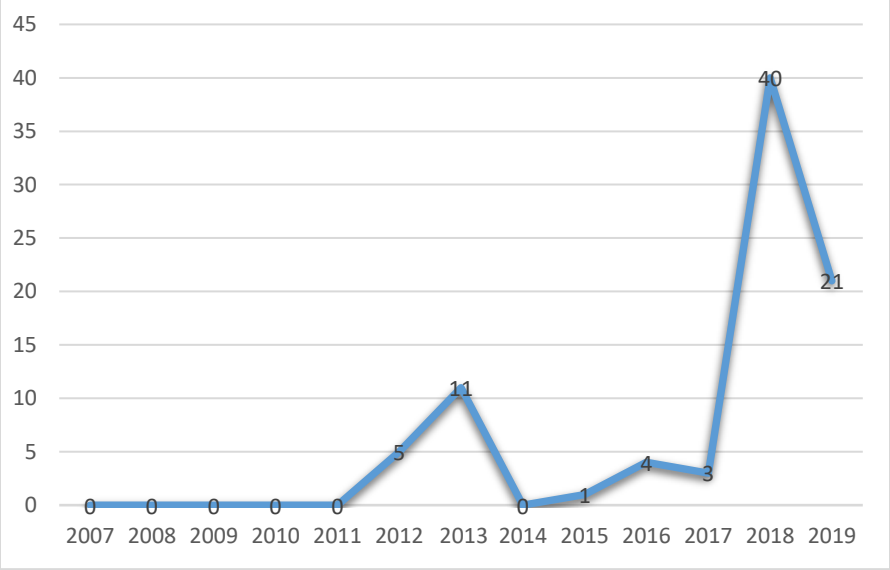

Figure 1. Annual number of Leptospirosis cases from 2007 to 2019

A significant decrease in cases was noted in 2019 showing an effective campaign of the Department of Health (Philippines) against Leptospirosis. Based on their report, there was a decrease of 58% in the reported cases all over the country.[2] Cases were observed all year-round and significantly peaked during the month of August which is typically a rainy season in the country (see Figure 2). In this study, cases were only reported during the rainy months in our country.

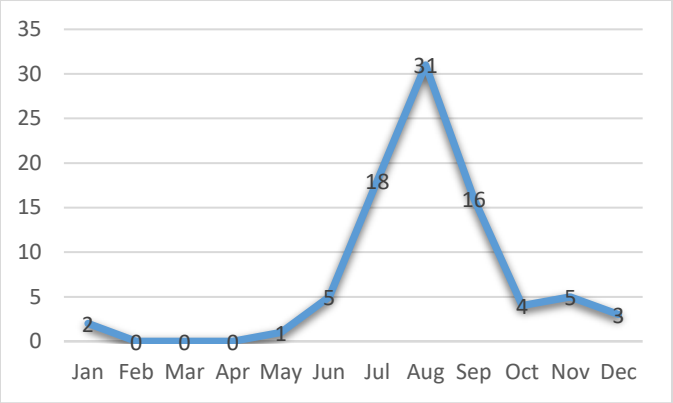

Figure 2. Number of cases per month (2007-2019)

Our study also corroborated previous reports that wading or swimming through possible contaminated water topped the exposition factor for leptospirosis transmission (see Table 3).

TABLE 3. Number of cases per type of exposure

Type of Exposure	Freq	%
Wading	60	54.5
Denies	12	21.8
Evacuation center	1	1.8
No data	12	21.8
Total	85	100.0

The most common presenting symptoms was fever (98.8%), while the mean average duration of symptoms was 3.6 days with a range from one to four days (76.5%). Similarly, fever (70.6%) was the most frequently encountered chief complaint among patients, followed by abdominal pain (7.1%), vomiting (4.7%), anuria (3.5%) and chills (2.4%) (see Tables 5 – 8).

TABLE 5. Number of cases per initial symptoms

Initial symptoms	Freq	%
Fever	84	98.8
Vomiting	1	1.2
Total	85	100.0

TABLE 6. Number of cases per duration of symptoms

Duration of symptoms (days)	Freq	%
1-4	65	76.5
5-7	19	22.4
8-10	1	1.2
Total	85	100.0

TABLE 7. Summary statistics of duration of symptoms

	n	Mean	SD	Min	Max
Duration of symptoms	85	3.6	1.6	1	8

TABLE 8. Number of cases per chief complaint

Chief Complaint	Freq	%
Fever	60	70.6
Abdominal pain	6	7.1
Vomiting	4	4.7
No urine output	3	3.5
Chills	2	2.4
Blank stare	1	1.2
Body malaise	1	1.2
Body weakness	1	1.2
Conjunctival suffusion	1	1.2
Difficulty of breathing	1	1.2
Epigastric pain	1	1.2
Gasping	1	1.2
Headache	1	1.2
Hypogastric pain	1	1.2
Jaundice	1	1.2
Total	85	100.0

Genito-Urinary Tract Manifestations

Oliguria was seen in 28 patients (32.9%), anuria in 1 patient (1.1%), dysuria in 3 patients (3.5%) while 53 patients had no genito-urinary symptoms. Twenty-nine cases developed acute kidney injury (34.1%), where twelve patients underwent renal replacement therapy (7 hemodialysis, 5 peritoneal dialysis).

Bleeding Manifestations

Sixty-six patients (77.6%) did not have any hemorrhagic manifestations, while 9 patients each had hemoptysis (10.5%) and hematuria/tea colored urine (10.5%), and 1 patient had epistaxis (1.1%).

Gastro-Intestinal Manifestations

Most cases in our study developed vomiting which was noted in 51 patients (60%) followed by abdominal pain in 38 patients (44.7%), and diarrhea in 15 patients (17.6%). Nineteen patients did not develop any gastrointestinal symptoms.

Central Nervous System Manifestations

Twenty-two patients presented with headache (25.8%), 2 cases of change in sensorium and 60 cases (70.5%) did not have any central nervous system manifestations.

Other Clinical Manifestations

Other manifestations seen were conjunctival suffusion (57.6%), calf tenderness (25.8%), presence of wound/skin lesion (20%), muscle/joint pains (20%), jaundice (17.6%), icteric sclerae (14.1%), cough/dyspnea (14.1%), malaise (12.9%), rales (7%), chills (5.8%), edema (2.3%) and shock (2.3%).

Laboratory Characteristics

Thirty-eight patients (45.2%) were found to be thrombocytopenic and the remaining forty-six had normal platelet counts (see Table 10).

Leukocytosis is present in 47 patients (55.9%), and anemia in 34 patients (40.4%). Fifty-one patients had elevated creatinine (60%) coinciding with 49 patients who had elevated BUN (57.6%). Twenty-three patients showed hematuria (27.3%), 34 had albuminuria (40.4%) and 32 patients (38%) showed pyuria. Not all patients underwent liver function testing; amongst the patients tested, only 7 had elevated ALT (13.7%) and 17 patients with elevated AST (32.6%); 4 patients had elevated bilirubin levels; 5 patients had prolonged prothrombin time (15.1%) and 15 cases with prolonged aPTT (45.4%). In terms of electrolytes, 40 cases had hyponatremia (47%) and 38 cases had hypokalemia (44.7%).

TABLE 9. Clinical manifestations

	Frequency	Percent
Genito-urinary tract manifestations		
None	53	62.3%
Oliguria	28	32.9%
Dysuria	3	3.5%
Anuria	1	1.1%
Bleeding manifestations		
None	66	77.6%
Epistaxis	1	1.1%
Hemoptysis	9	10.5%
Hematuria/tea colored urine	9	10.5%
Gum Bleeding	0	-
Gastrointestinal manifestations		
None	19	22.3%
Abdominal Pain	38	44.7%
Vomiting	51	60%
Diarrhea	15	17.6%
Central nervous system manifestations		
None	60	70.5%
Headache	22	25.8%
Seizure	0	-
Change in sensorium	2	2.3%
Behavioral Changes	1	1.1%
Other clinical manifestations		
Edema(facial)	0	-
(bipedal)	2	2.3%
(scrotal)	0	-
Conjunctival Suffusion	49	57.6%
Chills	5	5.8%
Icteric Sclerae	12	14.1%
Jaundice	15	17.6%
Malaise	11	12.9%
Muscle/Joint pains	17	20%
Shock	2	2.3%
Cough/Dyspnea	12	14.1%
Rales	6	7%
Presence of wound/skin lesion	17	20%
Calf Tenderness	22	25.8%

TABLE 10. Laboratory Results

	N	n	%
Blood			
Leukocytosis	84	47	55.9%
Neutrophilia	84	77	91.6%
Thrombocytopenia	84	38	45.2%
Anemia	84	34	40.4%
Renal			
Elevated Creatinine	85	51	60%
Elevated BUN	85	49	57.6%
Albuminuria	84	34	40.4%
Pyuria	84	32	38%
Hematuria	84	23	27.3%
Liver			
Elevated ALT	51	7	13.7%
Elevated AST	52	17	32.6%
Elevated Bilirubin	9	4	44.4%
Prolonged PT	33	5	15.1%
Prolonged PTT	33	15	45.4%
Electrolytes			
Hypokalemia	85	38	44.7%
Hyponatremia	85	40	47%

TABLE 11. Cases of MAT/ LATS Positive and Outcome

		Outcome		
		Discharged	Expired	Total
MAT/LATS	Positive	4	0	4
	Negative	72	3	75
Not done		2	4	6

Serologic test such as MAT/LATS were done in 79 patients. MAT/LATS were not done in 6 patients because patient expired even before test was done or due to unavailability of the test during admission (see Table 11).

