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Delos Reyes CA. Navigating Through the Web of Science (or Web of Lies)
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EDITORIAL

NAVIGATING THROUGH THE WEB OF SCIENCE (OR WEB OF LIES)

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Editor-in-Chief, PIDSP Journal

Evidence based medicine (EBM) refers to the conscientious, explicit, judicious and reasonable use of modern, best evidence in making decisions about the care of individual patients. The practice of EBM integrates clinical experience, patient values and the best available research information.[1]

It adds up to the challenge to practice EBM when the best available scientific evidence is not available. Then there's an influx of predatory journals – fraudulent, deceptive pseudojournals which claim to be legitimate and scholarly but thrive on dishonesty, lack of transparency and exist for profit. When articles are published in predatory journals, they do not receive the benefit of peer review hence the danger of publishing inaccurate information.[2]

In this era of false stories that appear to be news, misinformation and disinformation, use of the correct evidence to combat the scourge of fake news is paramount. As researchers, we should fight misinformation and fight more for the correct information. We can do this through our continuing pursuit of the best available evidence, where information is not yet available.

There are values to swear by in this pursuit: truth, honesty, integrity, honor, and transparency. We need to navigate brilliantly through the web of science, lest we get drowned in a web of lies.

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DECLARATION OF CONFLICTS OF INTEREST

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REVIEW ARTICLE

MENINGOCOCCAL DISEASE AND CARRIAGE IN THE PHILIPPINES: A REVIEW OF RECENT DATA

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ABSTRACT

This article reviews recent data on meningococcal disease and carriage in the Philippines. It aims to provide information on the epidemiology of meningococcal disease, its carriage, data on prevention, and the impact of vaccination on disease and carriage. The World Health Organization considers the Philippines as having low endemicity for meningococcal disease. However, current data underestimates the true burden in the country due to many factors. In recent years, data from the Philippines show a high case-fatality rate since only the septicemic form is being reported. Studies on asymptomatic meningococcal carriage rates are sparse, with one study by Gonzales, et al. investigating the prevalence of meningococcal nasopharyngeal carriage in Filipinos aged 5-24 years old living in an urban setting. The study showed that the overall prevalence of carriage was 3.7% and was highest (9%) among the 10-14 age group. Serogroup B was the most common isolate. Effective meningococcal vaccines are available. Although not included in the National Immunization Program, medical societies recommend giving vaccines to individuals at high risk of infection. Data on local epidemiology accounting for the disease and asymptomatic carriage are important to strengthen future programs on immunization and prevention of meningococcal disease.

KEYWORDS: *Meningococcal disease, Meningococcal vaccine, Meningococcemia*

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The author declares 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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INTRODUCTION

Neisseria meningitidis (meningococcus) is a gram negative obligate human pathogen with no other reservoir. Thirteen serogroups have been identified, of which six (A, B, C, W-135, X and Y) cause almost all worldwide life-threatening disease.[1]

The virulence of *N. meningitidis* is thought to depend on several factors, such as the circulating strain, the environment, and host factors. Although colonization may not necessarily lead to illness, the microbe can cause invasive disease, for reasons not yet fully understood.[2]

Infection requires nasopharyngeal carriage as a prerequisite. Carriage of the microbe, therefore, is important in disease transmission. Asymptomatic colonization is estimated to affect between 10% to 35% of human populations.[3]

METHODOLOGY

A literature search on the local and regional epidemiology of meningococcal disease, prevalence of asymptomatic carriage, and data on vaccination was done.

DISCUSSION

Epidemiology of meningococcal disease

A wide range of clinical presentations are associated with the meningococcus. Invasive meningococcal disease (IMD) in the form of meningitis and meningococcemia are the most common.[4] Although meningococcal disease affects all ages, peak incidences are observed among infants less than 1 year old, among adolescents and the elderly.[4]

The World Health Organization classifies the Philippines as having low endemicity for meningococcal disease (<2 cases/100,000 per year).[4] Despite being a reportable disease, data on the incidence and prevalence of meningococcal disease in the Philippines is sparse.[5]

The Philippine Integrated Disease Surveillance and Response Report is cited in a publication authored by The Global Meningococcal Initiative, stating that the number of meningococcemia cases increased from 73 in 2008 to 182 in 2013.[6]

In 2016 and 2017, there were 183 and 197 cases of meningococcal disease respectively with a case fatality rate (CFR) of 57.38% in 2016[7,8] and 52.79% in 2017.[8] The number of reported meningococcal cases from 2018 to 2019 were mostly from the National Capital Region (NCR) (n=50) and Region IV-A (n=38).[9] From January to June 2019, 130 cases of meningococcal disease were reported. Of these, 68 died (CFR = 50%), with a median age of 3 years old (range 1 month to 63 years).[9]

Thirty-two cases were reported between January to April 2020, representing a decrease of 66% compared to the same period in the previous year. Many of the reported cases (18%) came from region 4A and were between one to four years old. The case fatality rate for this period was 53%. Of the 17 deaths, the majority likewise belonged to the age group between one to four years.[10]

The Global Meningococcal Initiative estimates the incidence of meningococcal disease in the country at 0.02 to 0.1/100,000 population/year, with the greatest number among infants and young children. However, this incidence likely does not reflect the true burden, because only the septicemic form of disease (meningococcemia) is reported. As such, local data may be skewed to reflect high CFRs. *N. meningitidis* serogroup A predominates as the cause of meningococcal disease although serogroup B has also been reported.[6]

Nasopharyngeal carriage

In invasive meningococcal disease (IMD), nasopharyngeal carriage is a prerequisite for infection and has been considered an immunizing process that results in a protective antibody response.[2]

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It is estimated that as many as 350 million to 1 billion people are asymptomatic carriers worldwide.[1] Across the world, it has been established that asymptomatic carriage plays a major role in disease transmission.[5] A recent literature review by Serra, et al. estimates carriage prevalence in Asia to range between 1.4-14.2% based on limited data,[12] compared to rates ranging from 3-30% reported in the African meningitis belt.[11]

In America and Western Europe, adolescents and young adults have the highest rates of carriage[9], while studies from the African meningitis belt noted that peak carriage occurs in children and adolescents 5 to 14 years of age.[12] Limited studies in Asia show a wide range of carriage rates among close contacts of patients with IMD, from 5.7% (among household members) to 62.5% (among prisoners sharing the same cell).[10] However, according to Serra, et al., studies investigating nasopharyngeal carriage particularly in low to middle income Asian countries are difficult to compare due to differences in populations sampled, sampling techniques, and time variations.[12]

Risk factors identified for nasopharyngeal carriage in the African meningitis belt include smoking and exposure to wood smoke.[12] A systematic review identified endemicity in the country of origin as a factor in carriage among Hajj pilgrims, while smoking, male sex and frequent attendance at parties increased nasal carriage among university students.[13] Serra, et al. also included risk factors for nasopharyngeal carriage among low and middle income Asian countries in their review; they concluded that these were inconsistently assessed in the studies they included. In particular, the Asian studies did not reflect the usual associations drawn between smoking and carriage.[12]

A local cross-sectional carriage prevalence study done by Gonzales, et al. involving 937 healthy Filipinos, 5 to 24 years old, conducted in three different sites in Manila investigated the prevalence of meningococcal carriage in children and adolescents.[5]

Only 35 participants were found to be carriers, which translated to an overall carriage prevalence of 3.7%. The most common isolate was serogroup B (65.7%), but serogroups C, Y and W were also found. Two individuals were discovered to be carrying multiple serogroups, while capsular serogroups were unidentified in five (probably reflecting unencapsulated strains).

Carriage prevalence was shown to be highest in the 10 to 14 age group; the rate was higher among those with more siblings and those living in larger households. The authors suggest that older children and young teens play a key role in the local transmission of the disease.[5]

Prevention

Currently, meningococcal vaccination is not included in the country's National Immunization Program but is recommended by professional medical societies for high-risk children.[15,16] In the Philippines, tetravalent (ACYW-135) meningococcal vaccines conjugated to different protein carriers such as diphtheria toxoid (MCV4-D), tetanus toxoid (MCV4-TT) and modified cross-reacting material (MCV4-CRM) are available. Tetravalent meningococcal polysaccharide vaccine (MPSV4) is also available. These vaccines are indicated for those at high risk of invasive disease, including individuals with complement component deficiencies, anatomic or functional asplenia, HIV, and travelers or residents in areas where meningococcal disease is hyperendemic or epidemic. Those who belong to a defined risk group during a community or institutional meningococcal outbreak are also indicated to receive these vaccines as well.[16]

Impact of vaccination on disease and carriage

The first effective vaccines against meningococcal disease contained purified capsular polysaccharide; these formulations provided short-term protection. The subsequent development of conjugate vaccines addressed this problem, providing both long-term protection as well as herd immunity.[2]

De Oliveira, et al. reviewed the literature on meningococcal vaccination to evaluate the evidence supporting immunization programs. The studies reviewed showed that both polysaccharide and conjugate vaccines were effective and had a positive impact on vaccine-serogroup meningococcal disease. The conjugate vaccines showed higher impact and effectiveness (VE 66%-100%) with longer-lasting protection, compared to polysaccharide vaccines (VE 65%-83.7%).[17]

A 2018 review by Balmer, et al. investigated available data on the impact of vaccination on meningococcal nasal carriage. The authors noted that only few clinical trials assessing the role of carriage as a pre-defined study endpoint have been established, compared to observational studies assessed. The review concluded that while carriage studies for other serogroups were often not sufficiently powered to provide robust statistical evidence, carriage of serogroups A and C significantly decreased 1 to 2 years after vaccination with MenA and MenC vaccines.[2]

In the local setting, data from the study of Gonzales, et al. may assist in the formulation of vaccination strategies against meningococcal disease. The authors suggested that for reduction of carriage rates and achieving herd immunity, immunization may be required before the peak carriage age of 10 years.[5] Furthermore, knowledge of prevalent serogroups among carriers is an important aspect of planning vaccination strategies. Although serogroup B was the most common strain identified in this study, other strains, also associated with invasive forms of the disease were likewise isolated.

CONCLUSION AND RECOMMENDATIONS

It is difficult to determine the true burden of meningococcal disease in the Philippines due to many factors. Pioneering studies show that a small percentage of the study population are carriers of the meningococcus, with the rates highest in older children and with serogroup B prevailing.

Since asymptomatic carriage is an important driver of transmission and disease, more extensive data on its prevalence is needed to support programs on prevention. Data on local epidemiology accounting for the disease and asymptomatic carriage are important to strengthen future programs on immunization and prevention of meningococcal disease. Its high case-fatality rate should lead physicians to explore ways to prevent IMD.

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FEATURE ARTICLE

2022 UPDATED PEDIATRIC INFECTIOUS DISEASE SOCIETY OF THE PHILIPPINES (PIDSP) RESEARCH AGENDA

Robert Dennis J. Garcia, MD, MHSA, Ma. Cecilia G. Ama, MD, and Rosemarie Arciaga, MD, MSc
Pediatric Infectious Disease Society of the Philippines Research Committee

The Pediatric Infectious Disease Society of the Philippines (PIDSP) has a mandate to promote and conduct relevant infectious disease-related research by its members, fellows in training institutions, and resident physicians in training hospitals. Part of such a mandate is the creation of a priority list of research topics, which directs the researcher to what information is deemed important by the PIDSP, if the research is to receive funding from the Society, should such be requested. This list was first created in 2016.

In April 2021, the PIDSP Research Committee met and agreed to update the list, by conducting a series of three internal surveys to determine if the items in the existing list were still relevant, and if new topics should be included. Twenty-three PIDSP members, which included board members, known researchers, and university faculty, were surveyed using an online Google form, over three surveys between May 31, 2021 and October 3, 2021. New items were elicited from the respondents, and the old and new items were asked to be prioritized into the headings: high, medium, low, and not a priority. Only the high and medium priority items were included in the final updated list.

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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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RESULTS

1st survey (May 31, 2021):

A. Priority levels (high, medium, low) were requested for the 116 hitherto research topics.
B. The response rate was 19/23 (83%).
C. There was a general agreement with the pre-listed priority level, except for eight topics.
D. The 1st survey also elicited new proposed research topics. The result was a list of new topics.

2nd survey (August 17, 2021):

A. Priority levels (high, medium, low, not a priority) were requested for the newly proposed research topics.
B. The response rate was 12/23 (52%).
C. There was a general agreement with a specific priority level, except for seven topics.

3rd survey (September 27, 2021):

A. Priority levels were requested for topics with which there was disagreement in priority level (high vs. medium for old topics; medium vs. low for new topics).
B. The response rate was 7/23 (30%).
C. For the old topics, a majority preferred a change in priority from medium to high for five items; a change from high to medium for one item; while two items stayed in the same category.
D. For the new topics, a majority favored five items in medium priority, while two were placed at low priority.