Our study showed that nine out of ten patients survived the disease (91.8%). With this, we further tried to look at some factors that could be significantly associated with mortality.

TABLE 12. Number of cases per mortality

Mortality	Freq	%
Survivor	78	91.8
Non-survivor	7	8.2
Total	85	100.0

Using Chi-square test of Independence or Fisher's exact test (whichever is applicable), tests of associations were done. Table 13 below shows that survival rate for Leptospirosis incidence cannot be linked to any of the following demographic factors.

TABLE 13. Mortality rate per socio-demographic characteristic

Characteristic	Mortality			
	Survivor	%	Non-survivor	%
Age group (years)				
1-3	1	1.3	0	0.0
4-6	4	5.1	1	14.3
7-9	13	16.7	0	0.0
10-12	20	25.6	0	0.0
13-16	28	35.9	1	14.3
17-18	12	15.4	5	71.4
Sex				
Male	66	84.6	6	85.7
Female	12	15.4	1	14.3
Location				
Navotas	29	37.2	1	14.3
Malabon	22	28.2	2	28.6
Samar	0	0	1	14.3
Caloocan	6	7.7	0	0.0
Tondo	21	26.9	3	42.9
Total	78	100	7	100.0

On the other hand, Table 14 shows that there is a significant association between the type of exposure and the form of leptospirosis with the chances of a patient to survive (p-value < 0.05).

TABLE 14. Mortality rate per type of exposure and final diagnosis

Exposure/Diagnosis	Mortality					
	Survivor	%	Non-survivor	%		p-value
Type of Exposure*						0.024
Wading	58	74.4	2	28.6		
Denies	9	11.5	3	42.9		
Evacuation center	1	1.3	0	0.0		
No data	10	12.8	2	28.6		
Final Diagnosis*						<0.0001
Leptospirosis	56	71.8	0	0.0		
Weil's disease	22	28.2	7	100.0		
Total	78	100.0	7	100.0		

Finally, to determine the risk factors independently associated with mortality rate, simple logistic regression analysis was done (see Table 15). Using not having pulmonary hemorrhage as the reference group, results showed that pulmonary hemorrhage was the only significant risk factor, (OR=25.4, 95% CI: 4.1–155.6).

TABLE 15. Laboratory risk factors for mortality rate among pediatric patients

Laboratory Results	Mortality				Odds ratio	95% CI		p-value
	Survivor	%	Non-survivor	%				
Anemia	30	38.5	4	66.7	3.2	0.55	18.56	0.195
Leukocytosis	41	52.6	6	100.0	_	_	_	_
Neutrophilia	72	92.3	5	83.3	0.4	0.04	4.17	0.456
Thrombocytopenia	33	42.3	5	83.3	6.8	0.76	61.14	0.086
Elevated creatinine for age	44	56.4	7	100.0	_	_	_	_
Elevated BUN for age	42	53.8	7	100.0	_	_	_	_
Pyuria	28	35.9	4	66.7	3.6	0.61	20.74	0.156
Albuminuria	29	37.2	5	83.3	8.4	0.94	75.91	0.057
Hematuria	21	26.9	2	33.3	1.4	0.23	7.96	0.735
Elevated ALT	6	13.3	1	16.7	1.3	0.13	13.13	0.824
Elevated AST	14	30.4	3	50.0	2.3	0.41	12.75	0.346
Prolonged PTT	11	39.3	4	80.0	6.2	0.61	62.83	0.124
Prolonged PT	4	14.3	1	20.0	1.5	0.13	17.10	0.744
Elevated bilirubin	4	44.4	0	0.0	_	_	_	_
Hyponatremia	36	46.2	4	57.1	1.6	0.33	7.42	0.579
Hypokalemia	35	44.9	3	42.9	0.9	0.19	4.39	0.918
Hemodialysis	7	9.0	0	0.0	_	_	_	_
Pulmonary hemorrhage	7	9.0	5	71.4	25.4	4.13	155.62	0.000*

DISCUSSION

Leptospirosis is a disease caused by bacteria of the genus Leptospira which affect both humans and animals. If not properly treated, it can lead to kidney damage, meningitis, liver failure, respiratory distress, and even death. It occurs in all countries especially those with temperate or tropical climates such as the Philippines and the risk is greater in those who participate in activities like swimming or wading in contaminated environments. In recent years, there has been an increasing incidence of Leptospirosis infection among children in urban settings.[3]

Leptospires enter humans through mucous membranes or abraded skin or by ingestion of contaminated water. After they have penetrated the body, they circulate into the blood stream and spreads to all body organs causing endothelial lining damage of small blood vessels with secondary ischemic damage to end organs.[4]

This study was consistent with other reports that the disease predominantly affects the male population in the adolescent age group, and is more frequent during the rainy or wet season. Males were mostly affected because they were more frequently exposed to outdoor environments or activities as compared to females. Our study also showed that Navotas tops the list of those who are affected by the disease followed by Malabon and Tondo, most likely because these areas are flood-prone during the rainy season, increasing the risk for exposure to contaminated flood waters through skin abrasions and mucous membranes.

Our study showed that fever is the usual initial symptom among patients and is also the most common chief complaint. Our study reflects the reports of Enoval in 2012 and Bonus et al in 2016. With regards to clinical manifestations, we noted in this study that the most frequent symptom noted was fever, followed by gastrointestinal symptoms, conjunctival suffusion, oliguria, calf tenderness and headache which were also similar with the studies of Alfiler, Ho, Enoval, Sulit, Manoloto et al. and Karande et al.[5-10] We noted in this study that conjunctival suffusion, calf tenderness, and presence of skin lesions or wound, which were all suggestive of leptospirosis were present only in a number of patients. Those presenting with oliguria/anuria with concomitant increase in levels of BUN and creatinine are cases which were highly suggestive of acute kidney injury (AKI), which is one of the most common complications of leptospirosis, and is a marker of severity and an indication for hospitalization. Among patients who developed AKI, only 12 cases (14%) underwent peritoneal/hemodialysis; the rest were converted to a non-oliguric state without the need for renal replacement therapy. The most common bleeding manifestations were hemoptysis and hematuria (10.5%) which were prominent in thrombocytopenic patients. The most common CNS manifestation in pediatric patients was headache which is consistent with other studies. Hypotension and hypovolemia presenting as shock which was noted in some of our patients could be due to decreased fluid intake, increased insensible fluid loss, increased vascular permeability due to kinins, histamine, serotonin and prostaglandins or a cytotoxin.

The most frequent abnormal laboratory findings seen in the study of Enoval showed hematuria, elevated creatinine, albuminuria and elevated BUN; the study of Santos-Ocampo on the other hand showed elevated BUN, neutrophilia, proteinuria, leukocytosis and pyuria. In this study, neutrophilia and leukocytosis were very prominent signifying a bacterial infection; also noted were elevated creatinine, elevated BUN levels and thrombocytopenia. Anemia was seen in only 40.4% of cases, in contrast to the study of Bonus et al where anemia was a prominent feature. Bleeding parameters were not available in all patients but where available, most showed normal results. This shows that in the presence of a bleeding tendency and a normal coagulation profile, capillary wall damage could be the source of bleeding.[11] Hypokalemia and hyponatremia are common findings due to tubular dysfunction.

It was also seen in our study that those patients who developed Weil's disease have a higher mortality probably due to progressive renal failure, severe thrombocytopenia leukocytosis and the development of pulmonary hemorrhage which is a significant finding in our case.

We tried to correlate/identify the risk factor/s associated with mortality among our patients and found out that only pulmonary hemorrhage is statistically significant as shown in Table 19. This finding was similar with the study of Roxas et al.[12] where they found out that pulmonary hemorrhage is a strong independent predictor of mortality. Pulmonary involvement was also cited as a strong predictor of mortality among 55 severe

leptospirosis patients admitted at Dr. Sardjito Hospital, Yogkakarta, Indonesia from 2003 to 2007.[13] As early as 1997, a study made in France[14] found out that pulmonary manifestations such as dyspnea and alveolar infiltrates on chest radiographs were included in the five factors identified to be independently associated with mortality. Acute respiratory distress syndrome is the usual complication of pulmonary hemorrhage and is an immediate cause of death among patients. Pulmonary hemorrhage can also be linked to hypotension, which is a finding among our patients who succumbed to death, because it indicates impairment of the microcirculation and increased capillary permeability from vasculitis or even unrecognized bleeding.

CONCLUSION

In this 12-year study, a total of 85 cases of leptospirosis in children were reported, which predominates in male adolescents. It is noted all year round but noted mostly during the rainy months which increases the risk of exposure to contaminated water through wading, especially in the cities of Navotas, Malabon and Tondo in Metro Manila. The mean duration of symptoms was 3.6 days with a range from one to four days.

The most common clinical findings were fever, gastrointestinal symptoms, conjunctival suffusion, oliguria, calf tenderness and headache. Abnormal laboratory findings were leukocytosis, neutrophilia, thrombocytosis, elevated BUN and creatinine, hypokalemia and hyponatremia.

Significant correlation with poor outcome was found in patients with pulmonary hemorrhage.

RECOMMENDATION

Further prospective studies with larger populations are hereby recommended. Active reporting by the surveillance group should be done judiciously since this is a reportable disease. Availability of MAT/LATs on all government hospitals to help aid in the diagnostic needs of our patients should be ensured. Local government programs on health information dissemination to lessen cases of leptospirosis among flood-prone areas should be sustained.

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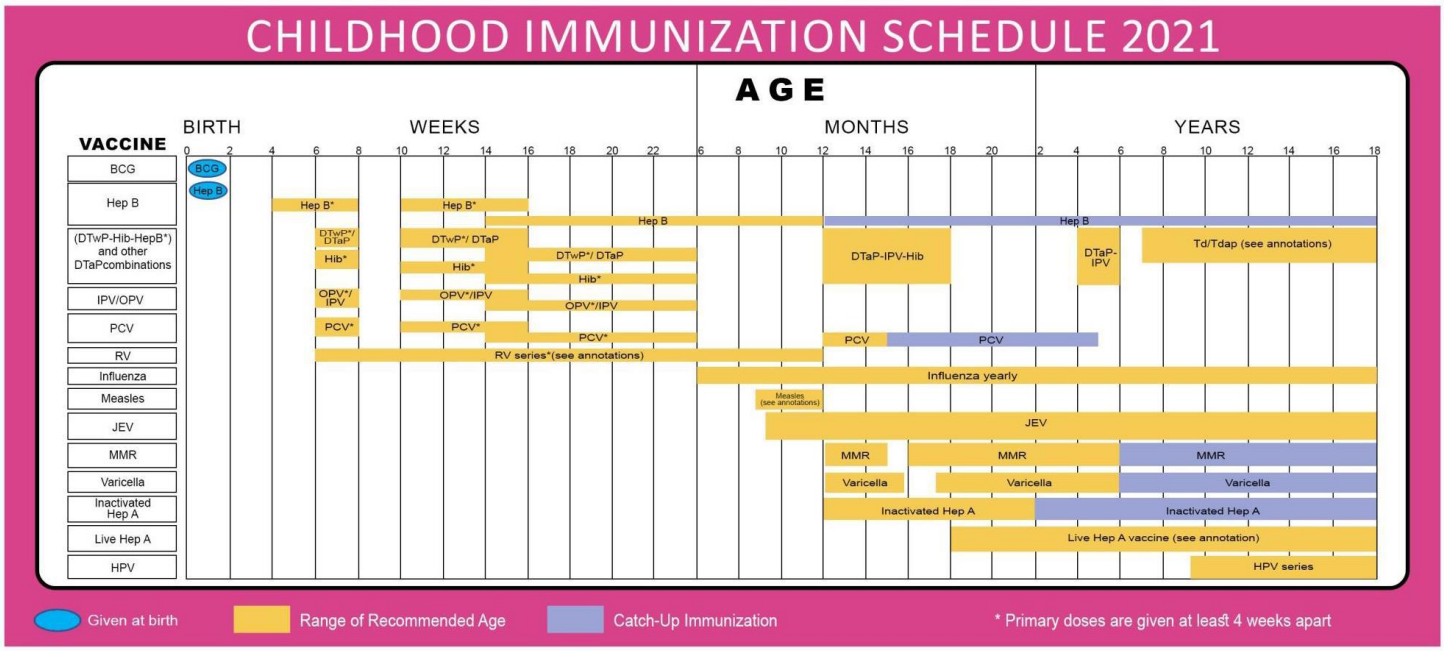

PLEASE READ ANNOTATIONS

DISCLAIMER: The Childhood Immunization Schedule presents recommendations for immunization for children and adolescents based on updated literature review, experience and premises current at the time of publication. The PPS, PIDSP and PFV acknowledge that individual circumstances may warrant a decision differing from the recommendations given here. Physicians must regularly update their knowledge about specific vaccines and their use because information about safety and efficacy of vaccines and recommendations relative to their administration continue to develop after a vaccine is licensed.

Vaccines in the Philippine National Immunization Program (NIP):
The following vaccines are in the 2021 NIP:
BCG, monovalent Hep B, Pentavalent vaccine (DTwP-Hib-HepB), bivalent OPV, IPV, PCV*, MMR, MR, and Td

Recommended Vaccines:
These are vaccines not included in the NIP which are recommended by the Philippine Pediatric Society (PPS), Pediatric Infectious Disease Society of the Philippines (PIDSP) and the Philippine Foundation for Vaccination (PFV).

***Available in selected areas only.**

ANNOTATIONS

BACILLE CALMETTE GUERIN (BCG)

Given intradermally (ID)

- The dose of BCG is 0.05 ml for children < 12 months and 0.1 ml for children ≥ 12 months
- Given at the earliest possible age after birth preferably within the first 2 months of life
- For healthy infants and children > 2 months who are not given BCG at birth, PPD prior to BCG vaccination is not necessary. However, PPD is recommended prior to BCG vaccination if any of the following is present:
    - Congenital TB
    - History of close contact to known or suspected infectious cases
    - Clinical findings suggestive of TB and/or chest x-ray suggestive of TB

  In the presence of any of these conditions, an induration of 5 mm is considered positive and BCG is no longer recommended

DIPHTHERIA, TETANUS, PERTUSSIS VACCINE (DTP)

- Given intramuscularly (IM)
- Given at a minimum age of 6 weeks.
- The primary series consists of 3 doses with a minimum interval of 4 weeks
- Booster series consists of 3 doses until adolescence with the following schedule:
    - 12-23 months (DTP)
    - 4-7 years (DTP)
    - 9-15 years (Td/Tdap)

  Ideally, the minimum interval between booster doses should be at least 4 years
- Full-dose DTP should preferably be used only until age 7 years, but package inserts should be consulted for maximum age indications of specific products

HAEMOPHILUS INFLUENZAE TYPE B CONJUGATE VACCINE

- Given intramuscularly (IM)
- Given as a 3-dose primary series with a minimum age of 6 weeks and a minimum interval of 4 weeks
- A booster dose is given between age 12-15 months with an interval of 6 months from the third dose

  Refer to Vaccines for Special Groups for Hib recommendation in high risk children

HEPATITIS A VACCINE (HAV)

Inactivated Hepatitis A Vaccine

- Given intramuscularly (IM)
- Minimum age: 12 months
- 2 dose series: minimum interval between first and second dose is 6 months

Live attenuated Hepatitis A Vaccine

- Given subcutaneously (SC)
- Minimum age: 18 months
- Given as single dose

HEPATITIS B VACCINE (HBV)

- Given intramuscularly (IM)
- Administer the first dose of monovalent HBV to all newborns ≥2kgs within 24 hours of life
- A second dose is given 1-2 months after the birth dose
- The final dose is administered not earlier than 24 weeks of age
- Another dose is needed if the last dose was given at age <24 weeks

For infants born to HBsAg (+) mothers (preterm or term infants):

- Administer HBV* and HBIG (0.5ml) within 12 hours of life. HBIG should be administered not later than 7 days of age, if not immediately available.

For infants born to mothers with unknown HBsAg status:

- With birth weight ≥2 kgs, administer HBV within 12 hours of birth and determine the mother's HBsAg as soon as possible. If HBsAg (+), administer HBIG not later than 7 days of age.
- With birth weight <2 kgs, administer HBIG in addition to HBV* within 12 hours of life

**For infants born <2 kgs, the 1st dose received at birth is not counted as part of the vaccine series. Additional 3 HBV doses are needed*

HUMAN PAPILLOMAVIRUS VACCINE (HPV)

- Given intramuscularly (IM) For ages 9-14 years, a 2-dose series is recommended
    - Bivalent HPV (2vHPV), quadrivalent (4vHPV) or nonavalent (9vHPV) given at 0 and 6 months
    - If the interval between the first and second dose is less than 6 months, a third dose is needed, the minimum interval between the second and third dose is 3 months

  For ages 15 years and older, a 3-dose series is recommended.
    - Bivalent HPV (2vHPV), quadrivalent (4vHPV) or nonavalent 9vHPV) at 0, 2 and 6 months
    - The minimum interval between the first and the second dose is 1 month and the minimum interval between the second and third dose is 3 months, the third dose should be given at least 6 months from the first dose
    - For males age 9-18 years, a 4vHPV and 9vHPV can be given for the prevention of anogenital warts and anal cancer.

INFLUENZA VACCINE (TRIVALENT/QUADRIVALENT INFLUENZA VACCINE)

- Trivalent influenza vaccine (TIV) given intramuscularly (IM) or subcutaneously (SC)
- Quadrivalent influenza vaccine (QIV) given intramuscularly (IM)
- Given at a minimum age of 6 months
- For pediatric dose, follow the manufacturer's recommendations
- Children age 6 months to 8 years receiving influenza vaccine for the 1st time should receive 2 doses separated by at least 4 weeks
- If only one dose was given during the previous influenza season, give 2 doses of the vaccine then one dose yearly thereafter
- Children age 9 to 18 years should receive one dose of the vaccine yearly
- Annual vaccination should begin in February but may be given throughout the year

JAPANESE ENCEPHALITIS LIVE ATTENUATED RECOMBINANT VACCINE

- Given subcutaneously (SC)
- Given at a minimum age of 9 months
- Children age 9 months to 17 years should receive one primary dose followed by a booster dose 12-24 months after the primary dose
- Individuals 18 years and older should receive a single dose only

MEASLES VACCINE

- Given subcutaneously (SC)
- Given at the age of 9 months, but may be given as early as age 6 months in cases of outbreaks as declared by public health authorities
- If monovalent measles vaccine is not available, then MMR/MR vaccine may be given as substitute for infants below 12 months of age. In such cases, the recipient should receive 2 more MMR vaccines starting at 1 year of age, following recommended schedules

MEASLES-MUMPS-RUBELLA (MMR) VACCINE

- Given subcutaneously (SC)
- Given at a minimum age of 12 months
- 2 doses of MMR vaccine are recommended
- The second dose is usually given at 4-6 years of age but may be given at an earlier age with a minimum of 4 weeks interval between doses.