The above process resulted in an updated research priority list which contains:

A. 116 old topics; two were changed from "high" to "medium priority"
B. 30 new topics, of which 16 are of "high priority."
C. Three new sections:
   1. COVID-19
   2. Kawasaki disease
   3. DOH research priorities

The following is the list of topic sections and items, with the corresponding priority level per item:

I. Leptospirosis

Topic	High	Medium
A. Risk factors for severe leptospirosis	X	
B. Predictors for mortality among children with severe leptospirosis	X	

II. Tuberculosis

Topic	High	Medium
A. Epidemiology of MDR-TB in children	X	
B. Treatment of MDR-TB in children	X	
C. Validity of TB diagnostic criteria in children	X	
D. Improving laboratory diagnosis of TB	X	
E. Strategies to improve treatment compliance[1]	X	
F. Research priorities included in the DOH/PHILCAT document	X	
G. Prevention of MDR-TB in children	X	
H. Strategies to improve TB case detection	X	
I. Treatment monitoring parameters for extra-pulmonary TB	X	
J. Surveillance of TB in the private sector[2]	X	
K. Problems in the implementation of DOTS in children[2]	X	
L. Adherence to the TB guidelines[2]	X	
M. TB as a cause of childhood pneumonia[1]	X	
N. Strategies to improve private-public TB referral	X	
O. Strategies to decrease misconceptions regarding TB		X
P. Strategies in the dissemination of guidelines for TB management		X
Q. Education strategies targeting disease awareness/transmission		X
R. Determinants of TB disease in children		X
S. Strategies to increase isoniazid preventive therapy		X

[1] New topics
[2] Old topic, priority changed from medium to high

III. Influenza

Topic	High	Medium
A. Influenza surveillance among children	X	
B. Validation of rapid diagnostic tests for influenza in children	X	
C. Development of treatment guidelines for influenza	X	
D. Diagnostic criteria for influenza in children		X
E. Influenza vaccine studies		X

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IV. Pneumonia

Topic	High	Medium
A. Risk factors for severe pneumonia	X	
B. Predictors of pneumonia-related mortality in children	X	
C. Clinical and laboratory parameters to differentiate viral vs. bacterial pneumonia	X	
D. Etiologic agents of pneumonia for age >5 years old	X	
E. Strategies to improve vaccine coverage for pneumonia	X	
F. Adherence to the PCAP case-management guidelines		X
G. Efficacy of existing PCV		X
H. Criteria for switching from IV to oral antibiotics in hospitalized PCAP		X
I. Validity of diagnostic parameters for pneumonia		X
J. Adjuncts in the management of severe pneumonia		X
K. Etiologies of PCAP in < 5 years of age[1]		X
L. Atypical pathogens as a cause of PCAP[1]		X
M. *Staphylococcus aureus* as a cause of PCAP[1]		X

[1] New topics

V. Dengue/DHF

Topic	High	Medium
A. Risk factors for poor outcome in dengue	X	
B. Effect of the Case Management Protocol in improving survival	X	
C. Baseline hematocrit among Filipino children	X	
D. Strategies to improve disease management	X	
E. Effective strategies for the dissemination of the new case classification & management protocols	X	
F. Dengue vaccine studies	X	
G. Validation of disease definition based on clinical & lab parameters[1]		X
H. Community approaches to decrease morbidity & mortality		X
I. Interventions for vector control		X
J. Mortality rate in patients with severe dengue		X

[1] Old topic, priority changed from high to medium

VI. Meningitis/encephalitis

Topic	High	Medium
A. Age-specific etiologic agents of meningitis in children	X	
B. Risk factors for poor disease outcome of viral, bacterial and TB meningitis in children	X	
C. Clinical presentation of viral, bacterial & TB meningitis in children	X	
D. Etiology of encephalitis in children	X	
E. Empiric therapy for bacterial meningitis in children	X	
F. Antimicrobial sensitivity pattern of bacterial causes of meningitis		X
G. Role of imaging in the diagnosis of meningitis		X
H. Adherence of pediatricians to the CPG on meningitis		X
I. Cost-effectiveness analysis of vaccination programs		X
J. Anti-NMDA, dengue and *Mycoplasma sp.* as causes of encephalitis[1]		X
K. Strategies to ensure polio eradication[1]		X

[1] New topics

VII. Sepsis

Topic	High	Medium
A. Clinical and laboratory predictors for sepsis	X	
B. Validation of diagnostic tools for sepsis	X	
C. Adjuncts in the management of sepsis	X	
D. Criteria for the diagnosis of sepsis in neonates	X	
E. Aids in the diagnosis of sepsis	X	
F. New management approaches for sepsis	X	
G. Etiology of sepsis	X	
H. Clinical profile & outcome of sepsis due to MDR organisms[1]	X	
I. Epidemiology of sepsis		X
J. Risk factors for sepsis in children		X
K. Appropriate treatment of early-onset and late-onset neonatal sepsis[1]		X
L. *Staphylococcus aureus* as a cause of community-acquired bacteremia[1]		X

[1] New topics

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VIII. Diarrhea/rotavirus

Topic	High	Medium
A. Changing etiology and epidemiology of acute diarrhea in children	X	
B. Changing rotavirus serotypes with the introduction of rotavirus vaccine	X	
C. Impact of increasing rotavirus vaccine coverage among children < 2 years old	X	
D. Risk factors for diarrhea mortality	X	
E. Barriers to rotavirus vaccination	X	
F. Adjuncts in the management of diarrhea in children		X
G. Safety of rotavirus vaccines		X
H. Relationship between chronic diarrhea, IQ and growth		X
I. Adherence to the recommended diarrhea management		X
J. Herbal medicines for diarrhea in children		X

IX. Healthcare-associated infections

Topic	High	Medium
A. Site-specific surveillance for HC-associated infections	X	
B. Interventions to decrease HC-associated infections	X	
C. Risk factors for HC-associated infections in children	X	
D. Adherence to transmission-based infection control	X	
E. Multidrug-resistant HC-associated infections in children[1]	X	
F. Cost of HC-associated infections in private and public hospitals		X
G. Prevention of central catheter line infections		X

[1] New topics

X. Antimicrobial use

Topic	High	Medium
A. Effect of antibiotic stewardship on antibiotic use	X	
B. Antimicrobial resistance surveillance in children	X	
C. Appropriate antimicrobial use for common pediatric infections	X	
D. Antimicrobial prescription for common infectious diseases	X	
E. Optimal early switch to oral antibiotics in hospitalized children	X	

XI. Measles

Topic	High	Medium
A. Community programs to improve measles immunization rate	X	
B. Factors related to declining measles vaccination rate[2]	X	
C. Risk factors for persistence or outbreaks of measles[2]	X	
D. Risk factors for measles-associated complications and death		X
E. Adjuncts in the management of measles		X
F. Improving the accuracy of measles surveillance		X
G. *Staphylococcus aureus* as etiology of pneumonia in measles[1]		X

[1] New topics
[2] Old topic, priority changed from medium to high

XII. Pertussis

Topic	High	Medium
A. Age-specific incidence of pertussis in the community	X	
B. Clinical diagnostic criteria for pertussis in children	X	
C. Efficacy of chemoprophylaxis for prevention of disease transmission	X	
D. Predictors of mortality among infants	X	
E. Effectiveness of vaccination of pregnant women and/or adults to prevent disease transmission	X	
F. Cost-effectiveness analysis of rapid diagnostic tests for pertussis		X
G. Waning immunity following DPT vaccination		X
H. Risk factors for pertussis		X
I. Cost-effectiveness of drugs for prevention & treatment of pertussis		X

XIII. Rabies

Topic	High	Medium
A. Knowledge, attitudes and practices on rabies & its pre-exposure prophylaxis		X
B. Feasibility of pre-exposure prophylaxis		X
C. Cost-effectiveness of pre-exposure prophylaxis		X

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XIV. HIV/STI

Topic	High	Medium
A. Epidemiology of HIV/AIDS among children & adolescents	X	
B. Risk assessment & intervention programs for adolescents & various groups at risk	X	
C. Clinical course of HIV/AIDS in children	X	
D. TB & HIV comorbidity	X	
E. Efficacy of various ARV combinations among children	X	
F. Interventions to improve disease recognition & management	X	
G. Opportunistic infections among children with HIV/AIDS	X	
H. HIV/AIDS-defining diseases among children	X	
I. Strategies to increase HIV testing among women	X	
J. Comorbid diseases with HIV, other than TB		X
K. Approaches to decrease stigma of the disease		X
L. Yield of prenatal HIV testing in pregnant women[1]		X
M. HIV manifestations in children & adolescents[1]		X

[1] New topics

XV. Malaria

Topic	High	Medium
A. Evaluation of the malaria control program in the community		X
B. Risk factors for complications & deaths in malaria		X
C. Malaria vaccine studies		X

XVI. Kawasaki disease[1]

Topic	High	Medium
A. Clinical profile & outcome of children with complete vs. incomplete Kawasaki disease		X
B. Identifiable infectious & non-infectious etiologies in children with Kawasaki disease		X

[1] New topics

XVII. COVID-19[1]

Topic	High	Medium
A. Epidemiology of COVID-19 in children	X	
B. Clinical presentation & outcomes of COVID-19 in children	X	
C. Effect of co-morbidities on disease severity and death in childhood COVID-19	X	
D. Morbidity and mortality in childhood COVID-19	X	
E. Short/long-term outcomes in childhood COVID-19	X	
F. COVID-19 vaccines	X	
G. Management of COVID-19 in children	X	
H. The effect of the COVID-19 pandemic on routine childhood vaccination compliance	X	
I. The rate of COVID-19 positivity among infants born to COVID-19-positive mothers	X	
J. Inflammatory markers in children with COVID-19 and association with morbidity & mortality	X	
K. Use of telemedicine in infectious disease patients during the pandemic		X

[1] New topics

XVIII. Surveillance

Topic	High	Medium
A. Infectious Disease Surveillance to include the private sector	X	
B. Survey of immunization coverage by private practitioners	X	
C. Water potability in Metro Manila tap water[1]	X	
D. Emerging and reemerging infectious diseases	X	

[1] New topics

XIX. DOH research priorities[1]

Topic	High	Medium
A. Research priorities of infectious disease programs of the DOH		X

[1] New topics

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ORIGINAL ARTICLE

A SYSTEMATIC REVIEW AND META-ANALYSIS ON THE SAFETY AND EFFICACY OF SECOND DOSE IMMUNOGLOBULIN VERSUS HIGH DOSE PULSE METHYLPREDNISOLONE IN REFRACTORY KAWASAKI DISEASE

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1st PLACE 2022 PIDSP RESEARCH CONTEST

ABSTRACT

Background: There is limited information available regarding the management of IVIG-refractory Kawasaki Disease (KD).

Objectives: This study aimed to evaluate the safety and efficacy of a second intravenous immunoglobulin (IVIG) infusion versus intravenous methylprednisolone (IVMP) in patients with IVIG-refractory KD.

Methodology: Cochrane Library, PubMed, Medline, Elsevier (Science Direct), Springer Link and BMJ databases were searched from May 1, 2020 to December 31, 2020. We included randomized controlled trials (RCTs) and high-quality prospective and retrospective studies, with population restricted to children 0 months to 18 years, with KD refractory to initial IVIG at 2g/kg, who remained febrile for 24-48 hours after completion of initial IVIG, and who received second-line monotherapy with either a second dose IVIG or IVMP. We conducted a meta-analysis using Review Manager [RevMan] 5.4.1 software.

Results: A total of six studies (n=188 patients) were analyzed. The incidence of coronary artery lesions was comparable between a second dose of IVIG and IVMP (RR 0.82, 0.34-1.96, P=0.66) in patients with IVIG-refractory KD. The rate of fever resolution to a second IVIG, compared to IVMP, was not significantly different between groups (RR 0.97, 0.84-1.13, P=0.72). There was a significantly higher incidence of adverse events in the IVMP group (RR 0.42, 0.26-0.57, P=0.0002), but these were all transient and resolved without further treatment.

Conclusions: There is no significant difference in the incidence of coronary artery lesions and rate of fever resolution post-retreatment with a second dose of IVIG versus IVMP in IVIG-refractory KD. More adverse events were reported in the IVMP group.

KEYWORDS: *Mucocutaneous Lymph Node Syndrome, Kawasaki Disease, Refractory Kawasaki Disease, Immunosuppressant, Intravenous Immunoglobulin, Methylprednisolone, Second IVIG Infusion*

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INTRODUCTION

Kawasaki disease (KD) is an acute, self-limited, medium-vessel vasculitis which most commonly affects infants and young children less than 5 years of age.[1,2] The current standard therapy for KD is a combination of intravenous immunoglobulin (IVIG) and acetylsalicylic acid.[3] However, approximately 10-20% of patients fail to respond to IVIG and remain febrile ≥ 36 hours following completion of IVIG infusion.[4] These patients are considered to have IVIG-refractory KD and have a nine-fold higher risk of coronary lesions compared to those who respond to initial treatment.[5]

Corticosteroid is the treatment of choice for most vasculitides but its use in KD remains controversial.[6] Furukawa, et al. reported that among 65 patients with IVIG-refractory KD, 68% of patients treated with intravenous methylprednisolone (IVMP) became afebrile within one day of therapy compared to 63% of patients treated with a second dose of IVIG.[7] The difference in the incidence of coronary abnormalities was insignificant between the two groups, suggesting that IVMP is a viable treatment option for IVIG-refractory KD.[7] In another retrospective study by Kim, et al. on 38 patients with IVIG-refractory KD, all three who were given corticosteroid monotherapy, without a second IVIG treatment, developed coronary artery lesions, although the difference between the two groups was not statistically significant.[8] The inconsistencies and absence of significant differences between treatment arms in these studies may be due to inadequate sample size and the low frequency of IVIG-refractory KD.

The treatment goal for patients with KD is to suppress systemic inflammation as early as possible because prolonged elevation of serum inflammatory cytokines is associated with the development of coronary artery lesions (CALs).[8,9]

Miura, et al. found that IVMP use was associated with significantly lower plasma levels of tumor necrosis factor-alpha and monocyte chemoattractant protein-1, compared to levels in children who were given a second dose IVIG.[9] The American Heart Association recommends a second dose IVIG as reasonable therapy in IVIG-refractory KD patients and IVMP as an alternative, or as a third-line treatment, when there is resistance to a second dose of IVIG.[10] The role of IVMP in IVIG-refractory KD has not been firmly established due to inadequate clinical trials on its efficacy compared to a second dose of IVIG.[11] This study aimed to evaluate the safety and efficacy of a second IVIG infusion versus IVMP in children with IVIG-refractory KD using a meta-analysis approach. It is hypothesized that IVMP will be as effective, or more effective, than retreatment with a second dose of IVIG in patients who fail to respond to the initial IVIG dose. Incidence of CALs, post-retreatment fever resolution, and occurrence of adverse events were the specific parameters compared.

METHODOLOGY

Database Search Strategy

We searched the following databases from May 1, 2020 until December 31, 2020: Cochrane Library, PubMed, Medline, Elsevier (Science Direct), Springer Link and BMJ Journals. The search strategy used a combination of the following keywords - "Kawasaki disease / mucocutaneous lymph node syndrome AND intravenous immunoglobulin/intravenous gamma-globulin / immunoglobulin AND resistant / unresponsive / refractory / intractable / failure AND intravenous methylprednisolone / high pulse methylprednisolone OR steroid AND treatment / retreatment / therapy / management."

Filters were applied to retrieve only the studies available in English with full texts and published from the year 2000 to 2020. Manual review of references from published articles was also done to identify additional relevant studies.

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Selection Criteria and Process

We included RCTs, high-quality prospective and retrospective studies, with population restricted to children 0 months to 18 years, with KD refractory to initial IVIG at 2g/kg, who remained febrile ≥ 36 hours after completion of initial IVIG, and who received second-line monotherapy with either a second dose IVIG (1-2g/kg) or IVMP (30mg/kg/dose x 3 days). We included only original peer-reviewed, full-text publications with at least five patients. We excluded studies that were published prior to 2005, written in a language other than English, duplicate data, abstract proceedings and reviews, basic science studies, combination therapy, alternate dosing of initial IVIG or second-line therapy, and case reports or case series with < 5 patients. Screening and selection of articles was performed by the primary investigator.

Data Collection and Outcome Measures

Data extraction was performed by 1 primary and 2 co-investigators. Information collected included year of publication, country of origin, study characteristics, number of subjects, and the outcomes of interest - incidence of CALs (including coronary artery dilatation and coronary artery aneurysm), fever resolution and adverse events. Coronary artery dilatation is identified if the coronary artery diameter is ≥ 3mm in a child < 5 years old, or ≥ 4mm in a child ≥ 5 years old. Small coronary aneurysm is present when the coronary artery diameter is ≥ 4mmin a child < 5 years old, or an internal diameter of a segment measuring 1.5 to 4 times that of an adjacent segment if the child is ≥ 5 years old.