MEASLES-MUMPS-RUBELLA-VARICELLA VACCINE (MMRV)

- Given subcutaneously (SC)
- Given at a minimum age of 12 months
- MMRV may be given as an alternative to separately administered MMR and Varicella vaccines
- The maximum age is 12 years
- The recommended minimum interval between doses is 3 months, but a second dose given 4 weeks from the first dose is considered valid

PNEUMOCOCCAL CONJUGATE VACCINE (PCV)

- Given intramuscularly (IM)
- Given at a minimum age of 6 weeks
- Primary vaccination consists of 3 doses with an interval of at least 4 weeks between doses. A

booster dose is given 6 months after the third dose.

- For previously unvaccinated infants age 7-11 months, give a total of 3 doses. The first 2 doses are given 1 month apart. The interval between the second and third dose is at least 2 months but should ideally be given at or after the first birthday.
- For previously unvaccinated older children age 12 months to 5 years
    - **PCV 10**: 1-5 years old: give 2 doses at least 2 months apart
    - **PCV 13:** 12-23 months: give 2 doses at least 2 months apart
        - 2 to 5 years old: give 1 dose

POLIOVIRUS VACCINE

Inactivated Polio Vaccine (IPV)

- Given intramuscularly (IM), as a monovalent formulation or in combination with DPT-containing vaccines
- Given at a minimum age of 6 weeks, at least 4 weeks apart
- The primary series consists of 3 doses given at 6, 10, and 14 weeks.
- The first booster is given at 12-18 months. The minimum interval between the third dose and the first booster dose is 6 months.
- The second booster is given at age 4-6 years.
- If the fourth dose is given at age 4 years onward, no further doses are necessary

Oral Polio Vaccine (OPV)

- Only available as part of the government's NIP
- The primary series consists of 3 doses beginning at age 6 weeks with a minimum interval of ≥4 weeks; a dose of monovalent IPV is given together with the third dose

ROTAVIRUS VACCINE (RV)

Human (RV1)

- Given per orem (PO) as oral liquid formulation
- Given as a 2-dose series
- Given at a minimum age of 6 weeks with a minimum interval of 4 weeks between doses. The last dose should be administered not later than 24 weeks of age.

Human-Bovine live-attenuated reassortant (RV5) (oral liquid formulation)

- Given per orem (PO)
- Given as a 3-dose series
- First dose is given at age 6-12 weeks, with a minimum interval of 4-10 weeks between doses. The last dose should not be administered beyond 32 weeks of age.

Human-Bovine live-attenuated reassortant (RV5) (oral freeze-dried formulation)

- Given per orem (PO)
- Given as a 3-dose series, recommended at 2, 4 and 6 months
- Given at minimum age 6 weeks with a minimum interval f 4 weeks between doses
- The last dose should not be administered beyond 12 months of age.

TETANUS AND DIPHTHERIA TOXOID (Td)/ TETANUS AND DIPHTHERIA TOXOID AND ACELLULAR PERTUSSIS (Tdap) VACCINE

- Given intramuscularly (IM)
- For children who are fully immunized, Td /Tdap booster doses should be given every 10 years
- For children age >7 years a single dose of Tdap can be given to replace due Td. Tdap can be administered regardless of the interval since the last tetanus and diphtheria-toxoid containing vaccine. Subsequent doses are given s Td/Tdap.

Fully immunized is defined as 5 doses of DTP, or 4 doses of DTP if the 4th dose was given on or after the 4th birthday

- Give 1 dose of Tdap for every pregnancy
    - For fully immunized pregnant adolescents, administer 1 dose of Tdap vaccine at 27 to 36 weeks AOG, regardless of previous Td or Tdap vaccination
    - For unimmunized pregnant adolescents, administer a 5-dose tetanus-diphtheria (Td)-containing vaccine following a 0-,1-, 6-,18-, and 30-month schedule. Use Tdap as one of the 5 doses, preferably given at 27-36 weeks AOG

VARICELLA VACCINE

- Given subcutaneously (SC)
- Given at a minimum age of 12 months
- 2 doses of varicella vaccine are recommended
- The second dose is usually given at 4-6 years of age, but may be given earlier at an interval of 3 months from the first dose.
- If the dose was given 4 weeks from the first dose, it is considered valid.
- For children ≥ 13 years of age, the recommended minimum interval between doses is 4 week

VACCINES FOR HIGH RISK / SPECIAL GROUPS

PNEUMOCOCCAL CONJUGATE VACCINE (PCV)/ PNEUMOCOCCAL POLYSACCHARIDE VACCINE (PPSV23)

- Given intramuscularly (IM)
- Immunocompromised children and those with high-risk medical conditions should receive both PCV and PPSV23.
    - The two vaccines should not be co-administered. The minimum interval between PCV and PPSV23 is 8 weeks. If a dose of PPSV23 is inadvertently given earlier than the recommended interval, this dose need not be repeated.
    - All recommended PCV doses should be given prior to PPSV23 if possible.
- The following tables summarize the indication and schedule of PCV/PPSV23 administration to children with high risk conditions according to age group:

<table>
<tr><th>PCV-PPSV23 VACCINATION SCHEDULE</th><th>INDICATIONS FOR PNEUMOCOCCAL VACCINES</th></tr>
<tr><td>Age: 24 months to 5 years
• Administer 1 dose of PCV if only 3 doses of PCV was received previously; give 1* or 2** doses of PPSV23 at least 8 weeks after the most recent dose of PCV
• Administer 2 doses of PCV at least 8 weeks apart if unvaccinated or less than 3 doses of PCV was received previously; give 1 or 2* doses of PPSV23 at least 8 weeks after the most recent dose of PCV</td><td rowspan="2">ONE DOSE*
• Chronic heart disease, including congestive heart failure and cardiomyopathies
• Chronic lung disease, including chronic obstructive pulmonary disease, emphysema, and asthma
• Diabetes mellitus, Cerebrospinal fluid leaks, Cochlear implant(s), Alcoholism
• Chronic liver disease

TWO DOSES**
• Sickle cell disease and other hemaglobinopathies
• Congenital or acquired asplenia, or splenic dysfunction
• HIV infection
• Chronic renal failure and nephrotic syndrome
• Diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; or solid organ transplantation
• Congenita or acquiredl immunodeficiency (includes B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease)
• Leukemia or lymphoma
• Hodgkin disease
• Generalized malignancy
• Iatrogenic immunosuppression (diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy)
• Solid organ transplant
• Multiple myeloma

Any of the listed conditions is an indication for PCV
(*) indicates need for ONE dose of PPSV23 (**) indicates need for TWO doses of PPSV23</td></tr>
<tr><td>Age: 6 yrs to 18 years:
• Administer 1 dose of PCV13 if they have not previously received this vaccine; give 1 or 2* doses of PPSV23 at least 8 weeks after the most recent dose of PCV</td></tr>
</table>

RABIES VACCINE

- Given intramuscularly (IM) or intradermally (ID)
- Recommended regimens for pre-exposure prophylaxis (PrEP):
  - For immunocompetent individuals given WHO prequalified vaccines (Verorab ® or Rabipur®):
    - Intramuscular (IM) regimen: Purified Vero Cell Rabies vaccine (PVRV) 0.5 ml OR Purified Chick Embryo Cell vaccine (PCECV) 1 ml given on days 0 and 7
    - Intradermal (ID) regimen: PVRV or PCECV 0.1 ml given on days 0 and 7
  - For immunocompromised individuals or those given non-WHO prequalified vaccines, give 3 doses on days 0, 7, 21 or 28 Other pre-qualified vaccines in the list (Rabivax-S & Vaxirab-N) are not available in the country
- A repeat dose should be given if the vaccine is inadvertently given subcutaneously
- Rabies vaccine should never be given in the gluteal area since absorption is unpredictable
- In the event of subsequent exposures:
  - High-risk* individuals who have completed PrEP require booster doses, regardless of the interval between exposure and last dose of the vaccine. Booster doses may be given through either:
  - 1-visit regimen: 0.1 ml ID (PVRV or PCECV) on each of the 4 sites on day 0
  - 2-visit regimen: 0.1 ml ID (PVRV or PCECV) OR 0.5 ml PVRV or 1.0 ml PCECV IM at 1 site on days 0 and 3

**for high risk individuals, pls. refer to*: https://ais.doh.gov.ph/uploads/aopdf/ao2018-0013.pdf

MENINGOCOCCAL VACCINES

- Given intramuscularly (IM) or subcutaneously (SC)
- Tetravalent meningococcal (ACYW-135) conjugate vaccine MCV4-D, MCV4-TT, MCV4-CRM given intramuscularly (IM)
- Tetravalent meningococcal polysaccharide vaccine (MPSV4) given intramuscularly (IM)/subcutaneously (SC)
- Indicated for those at high risk for invasive disease:
- Persistent complement component deficiencies (including those with inherited or chronic deficiencies in C3, C5-9, properdin, factor D, factor H), anatomic/functional asplenia (including sickle cell disease), HIV, travelers to or resident of areas where meningococcal disease is hyperendemic or epidemic, including countries in the African meningitis belt or the Hajj, or belonging to a defined risk group during a community or institutional meningococcal outbreak

Conjugate vaccines

- MCV4-D: minimum age is 9 months
  - For children 9-23 months, give 2 doses 3 months apart
  - For children 2 years and above give one dose
  - Except in cases of asplenia, HIV, persistent complement component deficiency where 2 doses given 8 weeks apart are recommended
- MCV4-TT: minimum age is 6 weeks
  - For infants 6 to 12 weeks of age: give first 2 doses at least 2 months apart; the 3rd (booster) dose is at age 12 months
  - For children from 12 months of age to adolescence: 1 dose only
- MCV4-CRM: given to children 2 years and above as a single dose
  - Revaccinate with a MCV4 vaccine every 5 years as long as the person remains at increased risk of infection

Polysaccharide vaccines (MPSV4)

- Given to children 2 years and above as a single dose. If MPSV4 is used for high risk individuals as the dose, a second dose using MCV4 should be given 2 months later. Booster doses of MPSV4 are not recommended.

Co-administration

- MCV4-D and PCV13:
  - If MCV4-D is administered to a child with asplenia (including sickle cell disease) or HIV infection, do not administer MCV4-D until age 2 years and at least 4 weeks after the completion of all PCV13 doses

- •MCV4-D and DTaP:
    - If MCV4-D is to be administered to a child at high risk for meningococcal disease, it is recommended that MCV4-D be given either before or at the same time as DTaP
- MCV-TT with tetanus-toxoid (TT) - containing vaccines:
    - Whenever feasible, MCV4-TT should be co-administered with TT-containing vaccines, or administered 1 month before the other TT- containing vaccines

HAEMOPHILUS INFLUENZAE TYPE B CONJUGATE VACCINE (HIB)

- Given intramuscularly (IM)
- Indications for children with the following high risk conditions:
    - Chemotherapy recipients, anatomic/functional asplenia including sickle cell disease, HIV infection, immunoglobulin or early component complement deficiency
- Children aged 12-59 months:
    - Unimmunized* or with one Hib vaccine dose received before age 12 months, give 2 additional doses 8 weeks apart
    - With ≥ 2 Hib vaccine doses received before age 12 months., give 1 additional dose
- For children ≤ 5 years old who received a Hib vaccine dose(s) during or within 14 days of starting chemotherapy or radiation treatment, repeat the dose(s) of Hib vaccine at least 3 months after completion of therapy
- For children who are hematopoietic stem cell transplant recipients, revaccination with 3 doses of Hib vaccine given 4 weeks apart, starting 6-12 months after transplant, is recommended regardless of vaccination history.
- Unimmunized* children ≥ 15 months of age and undergoing elective splenectomy should be given 1 dose of Hib-containing vaccine at least 14 days before the procedure
- Unimmunized* children 5-18 years old and with either anatomic or functional asplenia (including sickle cell disease) or HIV infection, should be given 1 dose of Hib vaccine

**Unimmunized children are those without a primary series and booster dose or those without at least one dose of the vaccine after 14 months of age*

TYPHOID VACCINE

- Given intramuscularly (IM)
- Given at a minimum age of 2 years old with revaccination every 2—3 years
- Recommended for travelers to areas where there is a risk for exposure and for outbreak situations as declared by public health authorities

CHOLERA VACCINE

- Given per orem (PO)
- Given at a minimum age of 12 months as a 2-dose series two weeks apart.
- Recommended for outbreak situations and natural disasters as declared by health authorities

INACTIVATED HEPATITIS A VACCINE (HAV)

- Given intramuscularly (IM)
- Administer 2 doses of Hepatitis A vaccine, at least 6 months apart to unvaccinated individuals who are at increased risk for infection:
    - Travelers to or are working in countries with intermediate or high endemicity of infection
    - MSMs, Homelessness, Users of injection and non-injection illicit drugs,
    - Working with HAV infected primates or with HAV in research laboratories,
    - With clotting factor disorders, and chronic liver disease
    - HIV

HUMAN PAPILLOMAVIRUS VACCINE (HPV)

- Given intramuscularly (IM)
- Give 3 doses of HPV vaccine following the 0, 1-2, and 6 month schedule, regardless of age at vaccine initiation to the following:
    - Children with history of sexual abuse or assault starting at age 9 years

- Immunocompromised children including those with HIV infection

- HPV vaccination is not recommended during pregnancy. If HPV vaccine is inadvertently given during pregnancy, delay the remaining doses until after pregnancy. Pregnancy testing is not necessary before initiating HPV vaccination

SUMMARY TABLE: Immunization of Pre-Adolescents and Adolescents (9 to 18 years old)

Vaccine	Range Of Recommended Age	Dose(s) Needed	Schedule Of Immunization	Route Of Administration	Precautions And Contraindications
Hep B Vaccine	Unvaccinated 9-18 years old	3	0, 1, 6 months	IM	•Severe allergic reaction to vaccine component •Moderate to severe illness
Inactivated Hepatitis A Vaccine	Unvaccinated 9-18 years old	2	Second dose given at least 6 months from first dose	IM	•Severe allergic reaction to vaccine component •Moderate to severe illness
Live Hepatitis A Vaccine	Unvaccinated 9-18 years old	1	Anytime at this age group	SQ	•Severe allergic reaction to vaccine component •Moderate to severe illness •Immunosuppression •Pregnancy •Recent receipt of blood products
MMR	Unvaccinated 9-18 years old	2	4 weeks interval between doses	SC	•Severe allergic reaction to vaccine component •Pregnancy •Immunosuppression •Recent receipt of blood products •Moderate to severe illness
	Incompletely vaccinated 9-18 years old	1	2nd dose given anytime but at least 4 weeks from 1st dose		
Varicella	Unvaccinated 9-12 years old	2	Minimum interval between doses is 3 months	SC	•Severe allergic reaction to vaccine component •Pregnancy •Immunosuppression •Recent receipt of blood products •Moderate to severe illness
	Unvaccinated ≥13 years old	2	Minimum interval between doses is 1 month		
	Incompletely vaccinated 9-18 years old	1	Given anytime 9-12 years old: second dose at least 3 months from first dose ≥13 years old: second dose at least 1 month from first dose		
Influenza Vaccine	9-18 Y years old	1	Give annually beginning February	IM/SC	•Severe allergic reaction to vaccine component •Moderate to severe illness •History of Guillain-Barre syndrome following a previous dose

SUMMARY TABLE: Immunization of Pre-Adolescents and Adolescents (9 to 18 years old)

Vaccine	Range Of Recommended Age	Dose(s) Needed	Schedule Of Immunization	Route Of Administration	Precautions And Contraindications
Td/Tdap	Unvaccinated 9-18 years old	5	•For primary immunization, the 1st and 2nd doses should be given with an interval of at least 4 weeks, and the 2nd and 3rd doses within interval of at least 6 months. •Two booster doses are given - 1st booster is given at least 1 year after the 3rd dose - 2nd booster is given at least 1 year after the 1st booster	IM	•Severe allergic reaction to vaccine component •Moderate to severe illness
	Incompletely Vaccinated				
	With 1 dose	4	0, 1, 2, 6 months		
	With 2 doses	3	0, 1, 6 months		
	With 3 doses	2	0, 6 months		
	Fully vaccinated*	1	1 doseTd / Tdap every 10 years		
	*Fully vaccinated is defined as having received 5 valid doses of DTP or 4 valid doses of DTP if the fourth dose was administered on or after the fourth birthday.				
HPV Vaccine					
Bivalent HPV (2vHPV)	Females: 15-18 years old	3	0, 1-2, 6 months	IM	•Severe allergic reaction to vaccine component •Moderate to severe illness •If found to be pregnant after immunization, delay remaining doses until completion of pregnancy
Quadrivalent HPV (4vHPV) /Nonavalent HPV (9vHPV)	Females: 15-18 years old Males: 15-18 years old	3	0, 2, 6 months		
For females: **Bivalent HPV (2vHPV)/ Quadrivalent HPV (4vHPV)/ Nonavalent HPV (9vHPV)** **For males:** **Quadrivalent HPV(4vHPV)/ Nonavalent HPV (9vHPV)**	9-14 years old	2	0, 6-12 months		

GUIDELINES

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

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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.

INTRODUCTION

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

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

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

New in the Guidelines

Last Updated: February 6, 2021

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

PART 1. COVID-19 IN CHILDREN

I. LOCAL EPIDEMIOLOGY AND BURDEN OF ILLNESS IN CHILDREN

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

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

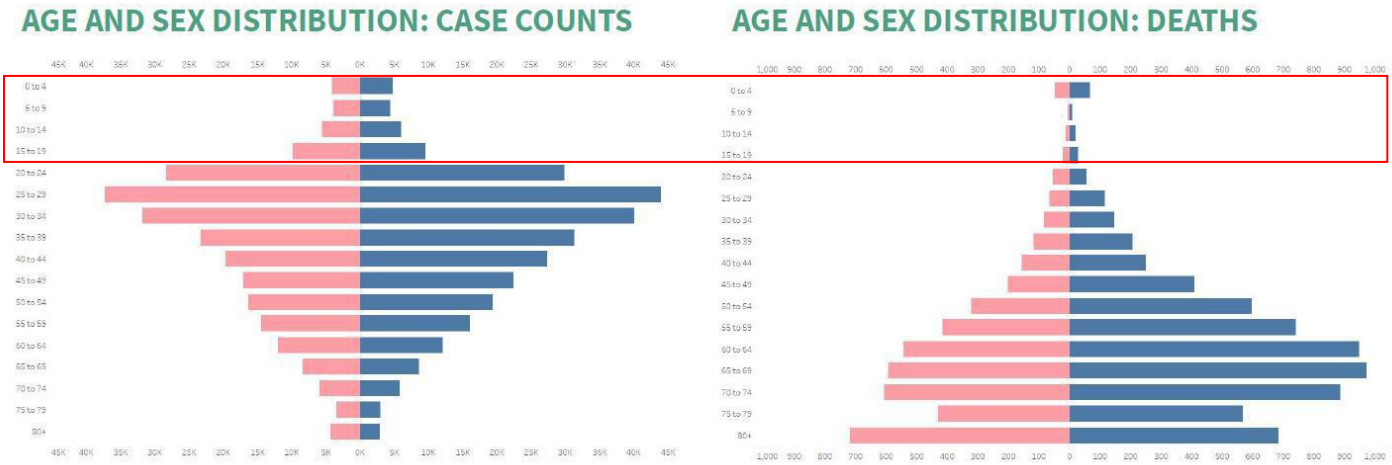


Figure 1. Age and sex distribution of COVID-19 cases and deaths as of 06 February 2021. The pediatric population is indicated by the red box.
(Source: Department of Health. Beat COVID-19 today Philippine situationer: full weekly report. Issue 286, February 7, 2021.)