Giant aneurysm is present when the coronary artery diameter is ≥ 8mm or if the child is > 5 years old, an internal diameter of a segment measuring > 4 times that of an adjacent segment.[8,10,13]

Transient coronary artery dilation refers to lesions that disappear within 28 days of illness.[10] Since only three out of six articles gave definitions for coronary artery lesions, the Japanese classification scheme on coronary artery abnormalities was adopted in this meta-analysis.[7,8,14] The assumption is that the AHA classification scheme on coronary artery abnormalities is based on Z-scores, while the Japanese classification is based on absolute or relative internal lumen diameter. Fever resolution is defined as temperature < 37.8°C, or a significant decrease in temperature in a patient with persistent fever, within 3 days of completing the drug infusion, and for which there is no other explanation for fever resolution. Adverse events included death or near-death, or any serious or non-serious medical event that may or may not warrant additional medical treatment to prevent another serious event. Data were retrieved as reported from the studies. In one study where the outcome of interest was indirectly reported, analysis of reported numbers was done to extract the desired information.[8]

Assessment of the Risk of Bias in Included Studies

The methodological quality of included RCTs and prospective studies were assessed using the Cochrane collaboration tool for the risk of bias. The Methodological Index for Non-Randomized Studies (MINORS) guidelines was used to assess methodological quality of all non-RCTs. The overall quality of evidence and strength of recommendations were evaluated using the GRADE system. Three investigators independently assessed the risk of bias per study and a consensus was generated among the reviewers.

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Statistical Analysis

A traditional pair-wise, meta-analysis was conducted. All statistical analyses and risk of bias assessment were performed using the Review Manager [RevMan] 5.4.1 software. The risk of bias assessment was performed in accordance with the guidelines outlined in the Cochrane Handbook (version 6.1). Risk ratios (RR) and 95% confidence interval (CI) for dichotomous outcomes were estimated and a random-effects model was used. Sensitivity analyses were performed to evaluate the effect of each study on the pooled RR. Between-study heterogeneity was tested using Chi-square and was considered significant at $I^2 > 50\%$ or $P < 0.1$. Funnel plot was not utilized to examine publication bias as it was deemed unnecessary.[15] Forest plot was employed to represent estimated results from studies. The desired sample size was calculated at 300 as derived from a priori estimated treatment effects.

RESULTS

Study Selection and Description

We retrieved 824 potentially eligible studies (Figure 1), six of which were published between 2005 and 2016 and were included in the meta-analysis following the inclusion and exclusion criteria (Table 1). Two studies were RCTs, two prospective and two retrospective studies. Neither the blinding nor the allocation concealment method was mentioned in any of the reports (Table 3). Recurrent or persistent fever in IVIG-refractory KD was defined in three studies as a body temperature of more than or equal to 37.5°C within 48 hours of receipt of IVIG, while two studies defined it as a body temperature of more than 38.0°C within 24 to 36 hours of initial IVIG treatment (Table 2). One study did not specify the body temperature used as the basis for fever, but defined treatment resistance as fever persistence or relapse within 36 hours of initial IVIG treatment. The six selected studies included 188 patients.

The control and treatment groups had similar baseline characteristics, including sex, ethnicity, age at fever onset, time from fever onset to diagnosis, and time from first treatment to retreatment. All studies reported a higher proportion of males than females, with an average age at diagnosis between two to three years old. The average day of illness upon initial treatment was between 4 - 5 days. The average day of retreatment was during the seventh to ninth day of illness. From the included studies, the rate of resistance to initial IVIG treatment was reported between 13-17%.

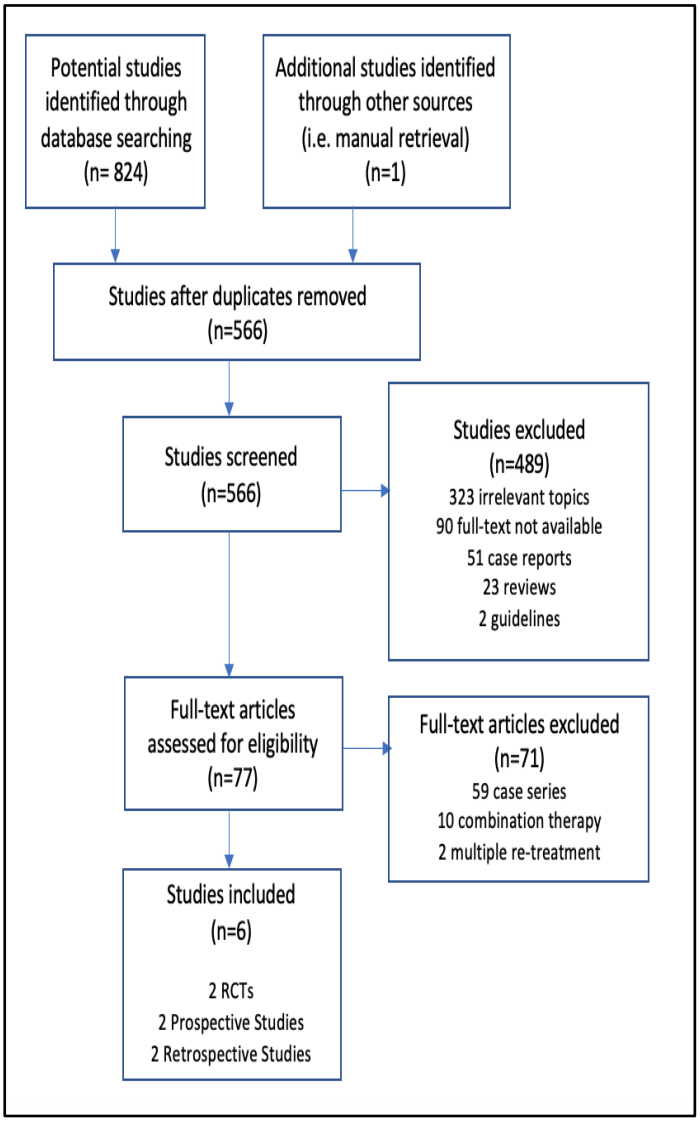

Figure 1. PRISMA Study flow diagram

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Table 1. Characteristics of included studies

AUTHOR, YEAR	COUNTRY	DESIGN OF STUDY	TOTAL PATIENTS	SEX (MALE %)	AGE (YEAR)	INITIAL TREATMENT		RATE OF RESISTANCE TO INITIAL IVIG	RE-TREATMENT		FF UP PERIOD POST RE-TREATMENT
						DAYS OF ILLNESS UPON TREATMENT			DAYS OF ILLNESS UPON TREATMENT		
						GROUP A (2ND IVIG)	GROUP B (IVMP)		GROUP A (2ND IVIG)	GROUP B (IVMP)	
MIURA 2005	JAPAN	RCT	22	NR	NR	NR	NR	NR	NR	NR	1 WEEK
FURUKAWA 2007	JAPAN	RETROSPECTIVE*	63	54%	2.4	5 (2-9)	4 (3-5)	13%	7 (6-8)	8 (5-11)	4 WEEKS
MIURA 2008	JAPAN	RCT	15	67%	2.6	4 (4-4)	5 (4-7)	NR	8 (6-9)	9 (8-10)	1 WEEK
OGATA 2009	JAPAN	PROSPECTIVE#	27	64%	2.5	4 ± 1.3	5 ± 0.3	16%	8 ± 2.4	7 ± 1.3	PRIOR DISCHARGE
TERAGUCHI 2013	JAPAN	PROSPECTIVE*	41	59%	2.3	NR	NR	17%	7 (6-10)	8 (5-14)	4 WEEKS
KIM 2016	KOREA	RETROSPECTIVE#	20	76%	2.7	NR	NR	NR	NR	NR	8 WEEKS

*Subjects who refused steroids were assigned to the IVIG group.
#Subjects were assigned to 2nd IVIG vs. IVMP based on location of care.
NR= not reported

Table 2. Characteristics of included studies

AUTHOR, YEAR	INITIAL IVIG TREATMENT				RE-TREATMENT					
	IVIG (G/KG/DOSE) [HRS] *	ASA (MKDAY)*	INITIAL IVIG RESISTANCE DEFINITION	RATE OF RESISTANCE TO INITIAL IVIG*	GROUP A			GROUP B		
					2ND IVIG		ASA*	IVMP		ADDITIONAL TX*
					(G/KG/DOSE)	# OF	(MKDAY)	(MKDAY)	# OF DAYS	
MIURA 2005	2 [NR]	NR	T≥37.5C W/IN 48HRS	NR	2	1	NR	30	3	HEPARIN 15-20U/KG/HR
FURUKAWA 2007	2 [12-24]	30	RELAPSE W/IN 36HRS	13%	1 TO 2	1	30	30	3	PRED (1) X 7D
MIURA 2008	2 [24]	NR	T ≥ 37.5C W/IN 48HRS	NR	2	1	NR	30	3	NR
OGATA 2009	2 [24]	30	T ≥ 37.5C OR DECREASE IN CRP <50% W/IN 48HRS	16%	2	1	30	30	3	NR
TERAGUCHI 2013	2 [24]	30	T≥38C W/IN 36HRS OR DECREASE IN CRP <50% IF T 37.5-38C	17%	2	1	NR	30	3	HEPARIN 10U/KG + PRED (1) X 7D
KIM 2016	2 [10-12]	50	T>38C W/IN 24-36HRS	NR	1 TO 2	1	50	30	3	TAPERING ORAL PRED

NR= not reported

Table 3. Quality assessment of included studies

AUTHOR, YEAR	RANDOMIZATION	BLINDING	ALLOCATION CONCEALMENT	LOST TO FF UP/ WITHDRAWAL	GRADE	MINORS
MIURA 2005	YES	NR	NR	NO	B	N/A
FURUKAWA 2007	NO	NR	NR	NO	C	19
MIURA 2008	YES	NR	NR	NO	B	N/A
OGATA 2009	NO	NR	NR	NO	C	20
TERAGUCHI 2013	NO	NR	NR	NO	C	20
KIM 2016	NO	NR	NR	NO	C	19

Risk of Bias of Included Studies

The four non-RCTs had scores ranging from 19 to 20 points according to the MINORS guidelines (Table 3), hence, all of these were marked as high quality studies. Additionally, the risk of bias assessed by the Cochrane collaboration tool (Figure 2) suggested possible sources of selection, performance and detection bias. In the two RCTs included, the papers discussed randomization, without providing information on allocation concealment or blinded measurements.

The published methodology, including outcome measures reported by the included studies, was consistent with that reported in the respective results section. The risk of selective reporting bias for these studies has been coded as low.

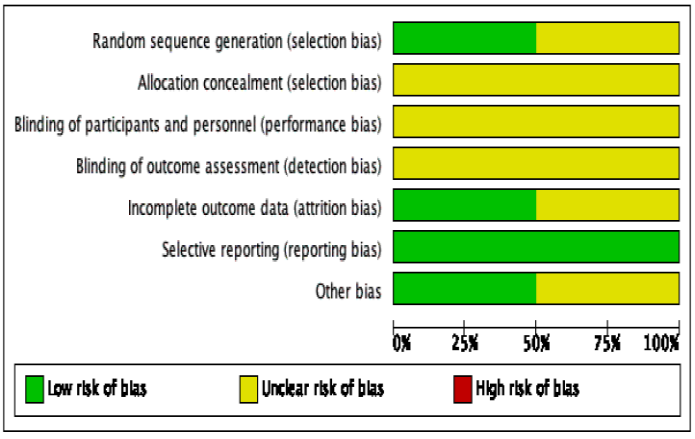

Figure 2. Assessment of the risk of bias

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Evaluation of Outcomes

CALs

Incidence of coronary artery lesions was not significantly different between a second IVIG infusion versus IVMP treatment in patients with refractory KD (RR 0.82, 0.34-1.96, P=0.66).

No significant heterogeneity was observed among the studies (I^2=38%, P=0.16) (Figure 3). The follow-up time point at which echocardiography was performed ranged from study entry to eight weeks post-treatment.

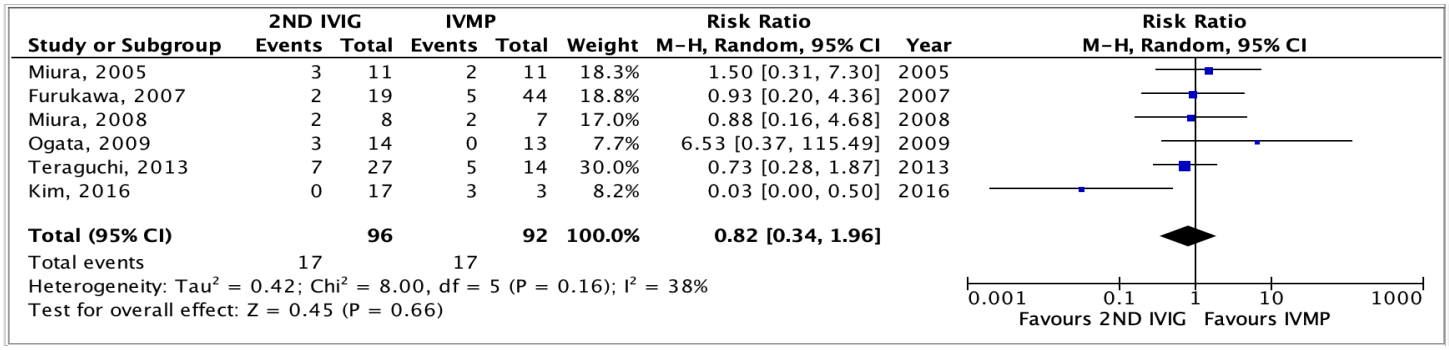

Figure 3. Forest plots of a traditional pair-wise meta-analysis of CALs post-retreatment in patients with refractory KD

Fever resolution

The rate of fever resolution was not significantly different after a second IVIG versus IVMP treatment in patients with refractory KD (RR 0.97, 0.84-1.13, P=0.72).

No significant heterogeneity was observed among the studies (I^2=12%, P=0.34) (Figure 4).