II. SARS-CoV-2 VIROLOGY

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

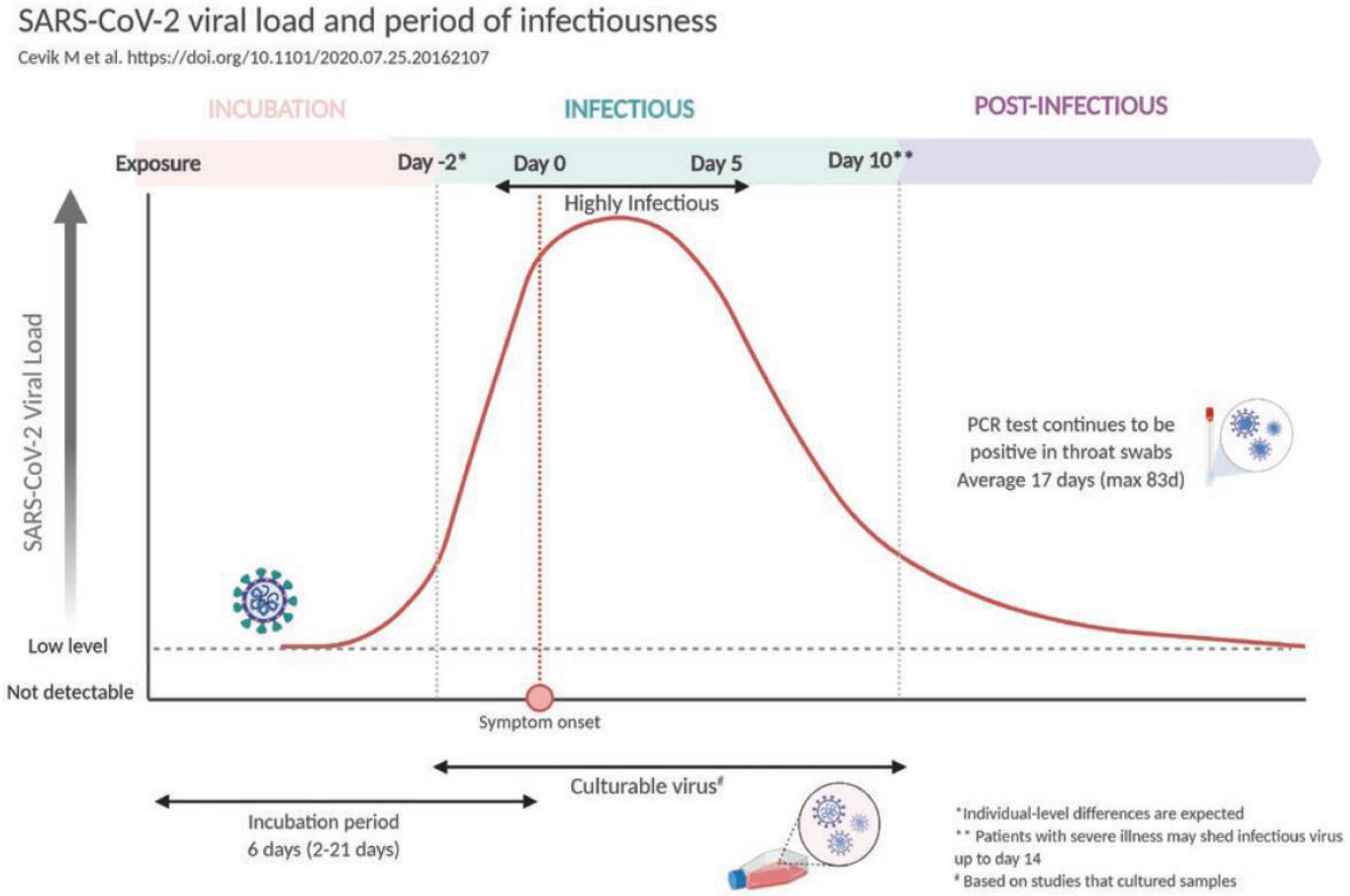


Figure 2. SARS-CoV-2 viral load dynamics and period of infectiousness. Incubation period (time from exposure to symptom onset) of 6 days (2–21 days), peak viral load levels documented from day 0 (symptom onset) to day 5, infectious period starts before symptom onset up to 10 days (this may be extended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

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

III. TRANSMISSION

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

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

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

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

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

IV. RISK FACTORS

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

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

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

V. CLINICAL MANIFESTATIONS OF COVID-19 IN CHILDREN

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

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

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

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

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

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

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

Additional comments:

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

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

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

VI. PATHOGENESIS OF COVID-19

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

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

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

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

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

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

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

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

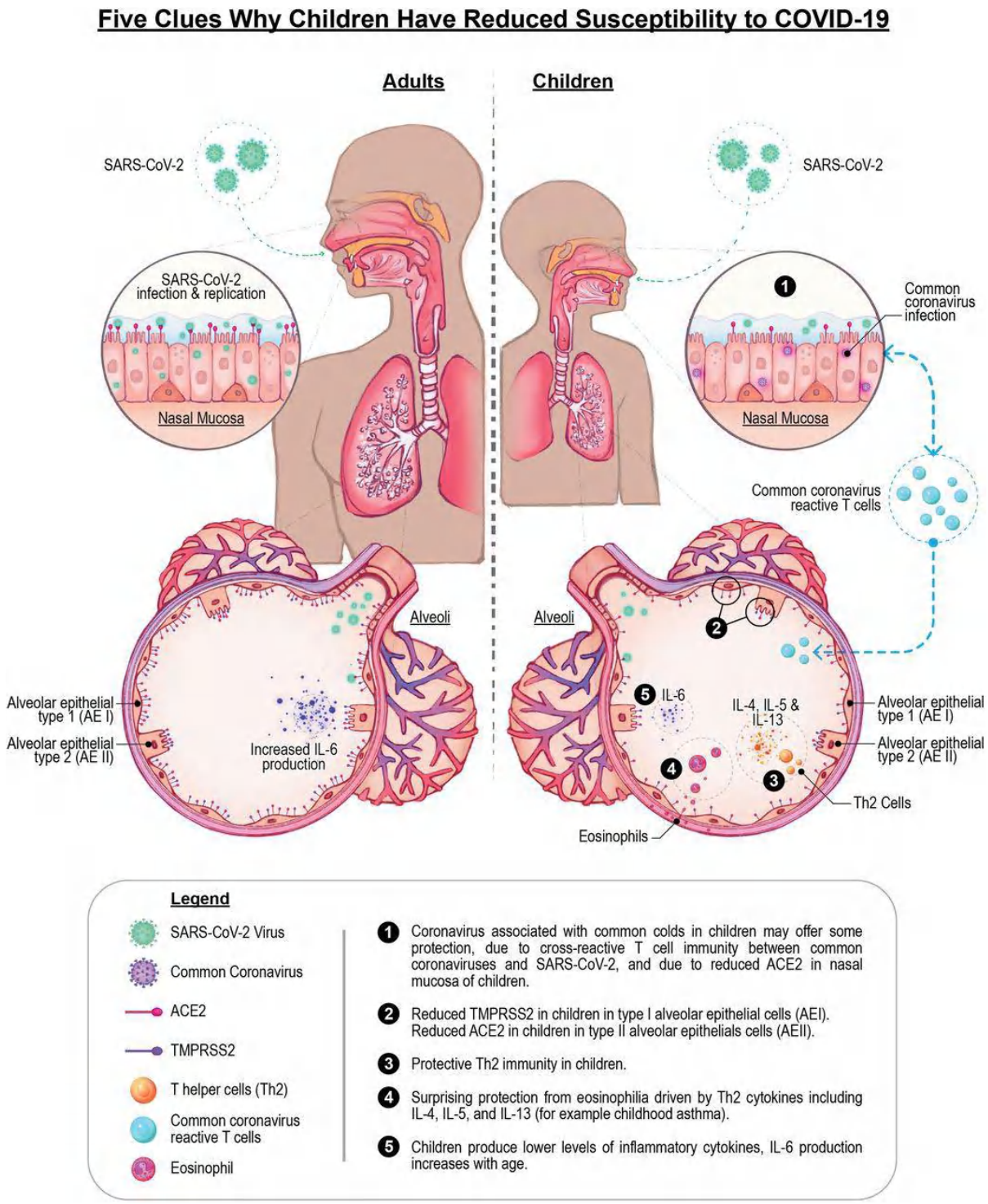


Figure 3. Illustrated concepts behind the reduced susceptibility of children to COVID-19

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

PART 2. SCREENING AND ASSESSMENT

I. SCREENING A CHILD FOR COVID-19

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

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

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

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

B. Exposure evaluation

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

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

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

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

C. Clinical evaluation

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

D. Laboratory evaluation

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

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

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

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

II. CASE DEFINITIONS FOR COVID-19

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

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

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

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

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

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

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

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

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

III. DISEASE SEVERITY CLASSIFICATION CRITERIA

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

Table 5. COVID-19 Disease Severity

Mild disease		Symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia.
Moderate disease	Pneumonia	Child with clinical signs of non-severe pneumonia (cough or difficulty breathing + fast breathing and/or chest indrawing) and no signs of severe pneumonia. Fast breathing (in breaths/min): • < 2 months: ≥ 60 • 2–11 months: ≥ 50 • 1–5 years: ≥ 40 Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including SpO_2 ≥ 90% on room air While the diagnosis can be made on clinical grounds, chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.