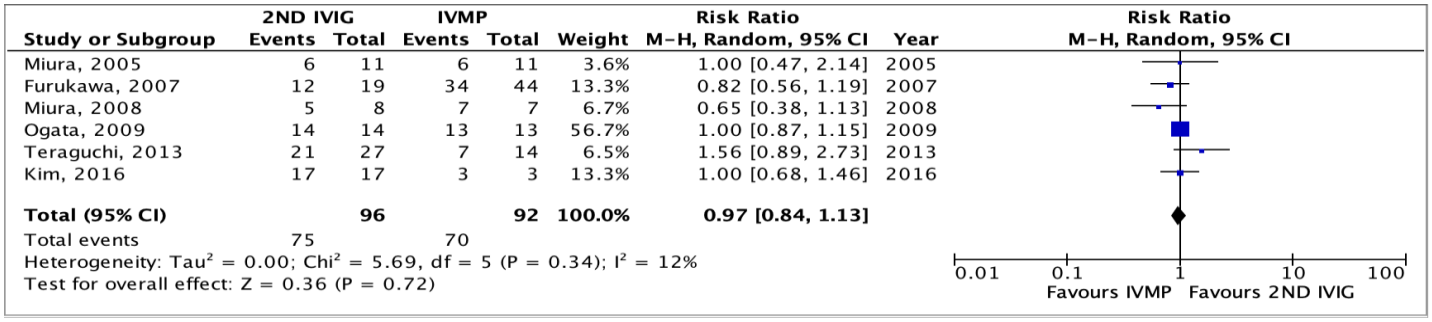

Figure 4. Forest plots of a traditional pair-wise meta-analysis of fever resolution post-retreatment in patients with refractory KD

Adverse events

Four studies reported adverse events during treatment. Miura, et al. and Furukawa, et al. reported more adverse effects in the IVMP group, particularly bradycardia (RR 0.26, 0.11-0.61, P=0.002), hypertension (RR 0.64, 0.42-0.97, P=0.04), and hypothermia (RR 0.32, 0.06-1.81, P=0.20).[7,9,16] The incidence of hyperglycemia (RR 0.07, 0.01-0.46, P=0.006) was also significantly higher in the IVMP group.

Gastrointestinal bleeding and nerve palsy were also reported in the IVMP group.[7,14] No significant heterogeneity was observed within each subgroup of adverse events (All I^2=0%, P>0.10). Overall effect revealed a significantly higher incidence of adverse events in the IVMP group (RR 0.42, 0.26-0.57, P=0.0002) (Figure 5).

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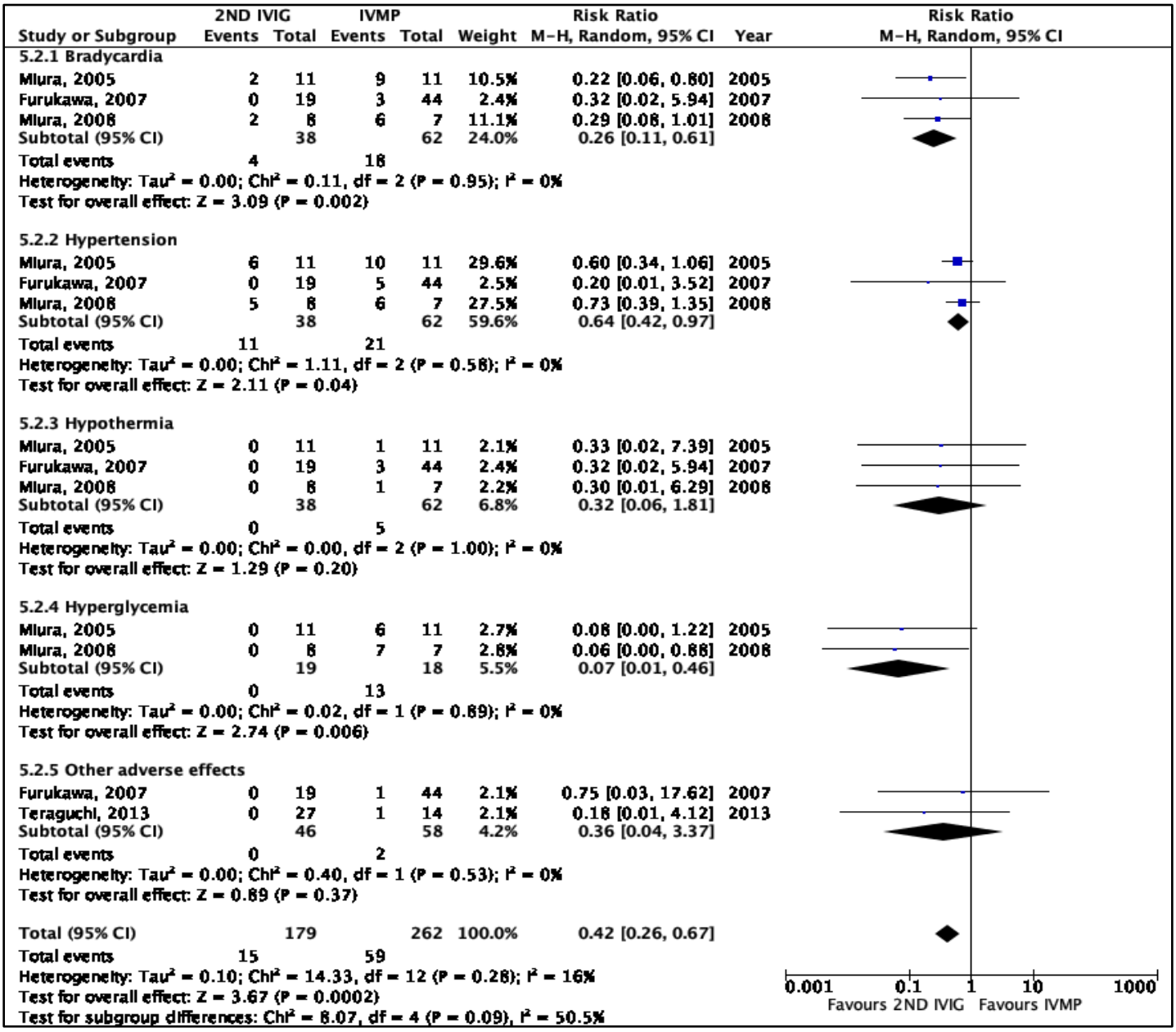

Figure 5. Forest plots of a traditional pair-wise meta-analysis of variable AEs during retreatment

Sensitivity Analysis and GRADE Evidence Profile

There is no significant heterogeneity observed among the included studies in terms of incidence of CALs, fever resolution, or adverse effects. Data reported by the studies of Ogata, et al. and Kim, et al. for CALs, and by Teraguchi, et al. for fever resolution, were outside of the range reported in the rest of the studies.[8,14,17] Sensitivity analysis showed no significant impact of individual outcomes on the overall results (Figure 6 and 7).

Heterogeneity was noted to have totally vanished (I^2=0% from 34%) in the analysis of CAL incidence when the study of Kim, et al. was excluded (Figure 6).

According to the GRADE system, the working group grades of evidence were moderate (Grade B) for incidence of CALs and rate of fever resolution, and low (Grade C) for the total rate of adverse events measured.[12]

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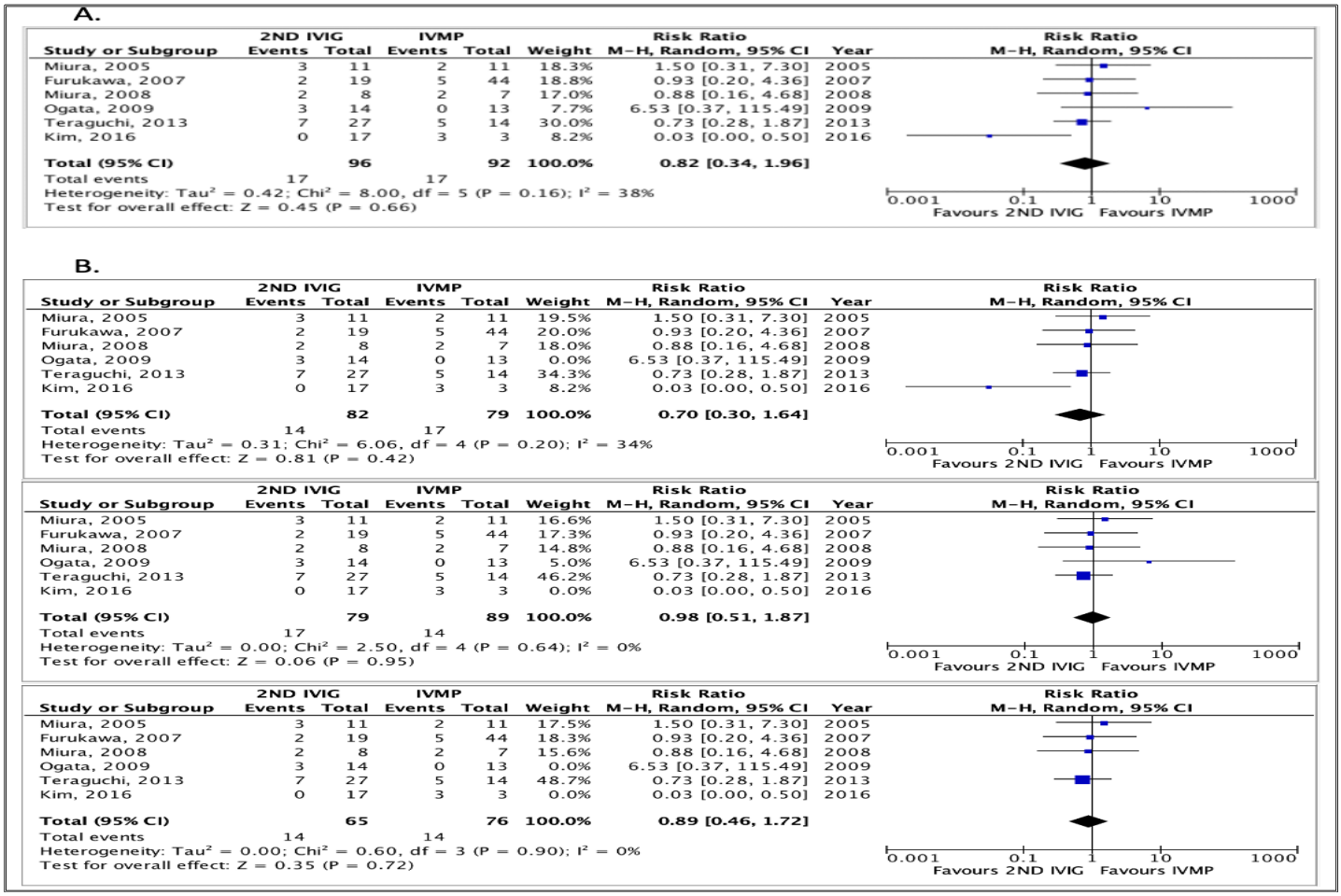

Figure 6. Forest plots of a traditional pair-wise meta-analysis on incidence of CALs post-retreatment of refractory KD patients: (A) before and (B) after sensitivity analysis

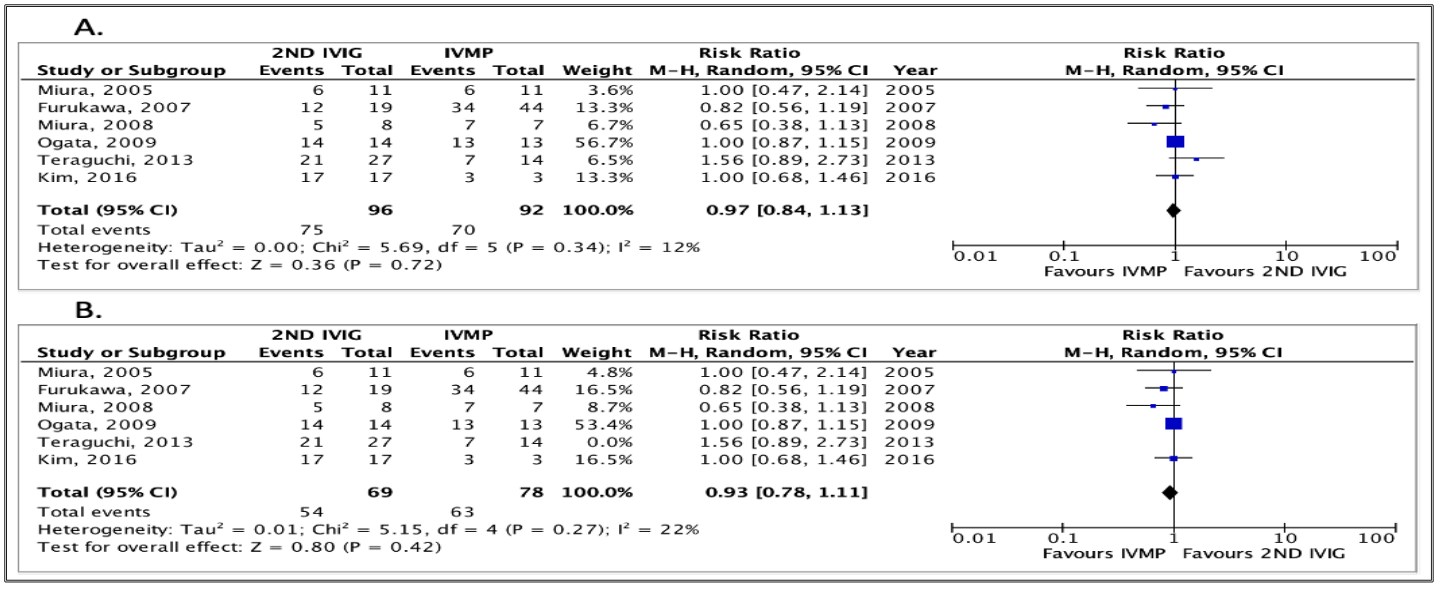

Figure 7. Forest plots of a traditional pair-wise meta-analysis on fever resolution post-retreatment of refractory KD patients: (A) before and (B) after sensitivity analysis

Publication Bias

There were only six studies included in this meta-analysis and screening of publication and reporting bias through funnel plot asymmetry or meta-regression analyses was unnecessary.[15]

DISCUSSION

This meta-analysis compared the outcomes of second-line IVIG versus IVMP in the treatment of children with IVIG-refractory KD. No significant differences between the two groups were seen in terms of incidence of CAL and rate of fever resolution. More adverse events were reported in those who received IVMP than those who were given a second dose of IVIG.

The incidence of CAL was similar in those who received a second IVIG infusion versus those given high-dose IVMP for IVIG-refractory KD. The longest follow-up period for repeat 2D echocardiography was eight weeks after re-treatment. The incidence of CAL for the different studies averaged around 20%-25% for both re-treatment groups, excluding the findings of one study which was out of the range of the other five. A sensitivity analysis showed a disappearance of heterogeneity, with the overall outcome being unaffected when the study of Kim, et al. was excluded. A Cochrane review based on seven randomized controlled trials evaluated the impact of corticosteroid use on the incidence of CALs in KD, as either first-line or second-line treatment, and found that the addition of corticosteroids significantly reduced the subsequent occurrence of CALs without serious adverse effects.[18] However, the review included some RCTs with participants predetermined to be high-risk for IVIG-refractory KD, which may be a possible source of bias in favor of steroid treatment. Zhu, et al., in their meta-analysis on the effect of corticosteroid therapy in Kawasaki disease, found no difference in the incidence of coronary artery aneurysms, with and without steroid therapy, irrespective of whether it was used as a primary or as an additional treatment for IVIG-refractory KD.[3]

Kobayashi, et al. reported that patients who were stratified as low-risk for IVIG-refractory KD, using the Kobayashi risk scoring system, had similar clinical and coronary outcomes despite the addition of corticosteroids to standard treatment, while significantly lowering the incidence of treatment failure and coronary artery abnormalities among high-risk patients, with corticosteroid use.[19] More recent meta-analyses also reported inconsistent findings.[4,11,20] Crayne, et al. analyzed 388 patients with IVIG-refractory KD from 8 papers, including comparative studies on second IVIG versus IVMP, or second IVIG versus infliximab, and noncomparative studies involving only second IVIG or infliximab. The study reported no significant differences in the incidence of persistent non-giant aneurysms at 4-8 weeks after re-treatment across the three treatment groups, but found second IVIG to have significantly reduced the presence of giant aneurysms by 90% versus IVMP (RR=0.1; [95% CI, 0.01-0.9], p=0.01).[4] Chan, et al. had the same objective as Crayne, et al. and analyzed 12 studies with 372 IVIG-refractory KD patients. They found that neither infliximab nor IVMP was significantly more effective than second IVIG infusion in lowering CALs (infliximab, 0.85, 0.43-1.69; IVMP, 0.99, 0.52-1.88).[11] Yang, et al. focused on comparison between second IVIG with IVMP in IVIG-refractory KD patients, and analyzed 4 studies with 127 patients. The study found no significant difference in the incidence of CALs between second IVIG and IVMP (odds ratio=1.55, 95% CI: 0.57-4.20, p=0.39).[20] This study reports similar findings as Yang, et al. and Chan, et al. Both studies reported no significant difference in terms of incidence of CALs between second IVIG and IVMP in IVIG-refractory KD.

The fever resolution rate was similar, post-re-treatment, with either IVMP or second dose IVIG. The antipyretic effect of IVMP has been shown to be superior than a second IVIG infusion in refractory KD in several studies.[3,7,9,11,16,17,20]

Fever resolution is defined as a significant decrease in temperature in a patient with persistent fever, within three days of completing the drug infusion, without another explanation for the fever other than Kawasaki disease. Although fever resolved faster in the IVMP treated group, recurrence of fever was identified in some studies, so the proportion of responsive patients was similar between the two groups.[7,9,14,16] Our study considered fever recurrence as an indication of non-response to treatment. Re-treatment resistance is therefore the reciprocal of fever resolution rate. Analysis of the final fraction of febrile patients revealed no significant difference in incidence of fever resolution and therefore treatment resistance between IVMP and second dose IVIG (Figure 4). The discrepancy of findings in this paper with previous studies is likely secondary to dissimilar fever resolution rates which were taken for comparison.[3,7,9,16,17,20] A recent meta-analysis compared the initial fever resolution rates between the two re-treatment groups despite fever recurrence in the IVMP group.[20] Other than fever, other objective quantifiable parameters, including 2-D echocardiogram findings, were also considered as possible proxies for outcomes when comparing the two treatment groups. In the assessment of included articles however, the 2-D echocardiography data provided were very disparate and incomplete to allow comparison of findings between the two treatment groups.

One of the articles in this meta-analysis, by Miura, et al., found that children who received IVMP had cytokine levels that decreased faster than those seen in children who received a second IVIG initially, but with similar levels subsequently.[9] Monocyte chemo-attractant protein 1 (MCP-1), tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) were significantly lower in IVMP-treated patients, compared with the IVIG-treated group, on day 4 but not on day 7. Rebounds in cytokine levels may possibly explain the fever recurrence after treatment for KD.

This is the reason why a tapering course of oral prednisone is suggested for continuation therapy, after systemic corticosteroid has been given, to prevent rebound inflammation.[9,10] Past reports have shown that MCP-1 is expressed at the sites of coronary arteritis of fatal KD patients and that the expression of MCP-1 genes persisted or was increased into the convalescent phase in KD patients with coronary artery lesions.[21,22] Serum level of TNF-α has also been reported to be higher in KD patients with coronary artery lesions than in those without coronary artery lesions.[23] Oral steroids, after the systemic doses, is therefore suggested to continuously suppress cytokine levels to reduce the chance of fever recurrence and the incidence of coronary artery lesions in children who receive IVMP.[9, 24]

The IVMP group reported more adverse events during treatment, including bradycardia, hypertension and hyperglycemia. These are common side effects of high dose IVMP therapy and these were all transient and non-serious.[7,9,16,25] Chan, et al. pointed out a possible reporting bias as methylprednisolone has been extensively reported in several studies as an anti-inflammatory drug administered to IVIG-refractory KD patients.[20] Other adverse events reported in the IVMP group included a case of gastrointestinal bleeding and a case of nerve palsy.[7,14]

Relevance and Implications

The Philippine Health System is dominated by the private health sector and patients are often burdened by out-of-pocket payments for health services. IVIG is an expensive treatment. For patients with IVIG-refractory KD, the current recommendation of giving a second dose of IVIG imposes a significant financial burden. The efficacy of methylprednisolone, as non-inferior to a second dose of IVIG, can have significant utility as an acceptable, relatively inexpensive, and reliable choice, as a second-line treatment for IVIG-refractory KD.

Although this study did not address cost-effectiveness of the two treatment options, it is well known that IVIG is very expensive, while corticosteroids are relatively inexpensive medications.

Limitations of the Study

IVIG-refractory KD is rare, making an adequately powered prospective randomized controlled trial difficult to conduct.[4] Only two of the included studies in this report were randomized controlled studies. The dosage and administration of corticosteroids, immunoglobulins, acetylsalicylic acid and other additional drugs in all included studies, as presented in Table 2, demonstrated minimal variation which can also affect the outcomes for accurate comparison. Furthermore, the studies included small samples and could contribute to bias. The follow-up periods of each study were relatively short, which may not truly reflect the coronary artery outcomes post-retreatment. In a meta-analysis, it can be difficult to avoid publication bias. Nevertheless, short of adequately powered studies among published data, this type of evidence review is the best effort to improve the test power by combining several small clinical trials into a seemingly large clinical trial. The risk of selective reporting bias is deemed low as the published methodology, including outcome measures reported by the included studies, was consistent with that reported in the respective results section. The desired sample size of a meta-analysis is at least that of a large well-designed clinical trial.[26] The target sample size for this study was calculated at 300. Due to limited available evidence, the identified eligible studies accrued only to a total of 188 patients. The review process of the articles was done by three investigators independently, but the screening and retrieval of the included articles was solely done by the primary investigator which could have contributed to selection bias. More than one independent investigator involved in the retrieval of articles is ideal to limit the chance of missing out on relevant articles.

CONCLUSION

This study found no significant difference in the incidence of coronary artery lesions and the rate of fever resolution post-retreatment with IVMP versus a second dose of IVIG in IVIG-refractory KD patients. More adverse events were reported in the IVMP group, although all were noted to be transient and to have resolved without additional management.

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ORIGINAL ARTICLE

CLINICAL PROFILE AND COURSE ON FOLLOW-UP OF NEWBORNS OF SARS-CoV-2 POSITIVE MOTHERS

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2nd PLACE 2022 PIDSP RESEARCH CONTEST

ABSTRACT

Objective: This study aims to determine the clinical profile and course on follow-up of newborns delivered to a SARS-CoV-2 positive mother from two private tertiary hospitals.

Methodology: This is a retrospective, cross-sectional study. A chart review of all neonates delivered to SARS-CoV-2 positive mothers was conducted. Subsequent interview was done to determine their clinical course and neurologic status at 3-, 6-, 9-, 12-, and 15-month-old. Data collected was presented as frequencies, percentages, or proportions.

Results: Out of the 67 newborns born to SARS-CoV-2 positive mothers, three neonates tested positive for SARS-CoV-2. All three were delivered to mothers with mild symptoms, were full term, with good APGAR score and appropriate for gestational age. One was eventually intubated and managed as COVID-19 confirmed critical. Among the SARS-CoV-2 negative newborns, majority had an unremarkable neonatal outcome. Thirty-six neonates were available for follow-up: 1 expired due to aspiration pneumonia at 2 months of age, 4 were readmitted for pneumonia, UTI, acute gastroenteritis, and cow's milk allergy. Twenty-one had infection at one point prior to this study follow-up but were all mild not requiring admission. Two had abnormal head size, while 2 had developmental delay, these 4 infants with neurological findings on follow-up were all RT-PCR negative at birth.

Conclusion: Maternal COVID-19 infection does not necessarily result to a neonatal infection. For those neonates with mild symptoms, SARS-CoV-2 causality could not be established. On follow-up, there were a few who developed significant problems that have long-term implications in the overall growth and development of the child.

KEYWORDS: *Maternal COVID-19 infection (SARS-CoV-2 positive mother), Neonatal outcome, Long-term follow-up*

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INTRODUCTION

A novel pathogenic coronavirus named, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), causing Coronavirus Disease 2019 (COVID-19) was first identified in Wuhan City in China, as the cause of a rapidly spreading pneumonia. It initially resulted to an epidemic in China, that eventually spread to other countries, resulting to a pandemic as declared by the World Health Organization (WHO).[1,2]

According to the Surveillance and Analysis of COVID-19 in Children Nationwide (SALVACION) study by the Pediatric Infectious Disease Society of the Philippines (PIDSP) majority had mild symptoms with 42.1% and a few died (8.2%).[3] In the interim guidelines on COVID-19 of PIDSP, it showed a local data with greater number of mortalities seen in neonates and toddlers from 0-4 years old age group, comprising 54.8%.[4] The risk of developing COVID-19 during the perinatal period is relatively still unknown.[5] Vertical transmission of the SARS-CoV-2 may occur in a minority of cases, where the virus was also detected in other specimens like the cord blood (3.6%), placenta (7.7%), recto-anal swab (9.7%) and serology (3.7%).[6] In comparing symptomatic versus asymptomatic SARS-CoV-2 positive mothers, those who are symptomatic were more likely to have premature deliveries resulting to their newborns requiring intensive care.[7,8]

There is limited evidence on the impact of SARS-CoV-2 virus infection on children, especially in infants born to positive mothers and their long-term sequelae. The outcome of neonates delivered to SARS-CoV-2 positive mothers are unlikely to be directly related to the virus itself, studies showed that maternal comorbidities may have contributed to their adverse outcomes.[9] But for those SARS-CoV-2 positive neonates, they may show typical mild to moderate symptoms like fever, hyperbilirubinemia, cough, respiratory distress, and pneumonia.[7,10] However, data on the long-term follow-up of these newborns is scarce.

This study aims to determine the clinical profile and course on follow-up of the newborns delivered to SARS-CoV-2 positive mothers in private tertiary institutions from April 2020 to May 2021.

METHODOLOGY

Study design

This is a descriptive, retrospective study with 2 components. Data on maternal and neonatal demographics, their clinical profile, and the neonatal outcomes were retrieved through chart review. Information on the clinical course on follow-up of the study population was gathered through a cross-sectional survey by phone interview.

Study setting

The study was conducted in two private tertiary hospitals.

Study population

Purposive sampling was employed to include all subjects, who fulfilled the inclusion criteria. The newborns included in this study were all the neonates of SARS-CoV-2 positive mothers delivered from April 2020 to May 2021. Data from neonates of SARS-CoV-2 negative mothers or those who refused to undergo RT-PCR were not included in the study. Those without consent from the mother or attending physician and those lost to follow-up were likewise not included.

Data collection and analysis

The researcher coordinated with the pediatric residents of the two private tertiary hospitals for the list of all mothers, who delivered in their institutions from April 2020 to May 2021. The researcher only included those mothers who tested positive on RT-PCR for SARS-CoV-2 regardless of gestational age on testing. No a priori sample size computation was done since the exact incidence of the neonatal condition is not definite.

The mothers of the identified subjects were initially informed through text message and phone call regarding the study. Verbal informed consent, along with the rest of the interview were obtained, conducted, and documented. In addition, a soft copy of the informed consent was sent to their email or messaging application and was sent back to the researcher with an electronic signature attached for filing. In the preferred language of the mother (English, Filipino or Cebuano dialect), the actual interview included questions on: 1) clinical signs and symptoms that developed after hospital discharge, 2) any hospital readmissions, and 3) developmental milestones achieved by the infant at 3, 6, 9, 12 and 15 months of age as applicable to their chronological age during the interview. They were categorized as such based on the Denver chart. The developmental milestones can be assessed by direct observation of the examiner or reported by a primary caregiver based on four domains (gross motor, fine motor, language, and personal/social). For this study, the researcher collected the data through phone interview with questions guided by the Denver chart. The corresponding developmental age of the subjects was based on the report by the primary caregiver. The results of the evaluated milestones were reviewed and corroborated by a pediatric neurologist. In instances where there was discordance of results, the primary caregiver was re-interviewed for clarifications in the presence of pediatric neurologist. These neurodevelopmental milestones were then recorded as developmental quotients, which are computed by dividing the developmental age based on the Denver II developmental screening test by their chronological age on assessment. Data collected from chart review using the data collection tool and from the phone interview were encoded in Microsoft Excel spreadsheet and summarized as frequencies, percentages, or proportions.

Ethical Consideration

The research protocol was submitted to the Institutional Review Board (IRB) of the hospital before the commencement of the study.

The investigators have no conflicts of interest. There was no funding obtained for this study. The primary investigator safeguarded the rights and preferences of each newborn and his/her respective mother all throughout the duration of the study. Anonymity was ensured on all electronically gathered data, as well as the printed records. Informed consent was obtained prior to the start of the phone call interview.

All electronically gathered patient information were saved onto the investigator's laptop and were transferred to a password-protected hard drive. The hard drive and hard copies of files are kept in a drawer under lock and key with the author having sole access. At any time, data gathered will not be disclosed for use outside the scope of this study. After 5 years, all data will be appropriately discarded.

RESULTS

Out of the 1,924 mothers, only sixty-seven mothers had positive SARS-CoV-2 RT-PCR results. Only 36 mothers gave their consent to be interviewed regarding the course on follow-up of their children. One of the infants expired at 2 months of age and was assessed only up to that age, thus, she was not included in the assessment of neurodevelopmental outcome. Thus, only 35 were followed-up and included until their corresponding age during the time of interview.

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Table 1. Demographic profile of SARS-CoV-2 positive mothers

Variables		n= (67)	%
Age (years) *Mean age 31 years old*	≤ 17	0	0
	18 – 34	51	76
	≥35	16	24
Marital Status	Single	29	43.3
	Married	38	56.7
Ethnicity	Filipino	67	100
Residence	Urban	42	63
	Rural	25	37
Educational Attainment	College Graduate	47	70
	College Level	6	9
	High School Graduate	3	4.5
	High School Level	0	0
	No data available	11	16.4
Income	Above Minimum	40	60
	Minimum	13	20
	Below Minimum	2	3
	No data available	12	17

Sixty-seven mothers confirmed positive for SARS-CoV-2 RT-PCR were included in the study. Seventy-six percent were under the low-risk reproductive age with mean age of 31 years old, with the range of 20 to 43 years old.