Severe disease	Severe pneumonia	Child with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following:
		• Central cyanosis or SpO_2 < 90%; severe respiratory distress (e.g. fast breathing, grunting, very severe chest indrawing); general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions
		• Fast breathing (in breaths/min):
		  ○ < 2 months: ≥ 60
		  ○ 2–11 months: ≥ 50
		  ○ 1–5 years: ≥ 40
		Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO_2 < 90% on room air
		While the diagnosis can be made on clinical grounds, chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.

Critical disease	Acute respiratory distress syndrome (ARDS)	**Onset**: within 1 week of a known clinical insult (i.e. pneumonia) or new or worsening respiratory symptoms. **Chest imaging**: (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. **Origin of pulmonary infiltrates**: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. ECG) to exclude hydrostatic cause of infiltrates / edema if no risk factor present. **Oxygenation impairment in adolescents/adults**: a) Mild ARDS: 200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH_2O) b) Moderate ARDS: 100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg (with PEEP ≥ 5 cmH_2O) c) Severe ARDS: PaO_2/FiO_2 ≤ 100 mmHg (with PEEP ≥ 5 cmH_2O) **Oxygenation impairment in children**: note OI and OSI, use OI when available. If PaO_2 not available, wean FiO_2 to maintain SpO_2 ≤ 97% to calculate OSI or SpO_2/FiO_2 ratio: • Bilevel (NIV or CPAP) ≥ 5 cmH_2O via full face mask: PaO_2/FiO_2 ≤ 300 mmHg or SpO_2/FiO_2 ≤ 264

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

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

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

PART 3. CLINICAL MANAGEMENT

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

I. PATIENTS WITH MILD SYMPTOMS

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

Home interventions for children with mild COVID-19

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

Isolation

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

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

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

Caregiver

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

Hygiene and Sanitation

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

Laundry and Disposal of Soiled Linen and Diapers

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

Home Therapies

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

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

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

Emotional and Mental Support

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

Monitoring

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

II. PATIENTS WITH MODERATE, SEVERE OR CRITICAL SYMPTOMS

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

A. Inpatient Management

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

B. Diagnostics

1. **Molecular-based assays**

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

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

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

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

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

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

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

2. Antigen Tests

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

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

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

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

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

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

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

3. Serologic Tests

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

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

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

4. Ancillary Laboratory Tests

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

a. Complete blood count (CBC)

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

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

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

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

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

b. Inflammatory markers

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

Table 7. Inflammatory markers in children with COVID-19

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

c. Arterial Blood Gas (ABG) or pulse oximetry

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

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

d. Other tests to determine alternative etiology or secondary infection

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

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

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

5. Imaging studies

a. **Chest x-ray**

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

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

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

b. **Chest CT scan**

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

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

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

5. Chest ultrasound

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

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

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

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

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

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

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

Figure 4. Therapies for COVID-19 according to Severity

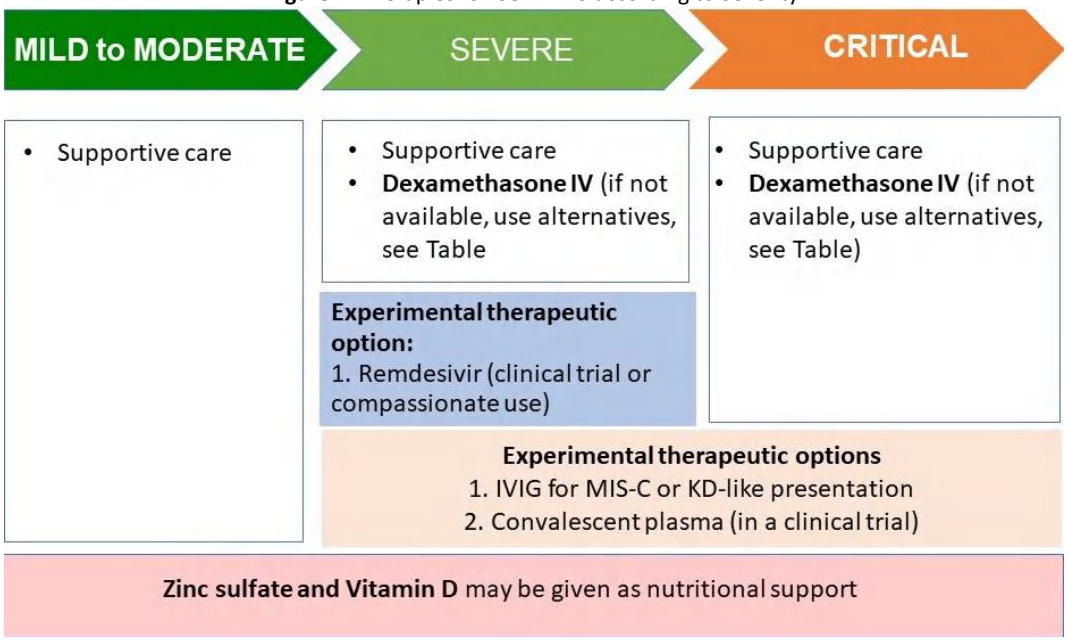


Table 10. Recommended therapy for severe and critical COVID-19

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

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

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

Table 12. Nutritional support

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

See Appendix C for the rationale for pharmacologic recommendations.

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

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

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

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

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

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

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

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

PART 4. COVID-19 PREVENTION AND CONTROL

I. PREVENTION OF COVID-19 IN CHILDREN

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

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

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

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

A. Face protection

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

B. Physical Distancing

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

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

C. Personal Hygiene and Handwashing

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

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

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

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

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

II. COVID-19 VACCINATION

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

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

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

A. Vaccine Virus Targets

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

B. Vaccine Technology Platforms

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

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

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

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

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

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

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

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

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

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

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

1. Pfizer-BioNTech (BNT162b2)

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

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

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

2. Moderna (mRNA-1273)

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

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

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

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

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

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

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

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

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

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

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

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

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

[c] Ramasamy MN et al. Lancet. 2020

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

1. Indications for use

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

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

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

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

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

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

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

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

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

2. Dose and administration

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

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

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

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

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

3. Contraindications and precautions

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

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

4. Patient counseling

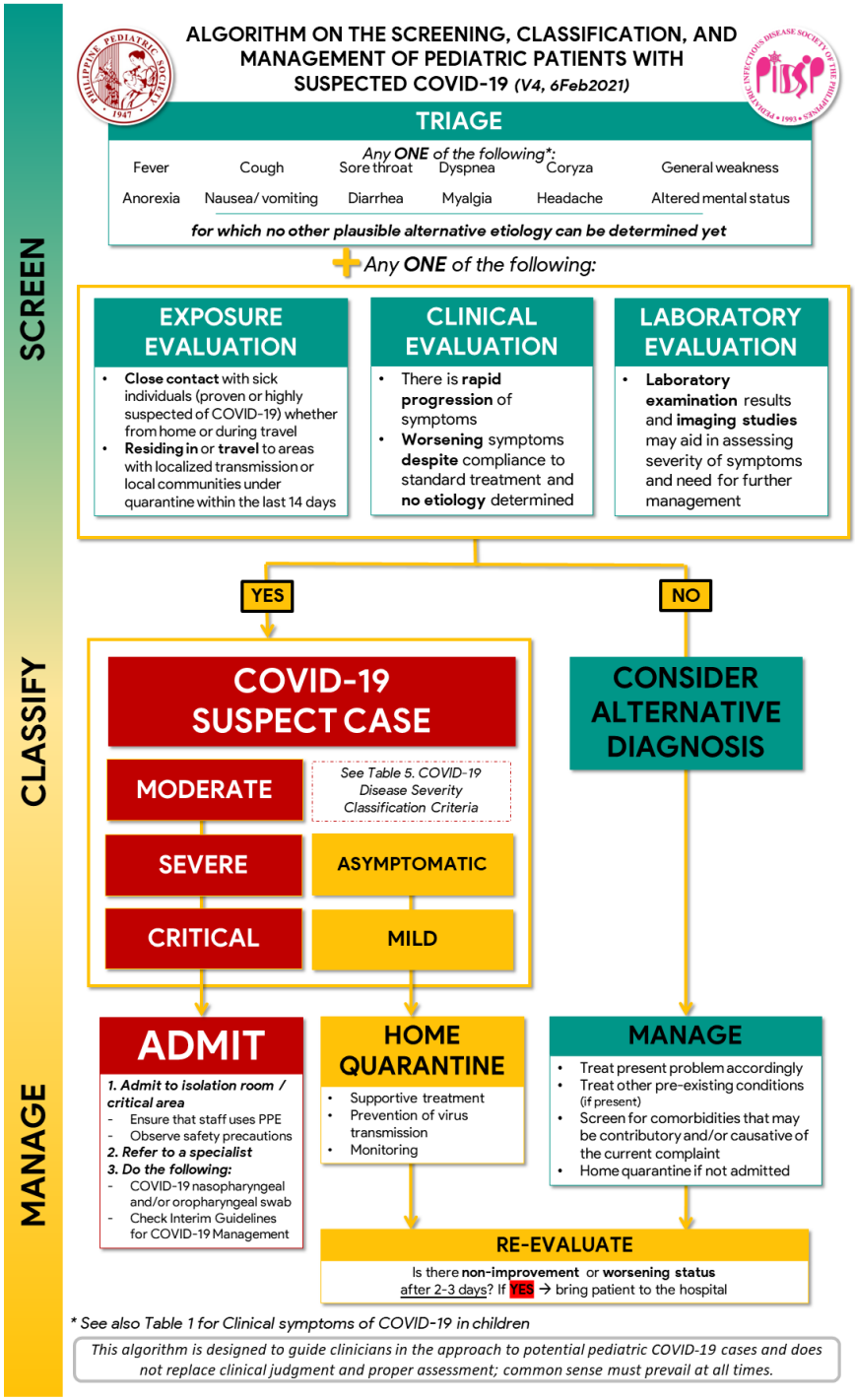
Vaccine recipients should be advised that side effects are common and include local and systemic reactions, including pain at the injection site, fever, fatigue, and headache. Patients should also be advised regarding reports of rare adverse effects such as anaphylaxis and Bell's palsy.