Majority were married and resided in urban areas. Most of them were college graduates earning above minimum income.

Table 2. Clinical profile of SARS-CoV-2 positive mothers

Variables		n= (67)	%
Obstetric Score	Primigravid	29	43
	Multigravid	38	57
Trimester Infected	First	1	1.5
	Second	0	0
	Third	66	98.5
COVID Symptoms			
Number of symptoms present	Asymptomatic	50	75
	1 symptom	1	1
	More than 1 symptom	16	24
Symptoms present*		17	25
	Fever	7	
	Cough	7	
	Coryza	7	
	Body Malaise	5	
	Anosmia / Ageusia	4	
	Sore Throat	2	
	Dyspnea	1	
Maternal Comorbidities**		39	58
	Gestational Diabetes Mellitus	17	
	Urinary Tract Infection	11	
	Bronchial Asthma	6	
	Gestational Hypertension / Pre-eclampsia	4	
	Coronary Artery Disease	3	
	Hypothyroidism	3	
	Hyperthyroidism	1	
	Bacterial Vaginosis	1	
	Uterine Atony	1	
No Maternal Comorbidities		28	42

**1 patient may have one or more symptoms*
***1 patient may have one or more comorbidities*

Fifty-seven percent were multi-gravid, 98.5% were infected with SARS-CoV-2 during the third trimester and majority of them (75%) were asymptomatic. Symptoms include fever, cough, and coryza. Thirty-nine mothers (58%) had comorbidities which included gestational diabetes mellitus, followed by urinary tract infection, bronchial asthma, and gestational hypertension.

Table 3.1. Demographics of neonates born to SARS-CoV-2 positive mothers

Variables		COVID Positive (n= 3)	COVID Negative (n= 45)	No RT-PCR (n= 19)	Total Newborns (n=67)
Gender	Male	1 (33%)	18 (40%)	8 (42%)	27 (40.3%)
	Female	2 (66 %)	27(60%)	11 (58%)	40 (59.7%)
Mode of Delivery	Spontaneous Vaginal Delivery	2 (66%)	26 (58%)	11 (58%)	39 (58%)
	Cesarean Section	1 (33%)	19 (42%)	8 (42%)	28 (42%)
Maturity	Preterm	0	7 (16%)	1 (5%)	8 (12%)
	Full term	3 (100%)	38 (84%)	18 (95%)	59 (88%)
APGAR Score	Good (7 – 10)	3 (100%)	44 (98%)	17 (89%)	64 (95.5%)
	Moderate (4 – 6)	0	1 (2%)	2 (11%)	3 (4.5%)
	Severe (0 – 3)	0	0	0	0
Ballard Score	28 and below	0	1 (2%)	0	1 (1.5%)
	32 to 35 6/7	0	1 (2%)	0	1 (1.5%)
	34 to 36 6/7	0	4 (9%)	0	4 (6%)
	37 and above	3 (100%)	39 (87%)	19 (100%)	61 (91%)
Birthweight (grams)	≤ 1,000	0	0	0	0
	1,000 – 1,499	0	1 (2%)	0	1 (1.5%)
	1,500 – 2,499	0	11 (24%)	2 (11%)	13 (19.4%)
	≥ 2,500	3 (100%)	33 (73%)	17 (89%)	53 (79%)
Classification	Small for gestational age	0	4 (9%)	2 (11%)	6 (9%)
	Appropriate gestational age	3 (100%)	40 (89%)	17 (89%)	60 (90%)
	Large for gestational age	0	1 (2%)	0	1 (1%)

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Three neonates were positive for SARS-CoV-2 naso/oropharyngeal RT-PCR swabs. They were all delivered to mothers with COVID-19 mild pneumonia with unremarkable maternal history, except for one mother who had gestational diabetes requiring insulin. Majority were born full term via normal spontaneous delivery, with good APGAR score, mean age of gestation at 38 weeks and weight of 2,885 grams, appropriate for gestational age.

Eight were born preterm, out of the eight mothers with preterm baby-one had severe COVID-19 disease, two with moderate disease while the rest of the five had mild symptoms. Three of them were delivered via primary cesarean section secondary to the following: preeclampsia, non-reassuring fetal heartbeat pattern and maternal morbidity with COVID-19 infection. Majority had a good APGAR score, but the neonate from the mother with severe COVID-19 had a low APGAR score (1, 7, 7). Meanwhile the newborn delivered from a mother with moderate COVID-19 infection had an APGAR score of 5, 8.

At 24 to 48 hours of life, RT-PCR was obtained from forty-eight (72%) newborns. The 19 (28%) newborns did not undergo RT-PCR as 3 mothers refused to have their neonates swabbed, while the remaining 16 mothers were cleared from the infection after completing 14 days isolation prior to the delivery. Out of these 19 mothers, only 4 of them had mild respiratory symptoms. Regardless of the RT-PCR result, or if an RT-PCR was obtained or not, all newborns delivered from SARS-CoV-2 RT-PCR positive mothers are included in the study.

Three of the newborns had positive RT-PCR test and the rest of the forty-five (67%) were negative. Two of the COVID-19 positive neonates were delivered via normal spontaneous delivery, while one via primary cesarean section secondary to maternal morbidity. These three newborns were full term, with good APGAR score, 38-39 weeks age of gestation, average weight of 2,970 grams and appropriate for gestational age.

Table 3.2. Clinical profile of neonates born to SARS-CoV-2 positive mothers

Variables		COVID Positive (n= 3)	COVID Negative (n= 45)	No RT-PCR (n= 19)	Total Newborns (n= 67)
Number of symptoms present	Asymptomatic	1 (33.3%)	23 (51%)	15(79%)	39 (58%)
	One symptom	1 (33.3%)	6 (13%)	3 (16%)	10 (15%)
	More than one symptom	1 (33.3%)	16 (36%)	1 (5%)	18 (27%)
Signs and Symptoms*	Jaundice	1	13	3	17
	Tachypnea	1	13	2	16
	Alar flaring	1	4	0	5
	Chest Retractions	1	5	0	5
	Desaturations	1	3	0	4
	Cyanosis	0	3	0	3
	Poor suck	1	1	0	2
	Seizure	0	1	0	1
	Vomiting	0	1	0	1
	Hypoglycemia	0	1	0	1
	Elevated CRP	0	3	0	3
Comorbidities**		2 (66.6%)	22 (49%)	4 (21%)	28 (42%)
	Neonatal Pneumonia	0	6	0	6
	Neonatal Sepsis	1	4	0	5
	Hyperbilirubinemia	0	3	2	5
	Transient Tachypnea of the Newborn	0	4	0	4
	Premature Rupture of Membranes	1	3	0	4
	Respiratory Distress Syndrome	0	2	1	3
	Cardiac Problem (First Degree AV block, Mobitz type II)	0	1	0	1
No Comorbidities		1 (33.3%)	23 (51%)	15(79%)	39 (58%)

*1 neonate may have one or more signs and symptoms
**1 neonate may have one or more comorbidities

Among the 42% newborns who were symptomatic, the majority had more than 1 symptom present. It was noted that jaundice was the most common manifestation, followed by tachypnea, alar flaring, and chest retractions. Six of the newborns developed neonatal pneumonia, followed by neonatal sepsis and transient tachypnea of the newborn.

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The majority of those with negative and no RT-PCR taken were asymptomatic. Of the three COVID-19 positive newborns, one was asymptomatic. The one who was born to a mother with a history of PROM for 19 hours presented with jaundice alone. The third COVID-19 positive neonate, however, had respiratory and septic manifestations. She was eventually assessed to have had critical COVID-19.

Table 4. Management and outcome of neonates

Variables		COVID Positive (n= 3)	COVID Negative (n= 45)	No RT-PCR (n= 19)	Total Newborns (n= 67)
Number of Interventions	None	1 (33.3%)	21 (47%)	14(74%)	36 (54%)
	One intervention	1 (33.3%)	9 (20%)	4 (21%)	14 (21%)
	More than one Intervention	1 (33.3%)	15 33%)	1 (5%)	17 (25%)
Interventions Given (n= 31)*	Antibiotics	2	14	0	16
	Antiviral	1	0	0	1
	Immunoglobulin	1	0	0	1
	Monoclonal antibody	1	0	0	1
	Steroid therapy	1	0	0	1
	Phototherapy	1	13	2	16
	Oxygen Inhalation	1	13	1	15
	CPAP	0	1	0	1
	Intubation	1	2	0	3
Length of Hospital Stay	1 to 2 days	1	11	9	21
	3 to 4 days	0	15	4	19
	5 to 7 days	1	10	3	14
	More than 7 days	1 *(32 days)*	9	3	13
Average Hospital Stay (days)		13	6.5	4	

*1 neonate may have one or more interventions

Forty-six percent of the newborns needed at least 1 to 2 interventions. The remaining 54% received no intervention during the initial admission. The length of hospital stay was longest among the COVID-19 positive newborns who stayed in NICU with an average of 13 days. For those with negative and no RT-PCR taken, they stayed in the hospital for less than a week.

The determinants of the length of hospital stay were mainly the interventions required or mode of delivery aside from the neonate's symptomatology. One COVID-19 positive neonate was asymptomatic and stayed in NICU for 2 days. The other SARS-CoV-2 positive newborn, who stayed for 5 days, had history of maternal premature rupture of membranes for 19 hours and was given antibiotics. The third newborn with critical COVID-19 was born preterm, had neonatal sepsis initially presenting with temperature instability, early jaundice, and respiratory distress. She had a positive blood culture growth of Methicillin Resistant *Staphylococcus epidermidis (MRSE)*. She was eventually intubated at 13 days of life and stayed in the NICU for 32 days but was discharged improved.

Table 5.1. Clinical manifestations on follow-up of neonates from SARS-CoV-2

Variables		COVID Positive (n= 2)	COVID Negative (n= 25)	No RT-PCR (n= 9)	Total Newborns (n= 36)
Number of symptoms present	Asymptomatic	1 (50%)	9 (36%)	5 (56%)	15 (42%)
	One symptom	1 (50%)	4 (16%)	2 (22%)	7 (19%)
	More than one symptom	0	12 (48%)	2 (22%)	14 (39%)
Symptoms*	Fever	0	14	3	17
	Cough	0	9	2	11
	Coryza	0	7	0	7
	Abnormal head size - Benign External Hydrocephalus - Scaphocephaly	0 0	0 1	1 0	1 1
	Vomiting	0	1	0	1
	Bloody stools	1	0	0	1
	Rashes	0	1	0	1
Month symptoms manifested	0 to 3	1	2	1	4
	4 to 6	0	6	1	7
	7 to 9	0	2	1	3
	10 to 12	0	6	1	7
	13 to 15	0	0	0	0

*1 neonate may have one or more symptoms

Out of the 67 newborns, only 36 were included in the follow-up study due to the inability to contact the parents with invalid contact numbers. Out of the 36 mothers who consented for the interview, 58% of the neonates developed at least 1 to 2 symptoms during the course on follow-up. Most of them had fever, cough, and coryza.

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Two neonates had abnormal head size during their follow-up at 2 months of age. Most of these symptoms were seen at 4-6 and 10-12 months of age, and none were reported at 13-15 months. For the 2 patients who presented with abnormal head size at 2 months of age, a magnetic resonance imaging (MRI) was done. The female patient had a benign external hydrocephalus, while the male patient showed obliteration of the sagittal suture that is related to the scaphocephaly. Both were advised to have a close monitoring for developmental delays or episodes of seizure of which none were seen during the follow-up interview.

Two out of the 3 COVID-19 positive newborns were available for follow-up. The critical COVID-19 neonate had bloody stools at 2 months of age, and this was due to cow's milk allergy. The other neonate remained asymptomatic.

Table 5.2. Hospital readmission of neonates born to SARS-CoV-2 positive mothers

Variables	COVID Positive (n= 2)	COVID Negative (n= 25)	No RT-PCR (n= 9)	Total Newborns (n= 36)
I. Asymptomatic	1 (50%)	9 (36%)	5 (56%)	15 (42%)
II. Symptomatic	1 (50%)	16 (64%)	4 (44%)	21 (58%)
A. Readmitted	1	2	1	4
Pediatric Community Acquired Pneumonia	0	0	1	1
Urinary Tract Infection	0	1	0	1
Cow's Milk Allergy	1	0	0	1
Acute Gastroenteritis	0	1	0	1
B. Not readmitted	0	13	3	16
C. Expired				
Asphyxia 2° to Aspiration Pneumonia	0	1	0	1

Four (11%) of the 36 newborns were admitted due to the following reasons: cow's milk allergy at 2 months old, pediatric community acquired pneumonia at 6 months old, urinary tract infection at 6 months old, and acute gastroenteritis at 11 months old.

All of these readmissions had no SARS-CoV-2 RT-PCR done, were all managed accordingly by their pediatricians. The neonate, who was admitted for cow's milk allergy and was provided supportive care, was one of the COVID-19 positive newborns. One infant, whose mother had moderate COVID-19 infection, died at 2 months of age due to asphyxia secondary to aspiration pneumonia but no RT-PCR was taken to confirm if it was related to COVID-19 infection.

Table 5.3. Developmental Quotient (DQ) on follow-up

Chronologic Age	n	Developmental Quotient		
		<1	1	>1
1 to 3 mos	35	0	35	0
4 to 6 mos	35	0	34	1
7 to 9 mos	27	0	25	2
10 to 12 mos	26	0	26	0
13 to 15 mos	21	2	19	0

*Developmental Quotient (Developmental age / Chronological age)
<1 = Delayed
1 = At par with age
>1 = Advance for age

Out of the 36 infants followed-up, the one who expired was not included in the neurodevelopmental milestones assessment. Table 5.3 shows the developmental quotient based on the Denver scale II of the 35 neonates. Based on the findings, majority of the subjects were at par with age. From the 3 neonates, who developed ahead of their age, two had negative RT-PCR, while one had no RT-PCR taken. The three who were advance for age: 2 were able to hold feeding bottle and transfer objects from hand to hand at 6 months of age. One neonate on follow-up at 7 months old was noted to sit without support and stand-alone while holding on to a chair. However, all 3 were at par with age upon reaching 15 months old. Two infants at 13-15 months were noted to have some degree of delay. One had expressive language delay while the other had both gross motor and expressive language delay. Both had tested negative for COVID-19 RT-PCR.

DISCUSSION

In this study, the maternal and neonatal demographic and clinical profile of newborns born to SARS-CoV-2 positive mothers were presented. According to a study in the Journal of Maternal and Child Health, extremes of ages are associated with several complications. If the mother is too young, from ages 11 to 18 years old, it is deemed prone to preterm delivery, mild pre-eclampsia and infections like chorioamnionitis and endometritis. For mothers above the age of 35, the risk for preterm delivery is imminent and they are more prone to hypertension with superimposed preeclampsia, and severe preeclampsia, but were noted to have a decreased risk for chorioamnionitis. Older women above 40 years old are at greater risk for preeclampsia that results in poor fetal growth and fetal distress.[11] The safest pregnancy and childbirth occur in women from ages 20-35 because of the reproductive age risk of complications is lower.[12] In this study, the majority (76%) were all within the low-risk reproductive age, and only a few (24%) were in the older age group above 35 years old. Although the majority was within the low-risk population, most of these mothers (58%) had 1 or 2 maternal comorbidities. Although the age of the COVID-19 positive mothers would classify their pregnancy as low risk, the presence of some comorbidities could have led to the development of symptoms in their neonates that required some degree of intervention beyond the scope of neonatal COVID-19 infection. This could explain why some neonates required treatment even if their SARS-CoV-2 RT-PCR results were negative. Living environment and socio-economic income in the Philippines has been a great challenge for most Filipinos pre-pandemic. More so during the pandemic, that it burdens not only the economic aspect but also the accessibility to health care facilities with new health protocols implemented. The socio-economic status of the mothers has implications likewise on their level of education.

According to Silva, et al., maternal education is associated with fetal growth. They found out that low maternal education led to slower fetal head growth.[13] In this study, most mothers were college graduates, with above minimum income, and currently residing in urban areas. Thus, they had adequate prenatal care with easy accessibility to health care facilities resulting in most neonates being full term, with appropriate weight for age, and a good APGAR score. Their level of education and socio-economic status could have also played a part to the low number of mothers getting infected with the SARS-CoV-2 during their pregnancy, as they would have better understanding of the significance in abiding to the standard health protocols. At the same time for those who were SARS-CoV-2 positive, they have better access to health care facilities capable of managing COVID-19, hence probably resulting also to better neonatal outcome.

Findings by Sulastri, et al. also showed the relevance of the number of pregnancies (gravida) to the development of complications. Repeated pregnancy and childbirth result in damage to the walls of the blood vessels in the uterus, causing a decrease in elasticity of tissues due to repeated stretching that may cause abnormal fetal and placental growth. It also showed increased risk (0.156 times more) for anemia and pre-eclampsia in multigravida women.[12] In this study, majority of mothers were multigravid, but only one was documented to have had uterine atony, though this did not affect neonatal outcome. By being multigravid, this can disrupt the uterine circulation leading to less optimal fetal growth. This may have contributed to why six neonates were small for gestational age and fourteen weighed below 2,500 grams.

In our study sites, protocol does not include testing SARS-CoV-2 of the placenta and amniotic fluid. The newborns are swabbed at 24 hours of life to determine if they are COVID-19 positive especially if the mother is documented to have SARS-CoV-2. A repeat swab at 48-72 hours of life is performed especially for those newborns with symptoms.

Though there were 3 neonates who tested positive for SARS-CoV-2 in their nasal and oropharyngeal swab, establishing an intrauterine transmission could not be done with the lack of testing of the placenta and the amniotic fluid for the presence of the virus in these specimens.

A study by Elhalik, et al. in Dubai, the clinical profile of 36 newborns from SARS-CoV-2 positive mothers showed that all newborns were stable and asymptomatic. Majority were term, with a median gestational age of 37 weeks and a weight of 2,985 grams.[14] This showed almost similar results with our study, they had two SARS-CoV-2 positive neonates and one neonate with an inconclusive report. All their neonates including those who were positive were asymptomatic with no mortality. In comparison to our study, with three SARS-CoV-2 positive neonates and only one was asymptomatic. One of our positive neonates was born preterm had a critical COVID-19 infection. In the study of Elhalik, et al., 25 out of 36 neonates they followed up showed that all neonates were healthy and in good condition, as compared to the results of our follow-up study with the majority being symptomatic at one point and with one mortality. However, they have no information on neurodevelopmental status of their patients since their study focused on respiratory and infectious diseases.

According to the Philippine Society of Newborn Medicine, neonates born to SARS-CoV-2 positive mothers should be started with antibiotics, like ampicillin and gentamicin, if there is high consideration for bacterial pneumonia or sepsis.[15] In this study, 16 were started with antibiotics as they had neonatal pneumonia and neonatal sepsis and completed the antibiotics for at least 7 days.

In a study by Bender, et al. of adult COVID-19 patients presenting with jaundice, there was higher risk for mortality. The main reason identified was due to liver dysfunction that was associated with sepsis, severe systemic inflammation and hypoxic/ischemic hepatitis.[16]

Among the 67 neonates included in our chart review, 16 underwent phototherapy. Their jaundice was secondary to neonatal comorbidities, which included neonatal sepsis, neonatal pneumonia, and hyperbilirubinemia secondary to breastfeeding jaundice. All of them had good outcome though.

The World Health Organization recommends supplemental oxygen therapy immediately for patients with respiratory distress and hypoxemia for timely respiratory support.[17] Out of the 67 newborns included in the study, 15 were given supplemental oxygen as they manifested with tachypnea, alar flaring, chest retractions, desaturations, or cyanosis. One out of the 8 preterm neonates was hooked to continuous positive airway ventilation (CPAP) due to severe transient tachypnea of the newborn. All these neonates had improvement of symptoms and were eventually discharged.

For severe cases, invasive ventilation is recommended to protect the lung from respiratory failure with use of low tidal volume and higher PEEP levels.[18] For the 3 neonates who were intubated, two were preterms with negative RT-PCR and one was a term neonate with COVID severe symptoms. The first neonate was a 32-week-old preterm delivered by a multiparous mother (G7P7 (6107)) with COVID-19 moderate infection with comorbidities including gestational diabetes and chronic hypertension. The patient was delivered via STAT primary cesarean section secondary to severe preeclampsia and had an APGAR score of 5 and 8, weighing 1,200 grams, and her RT-PCR result was negative. She had respiratory distress syndrome (RDS), was intubated and was given surfactant. She was eventually extubated and was discharged after 35 days. However, at 2 months of age, the patient expired due to aspiration pneumonia. She was dead upon arrival at the emergency room, but no RT-PCR was taken to confirm COVID-19 infection. The second neonate was a 29-week-old preterm delivered to a gravida 2 mother with COVID-19 severe infection. She was in respiratory distress with episodes of desaturations; thus, she was intubated and underwent STAT primary cesarean section.

The neonate had an APGAR score of 1, 7, and 7 and weighed 1,750 grams. She was intubated and given surfactant at 6 hours of life. Chest x-ray showed reticulo-granular pattern with air bronchograms suggestive of respiratory distress syndrome and RT-PCR was also negative. She was also discharged after 35 days. The third intubated neonate was born to a gravida 1 mother with no comorbidities and with mild COVID-19 infection. The baby had episodes of thermal instability and early jaundice. Her RT-PCR at 24 hours of life showed positive for SARS-CoV-2. The blood culture was positive for MRSE and was treated with antibiotics. She then developed signs of respiratory distress and was intubated at 13th day of life. She was managed with intravenous immunoglobulin, dexamethasone, remdesivir and tocilizumab. She was extubated after 15 days and was discharged at 32 days old. She was readmitted at 2 months old due to cow's milk allergy.

Long term follow-up of children born to COVID-19 positive mothers is lacking. Information on whether they will develop persistent or permanent complications has not yet been determined. This paper describes 36 neonates with data after discharge from their initial admission at birth. Though 64% of this population developed symptoms beyond the neonatal age, majority of the problems maybe unrelated to their initial exposure to the SARS-CoV-2, but instead reflects the typical risk of any infant being exposed to pathogens or stressors. COVID-19 infection cannot be totally ruled out since these patients did not have an RT-PCR swab to detect SARS-CoV-2 infection during their readmissions. The observed increased frequency of infections documented beyond 6 months of age among our subjects is consistent with the decrease in maternal immunoglobulins during this time. Three out of 4 subjects who were readmitted were due to infections like pneumonia, acute gastroenteritis and urinary tract infection occurring beyond 6 months of age.

A direct causality from the SARS-CoV-2 exposure cannot be established for the two infants who developed abnormal head size as they were both asymptomatic with negative RT-PCR at birth. The abnormal head size was an incidental finding during their follow-up at the OPD at 2 months of age.

Neurodevelopmental assessments entail detailed and comprehensive evaluation to help recognize future neurologic sequelae that can be prevented if there is early detection. The most widely used tool for screening is the Denver Developmental Screening Test (Denver Scale II). The results are then presented as developmental quotient which are based from raw scores that is calculated to measure the competence level of the child.[19] Majority of the subjects, who were followed-up are at par with age, except for 2 who were noted to have some degree of delay. It can be noted that 2 out of the 3 neonates who tested positive for SARS-CoV-2 have normal neurodevelopmental status. The one remaining COVID-19 positive newborn cannot be contacted and was not included in the follow-up study.

In the study of Chakravarty, et al., neurological symptoms like anosmia, ageusia, headaches, delirium, stroke and seizures may occur as there are several suggested mechanism for SARS-CoV-2's entry to the central nervous system by penetrating the blood brain barrier.[20] This further supports the involvement of neurologic manifestations seen in SARS-CoV-2 positive patients, but the direct impact of COVID-19 infection on infants born to SARS-CoV-2 positive mothers still warrants further investigation as the varied findings demonstrated in several study could not be directly linked to the eventual neurodevelopmental status of the infant.

In a similar study from Kuwait by Ayed, et al., they assessed the neurodevelopmental status of newborns of SARS-CoV-2 positive mothers using the ASQ-3 scoring during their follow-up at 10-12 months corrected age.

Out of the 298 infants involved in the study, it was documented that 10% of these infants showed developmental delays. Only 2 were positive for COVID-19 and both had normal ASQ-3 scores.[21] Those with developmental delays were noted higher among those mothers who had the COVID-19 infection during the first and second trimesters and born less than 31 weeks' gestation.[21] Similar with our study, the majority of those mothers in their study were infected during the third trimester. The 2 infants in our study who had developmental delay were born term from mothers with mild COVID-19 symptoms. Both of these infants were SARS-CoV-2 negative.

In another study by Zeng, et al. in Wuhan, China, out of the 72 newborns from SARS-CoV-2 positive mothers, five newborns tested positive for COVID-19. Out of these 5 neonates, three had abnormal MRI findings showing an abnormality in white matter signal w/ delayed myelination, delayed myelination and brain dysplasia, and abnormal signal in the bilateral periventricular areas. No abnormal physical growth seen in these newborns. The 2 other COVID-19 positive neonates did not show significant changes in their MRI findings.[22] In contrast to our study where the neurodevelopmental delay and abnormal head size were all seen in COVID-19 negative newborns. The two SARS-CoV-2 positive newborns in our study were at par for age. Only the 2 newborns with abnormal head size underwent an MRI and did not show similar findings as with the study of Zeng, et al. The 2 neonates showed benign external hydrocephalus and scaphocephaly. Both neonates are at par for developmental milestones for age. The fetal inflammatory response (FIRS) due to the maternal COVID-19 infection may have contributed to the neurologic manifestations seen in several studies of newborns from SARS-CoV-2 positive mothers. The increase of interleukin-6 (IL-6) may induce adverse neurological sequelae such as autism, psychosis, and sensory deficits later in life.

The direct involvement of SARS-CoV-2 with these varied findings is not yet established, however, long-term investigation is warranted as the neurological development of any child is of outmost importance.

CONCLUSION

The clinical profile of mothers in this study indicated that they had adequate support, preparedness, and access to health care during their pregnancy and during their COVID-19 infection. Maternal COVID-19 infection does not, however, necessarily result to a neonatal infection. For those neonates who developed mild symptoms while admitted, causality in relation to SARS-CoV-2 could not be established as several other risk factors were notably present. On follow-up, there were a few who developed significant problems like abnormal head size and developmental delays. These manifestations, however, have important long-term implications in the overall growth and development of a child, that further investigation to determine relationship of these clinical outcomes with maternal COVID-19 is warranted.

RECOMMENDATIONS

In dealing with a new disease like COVID-19, it is important to allocate resources for further studies with focus on the neurodevelopmental assessment of children with COVID-19 or born to SARS-CoV-2 positive mothers. A follow-up study with a larger population to include those from government hospitals may yield more information. The maternal vaccination status and occupational exposure may also be added in future research as they are potential risk or preventive factors that could affect neonatal outcome. Subsequent research with a case-control study design may be advisable to eliminate the confounders that were noted in this study.

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ORIGINAL ARTICLE

DIAGNOSTIC PERFORMANCE OF BRAIN NATRIURETIC PEPTIDE, BIOELECTRICAL IMPEDANCE ANALYSIS, AND LEFT VENTRICULAR END-DIASTOLIC DIAMETER IN THE DETERMINATION OF FLUID OVERLOAD AND MORTALITY IN PEDIATRIC SEPSIS

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3rd PLACE 2022 PIDSP RESEARCH CONTEST

ABSTRACT

Objective: This pilot study investigated whether serum B-type Natriuretic Peptide (BNP), bioelectrical impedance analysis (BIA), and left ventricular end-diastolic diameter (LVEDD) can be used to predict fluid overload and clinical outcomes in pediatric sepsis.

Methodology: Pediatric sepsis patients were enrolled. BNP, BIA, and LVEDD were obtained on admission and on Day 3. Diagnostic performances of BNP, BIA, LVEDD and correlation with fluid status were obtained.

Results: Twenty-two patients were enrolled. Day 3 BNP was higher in non-survivors (9241 vs. 682.2 pg/mL, p=0.04) and day 3 LVEDD Z-score was lower in non-survivors (-3.51 vs. -0.01, p=0.023). There was no difference in the fluid balance between survivors and non-survivors. Admission BNP >670.34pg/mL predicted vasopressor use with a sensitivity of 85.71% and specificity of 86.67% while ΔBNP>5388.13pg/mL predicted mortality with 100% sensitivity. Day 3 LVEDD <22mm predicted mortality with a sensitivity of 94.74%. Cumulative fluid balance was strongly correlated with BIA and LVEDD (r=0.65, p=0.001; r=0.74, p<0.001 respectively). The median length of stay in hospital days for non-survivors was not significantly different from survivors (4 [1-12] vs. 8 [6-12] days, p=0.21).

Conclusion: Rise in BNP levels appear to be independent of fluid status and is a good predictor of mortality, vasopressor, and mechanical ventilator use but not of length of hospital stay. LVEDD and BIA are good estimates of cumulative fluid balance but not as predictors of mortality, vasopressor, mechanical ventilator use, and length of hospital stay. Significance of the outcomes of the study was limited due to the small sample size.

KEYWORDS: *Pediatric Sepsis, Fluid Overload, Brain Natriuretic Peptide, Echocardiography, Bioimpedance Analysis*

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INTRODUCTION

Sepsis presents a continuing health burden and is part of the top ten leading causes of mortality in the country.[1] There is a trend towards search for biomarkers in pediatric sepsis to help prognosticate and predict medical outcomes. One biomarker being studied is the B-type natriuretic peptide (BNP). BNP physiologically causes diuresis, antagonizes the renin-angiotensin-aldosterone system, and produces vasorelaxation.[2] Recent studies indicate increased BNP levels in pediatric patients with sepsis and septic shock.[3-5] Parker, et al. first reported myocardial dysfunction associated with sepsis back in 1984.[6] With evidence pointing to cardiac dysfunction in sepsis, fluid administration should be monitored and regulated.