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

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

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

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



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

Appendix A. Case Definitions for Surveillance

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

SUSPECT CASE

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

Clinical criteria:

1. Acute onset of fever AND cough;

OR

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

AND

Epidemiological criteria:

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

OR

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

OR

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

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

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

PROBABLE CASE

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

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

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

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

CONFIRMED CASE

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

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

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

[1] Signs separated with slash (/) are to be counted as one sign
[2] NAAT is required for confirmation (see diagnostic testing for SARS-CoV-2)
[3] A group of symptomatic individuals linked by time, geographic location and common exposures, containing at least one NAAT-confirmed case or at least two epidemiologically linked, symptomatic (meeting clinical criteria of Suspect case definition A or B)

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

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

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

Definitions:

1. Close Contact

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

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

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

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

2. Influenza-like Illness (ILI)

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

3. Severe Acute Respiratory Infection (SARI)

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

Appendix B. Sample Symptom Monitoring Form

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

Name: _____

Quarantine period: _____ to _____

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

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

Important contact numbers to remember:

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

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

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

Pediatrician: (contact details / email address)

Appendix C. Rationale for Pharmacologic Interventions

A. Recommended Therapy for Severe and Critical COVID-19

Corticosteroids

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

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

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

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

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

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

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

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

1. Remdesivir

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

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

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

Remdesivir use in children

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

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

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

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

2. Intravenous Immunoglobulin

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

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

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

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

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

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

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

3. Convalescent Plasma

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

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

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

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

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

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

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

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

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

C. Treatments which are No Longer Recommended

1. Hydroxychloroquine/Chloroquine

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

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

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

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

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

2. Lopinavir/Ritonavir

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

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

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

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

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

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

3. Tocilizumab

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

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

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

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

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

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

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

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

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

D. Nutritional Support

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

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

1. Zinc

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

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

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

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

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

2. VITAMIN D3

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

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

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

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

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

Appendix D. Informed Consent Template

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

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

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

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

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

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

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

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

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

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

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

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

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COVID Bulletin No. 1

salvacion

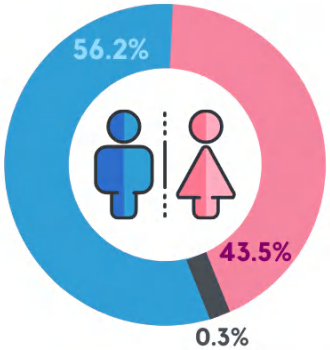
Surveillance and Analysis of COVID-19 in Children Nationwide

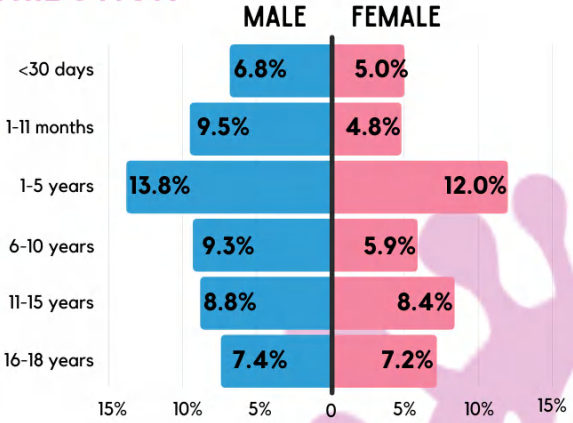
CASE BULLETIN #1 APRIL 30, 2021

Data collection is still ongoing. Submit your **CONFIRMED** and **PROBABLE** pediatric COVID-19 patients at salvacion.pidsphil.org

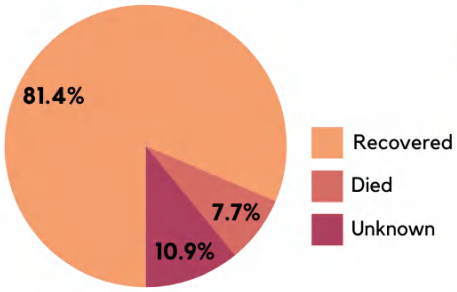
559
REPORTED CASES
JULY 3, 2020 TO APRIL 3, 2021

AGE AND SEX DISTRIBUTION



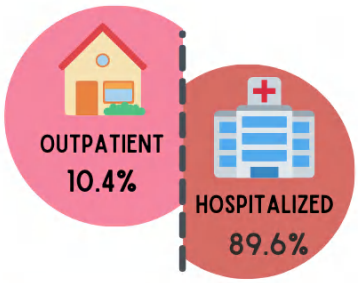


OUTCOME



DISEASE SEVERITY

22.2% ASYMPTOMATIC
40.6% MILD
23.6% MODERATE
6.8% SEVERE
6.8% CRITICAL



COMORBIDITIES

HEMATOLOGIC/ONCOLOGIC DISEASE	5.2%	ASTHMA	1.8%
CARDIAC DISEASE	4.3%	OBESITY	1.1%
NEUROLOGIC/DEVELOPMENTAL DISEASE	3.8%	PREGNANCY	1.1%
KIDNEY DISEASE	3.2%	TB/LTBI	0.7%
PREMATURITY	2.2%		

CO-INFECTIONS

2.0 % COVID-19 & DENGUE

2.0 % COVID-19 & TUBERCULOSIS

For inquiries or suggestions, please email pidsp.covid19@gmail.com or contact 0961-609-9661 or 0956-150-9002. Thank you for your significant contributions to the SALVACION registry!

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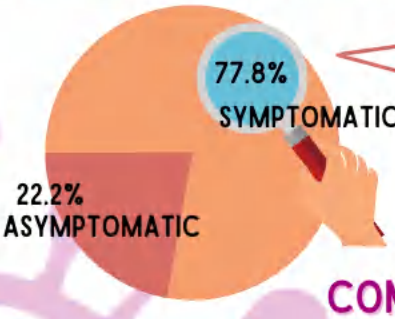
CLINICAL MANIFESTATIONS



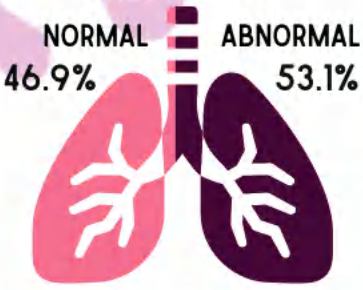
- 43.9% FEVER
- 34.5% COUGH
- 23.4% DIFFICULTY BREATHING
- 22.5% COLDS
- 13.6% DECREASED APPETITE
- 12.2% WATERY STOOLS
- 11.5% VOMITING
- 9.7% ABDOMINAL PAIN
- 8.0% SEIZURE
- 6.9% SORE THROAT
- 3.2% HEADACHE
- 2.5% LOSS OF SMELL
- 2.1% MYALGIA
- 1.6% LOSS OF TASTE

COMMON LABORATORY PARAMETERS

(MEDIAN)

	WBC x10³/uL	NEUTROPHILS	LYMPHOCYTES	PLATELETS x10³/uL	CRP mg/L	ESR mm/hr	PROCALCITONIN ng/L	D-DIMER mg/L	FERRITIN ng/L	LDH U/L
ASYMPTOMATIC	8.6	0.47	0.41	348	0.6	---	0.10	---	---	---
MILD	8.6	0.56	0.35	301	6	10	0.18	---	---	---
MODERATE	11.1	0.58	0.33	298	6	22	0.16	1.78	125	339
SEVERE	12.1	0.62	0.25	272	6	73	0.23	2.97	272	678
CRITICAL	11.1	0.60	0.29	259	12	38	5.18	5.77	395	908

CHEST X-RAY



MANAGEMENT

- 76.7% NO OXYGEN SUPPORT
- 23.3% WITH OXYGEN SUPPORT
- 0.2% LOPINAVIR/RITONAVIR
- 0.5% REMDESIVIR
- 0.5% OSELTAMIVIR
- 5.2% CORTICOSTEROIDS
- 2.3% IVIG
- 1.1% CONVALESCENT PLASMA

For inquiries or suggestions, please email pidsp.covid19@gmail.com or contact 0961-609-9661 or 0956-150-9002. Thank you for your significant contributions to the SALVACION registry!

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