Fluid resuscitation has been the cornerstone of treatment for pediatric septic shock to restore circulating filling pressure, guided by clinical markers of cardiac output.[7] There is evidence in a systematic review of pediatric sepsis that positive fluid balance is associated with poorer clinical outcomes.[8] The Fluid Expansion as Supportive Therapy (FEAST) trial challenged the established principles on aggressive intravenous boluses, especially for low-income countries.[9]

There is no consensus or standard method to assess fluid overload (FO) in the pediatric population. A proposed method was to determine % FO by a weight-based technique by taking the difference between the daily fluid intake and output and dividing by the baseline body weight. A value above 10% FO is the level at which clinicians intervene.[10]

There is potential for the use of BNP in guiding fluid therapy in patients with sepsis. A study showed that BNP level was closely correlated with fluid balance and that high levels were associated with mortality.[11] In patients with a high fluid load, BNP is a possible indicator of cardiac preload.[12]

Clinical assessment of a patient's volume status by physical examination provides limited reliability and accuracy. A better measure of total body water (TBW) and the extent of absolute fluid overload (AFO) can be assessed with bioimpedance analysis (BIA). Total body water is composed of intracellular water (ICW) and extracellular water (ECW). Several studies, mostly in the adult population, have already shown its advantage in providing useful information on volume status of certain groups, i.e., dialysis patients, congestive heart failure patients, and those with malnutrition.[13-15]

There are no known published studies, at the time of this research, that assesses the diagnostic performance of BNP, TBW, AFO, and LVEDD in pediatric sepsis patients. This study aimed to determine the diagnostic performance of BNP, TBW, AFO, EF, and LVEDD in predicting fluid overload and clinical outcomes in pediatric sepsis and septic shock. Specific objectives included determining the differences in BNP, TBW, AFO, and LVEDD between survivors and non-survivors; determining the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of BNP, TBW, AFO, and LVEDD with regards to clinical outcomes (mortality, vasopressor use, mechanical ventilator use, length of stay >7 days); and determining the correlation of BNP, TBW, AFO, and LVEDD with fluid status.

METHODOLOGY

Study design

This was a prospective observational cohort pilot study conducted in a tertiary public hospital.

Study population

Patients at the emergency room more than 28 days to 18 years old who fulfilled the criteria for sepsis on admission were included.

A pediatric resident or fellow diagnosed the patient as having sepsis following the definition of Systemic Inflammatory Response Syndrome (SIRS) plus a focus of infection, either clinically, radiologically or microbiologically. The entire clinical spectrum of sepsis, including severe sepsis, septic shock and Multiple Organ Dysfunction Syndrome, was included. Patients who expired within 72 hours of hospital stay were included in the study.

Exclusion criteria

Excluded were cases of traumatic injury, acute gastroenteritis, endocrine disorders, renal disorders, liver disorders, cardiac disorders, autoimmune disorders, burn injury, steroid use, hospital acquired sepsis, and weight and length z-scores below < -2.

Withdrawal criteria

A patient was withdrawn from the study if there was withdrawal of consent and inability to obtain BNP, TBW, AFO, or LVEDD on admission and/or on the third day of admission except for patients who expired within 72 hours of admission.

Sample size

A minimum of 22 patients was required for this study based on an odds ratio of mortality due to 10% fluid overload of 21.1, resulting in an alpha of 0.1, 90% level of significance and 80% power.[10]

Data collection

The principal investigator was not the primary healthcare provider for the patient and served only as a researcher. Eligible subjects were recruited through non-probability sampling as they were admitted to the emergency room. Informed consent was obtained and baseline characteristics were recorded by the principal investigator. If the patient needed resuscitation and emergency care, these were done first before proceeding to discuss the study involving the patient.

Extraction of one sample containing at least 0.5 mL blood for serum BNP was done by the physician on duty within the first hour of admission and on the third day, along with the other necessary blood extractions. Serial monitoring of fluid balance noted as the total daily fluid input (tube feeding, intravenous infusion, oral intake) minus daily fluid output (urine output and drainage of body fluid) was done by the nurse-on-duty assigned to the patient during the first three days of confinement. Fluid overload was computed as the fluid balance divided by the baseline weight.

Serial monitoring of total body water (TBW) and absolute fluid overload (AFO) using bioimpedance analysis (BIA) (Fresenius Medical Care Body Composition Monitor SN 7BJA4849) was taken on admission and on the third day of hospital stay by the pediatric nephrology fellow-on-duty.

Serial monitoring of the cardiac ejection fraction (EF) and left ventricular end-diastolic diameter (LVEDD) via point-of-care echocardiography on admission and on the third day was done by a senior pediatric cardiology fellow. It was done using a phased-array transducer (GE Vscan Extend™, frequency 1.7-3.8 MHz, USA) with the patient in supine position. At least three succeeding cardiac cycles were recorded for each session and it was done on the parasternal short-axis view at the level of the papillary muscle. The true-short axis view of the left ventricle was used to determine the left ventricular internal dimensions at end-diastole (LVEDD) and end-systole (LVESD). Corresponding Z-scores of the dimensions obtained were referenced using age-specific population means. Fractional shortening was determined using the formula: $FS = [(LVEDD-LVESD)/LVEDD] \times 100$.[14] The ejection fraction was determined using the formula: $EF = [(LVEDD^3-LVESD^3)/LVEDD^3] \times 100$.[16]

Direct participant involvement occurred only upon recruitment and during the first 72 hours of admission and ended after extraction of blood and monitoring of fluid balance.

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All other information such as the medical history, interventions and laboratory results were obtained from the patient's chart.

The study did not interfere with management of recruited patients and standard treatment was provided. An intake form that included all the necessary data was filled out by the principal investigator alone. All patient related information were kept confidential and only the principal and supervising investigators had access to the files.

Diagrammatic workflow

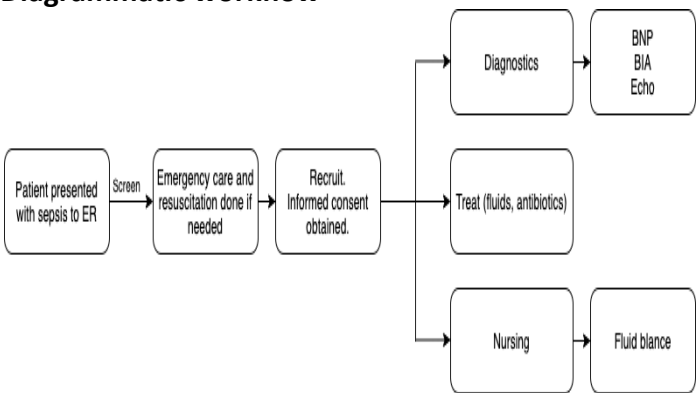

Figure 1. Graphic overview of research workflow at the emergency department

Outcome and Outcome measurements

Baseline characteristics such as patients' demographic and clinical profile were recorded.

Primary and Secondary Outcomes

The primary endpoint of the study was 28-day mortality. Correlation of BNP on admission, ΔBNP, TBW, AFO, EF, and LVEDD with mortality was determined. A patient who expired within 72 hours of admission was included in the analysis.

Secondary outcomes included the following:

1) Diagnostic performance of BNP on admission, ΔBNP, TBW, AFO, and LVEDD with use of vasoactive medications, mechanical ventilator days, and length of stay more than 7days
2) Correlation of ΔBNP, TBW, AFO, and LVEDD with fluid status

Statistical analysis

Descriptive statistics were used to summarize demographic and clinical characteristics of patients. Frequency and proportion were used for categorical variables and median with interquartile range (IQR) for non-normally distributed continuous variables. Mann-Whitney U test and Fisher's exact test were used to determine the difference of rank and frequency respectively, between survivors and non-survivors.

Cox Proportional Hazard Regression was used to determine significant covariates that were associated with mortality and reported as Hazard Ratio (HR). Death of a participant within 72 hours of admission was accounted for in the statistical analysis.

Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were used to determine the diagnostic accuracy of BNP, TBW, AFO and LVEDD on clinical outcomes. Optimal cut-off values of BNP, TBW, AFO and LVEDD for predicting clinical outcomes (28-day mortality, use of vasoactive medications, mechanical ventilator use and length of stay >7 days) were evaluated using receiver operating characteristic (ROC) curves.

Pearson product moment correlation was used to determine the linear correlation between ΔBNP, Day 3 TBW, Day 3 AFO, and Day 3 LVEDD to cumulative fluid balance and 10% fluid overload.

All statistical tests were two-tailed. Shapiro-Wilk was used to test the normality of continuous variables. Missing values were neither replaced nor estimated. Null hypotheses were rejected at 0.05 α-level of significance. STATA 13.1 was used for data analysis.

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RESULTS

Baseline demographic and clinical characteristics were similar for non-survivors (n=3) and survivors (n=19) (Table 1). The median Glasgow Coma Scale (GCS) of non-survivors was significantly lower (p=0.02) with a GCS of 6 (IQR 3 to 15) compared to survivors (GCS of 14, IQR 13-15). The median diastolic pressure of non-survivors versus survivors was statistically lower (48mmHg [IQR 40-56] vs. 65mmHg [IQR 60-69], p=0.05). Sources of infection were the abdomen, lungs, blood, and soft tissues. There was a statistically significant difference (p=0.02) in the sources of infection between non-survivors and survivors. For non-survivors, two patients (66.67%) had clinical sepsis while one (33.33%) had culture confirmed sepsis.

All 3 non-survivors had vasopressor use whereas only 21.05% (p=0.02) of survivors (n=19) used vasopressors. For patients who had vasopressor use, there was no significant difference between vasopressor days (p=0.86). There was also no significant difference between mechanical ventilator use (p=0.23) and mechanical ventilator days (p=0.87) between survivors and non-survivors. No patient in the non-survivor group developed hospital acquired infection compared to 5 patients in the survivor group. Fluid boluses were given to all non-survivors (n=8, 42.11%). Median length of stay in hospital days for non-survivors was not significantly different from survivors (4 [IQR 1-12] vs. 8 [IQR 6-12] days, p=0.21).

Table 1. Characteristics of included patients

Parameter	Total (n=22)	Non-survivors (n=3)	Survivors (n=19)	p-value
	Frequency (%); Median (IQR)			
Age (years)	3.5 (0.67 to 14)	0.67 (0.25 to 13)	4 (0.67 to 14)	0.34
Sex				0.27
Male	14 (63.64)	3 (100)	11 (57.89)	
Female	8 (36.36)	0	8 (42.11)	
Weight (kg)	14 (8 to 36)	8 (6.5 to 36)	13.6 (8 to 37.8)	0.47
Weight Z score	-1 (-1 to 0)	-1 (-1 to 0)	-1 (-1 to 0)	0.68
Height (cm)	98 (66 to 135)	64 (62 to 131)	99 (66 to 149)	0.18
Height Z score	-0.5 (-1 to 0)	-2 (-2 to 0)	0 (-1 to 0)	0.13
Weight at day 3 (kg)	14 (7.6 to 35)	21.25 (6.5 to 36)	14 (7.6 to 35)	0.86
GCS	15 (13 to 15)	6 (3 to 15)	15 (13 to 15)	0.02
Systolic BP (mmHg)	102 (99 to 120)	91.5 (81 to 102)	102 (99 to 120)	0.25
Diastolic BP (mmHg)	63 (60 to 65)	48 (40 to 56)	65 (60 to 69)	0.05
Heart rate (BPM)	133 (121 to 160)	152 (113 to 190)	133 (121 to 160)	0.81
Respiratory rate (RR)	39 (24 to 50)	45 (30 to 60)	39 (24 to 50)	0.59
O2 saturation (%)	98 (95 to 99)	92 (99 to 95)	98 (97 to 99)	0.11
Temperature (C)	37.5 (36.5 to 38)	36.8 (34 to 38.3)	37.5 (36.5 to 38)	0.63
MAP (mmHg)	89.7 (85 to 102)	77 (67.3 to 86.7)	90 (85 to 102)	0.12
Source of infection				0.02
Abdominal	9 (40.91)	0	9 (47.37)	
Blood	4 (18.18)	2 (66.67)	2 (10.53)	
Lung	7 (31.82)	0	7 (36.84)	
Soft tissue	2 (9.09)	1 (33.33)	1 (5.26)	
Diagnosed				0.76
Clinical	9 (40.91)	2 (66.67)	7 (36.84)	
Microbiological	7 (31.82)	1 (33.33)	6 (31.58)	
Radiological	6 (27.27)	0	6 (31.58)	
Vasopressor use	7 (31.82)	3 (100)	4 (21.05)	0.02
Vasopressor days	5 (1 to 7)	5 (0 to 8)	3 (1 to 6)	0.86
Mechanical ventilation use	7 (31.82)	2 (66.67)	5 (26.32)	0.23
Mechanical ventilation days	7 (5 to 9)	7 (5 to 8)	7 (5 to 9)	0.87
Nosocomial infection	5 (22.73)	0	5 (26.32)	1.00
Bolus given	11 (50)	3 (100)	8 (42.11)	0.21
Hospital days	7.5 (5 to 12)	4 (1 to 12)	8 (6 to 12)	0.21

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Table 2. Serum albumin and BNP of included patients

Parameter	Total (n=22)	Non-survivors (n=3)	Survivors (n=19)	p. value
	Median (IQR)			
Albumin (g/L)	36 (31 to 42)	21 (14 to 28)	37 (32 to 43)	0.05
BNP admission (pg/mL)	350 (135 to 3780)	670.34 (213.5 to 3780)	288.14 (91.5 to 5797)	0.53
BNP on Day 3 (pg/mL)	700.85 (274 to 1449)	9241.5 (5601 to 12881)	682.2 (121 to 1432)	0.04
ΔBNP (pg/mL)	450 (-207.7 to 934)	7244.92 (5388 to 9102)	361.87 (-1090 to 750)	0.04

The serum albumin of non-survivors was significantly lower (p=0.05) than survivors (21 [IQR 14-28] vs. 37 [QR 32-43] g/L). Median BNP levels on admission were comparable between non-survivors and survivors (670.34 [IQR 213.5-3780] vs. 288.14 [IQR 91.5-5797] pg/mL, p=0.53). Median serum BNP levels on day 3 of admission were significantly higher in non-survivors compared to survivors (9241.5 [IQR 5601-12881] vs. 682.2 [IQR 121-1432] pg/mL, p=0.04). Subsequently, median ΔBNP levels, which measured the difference between admission and day 3 BNP, were significantly higher in non-survivors compared to survivors (7244.92 [IQR 5388-9102] vs. 361.87 [IQR -1090-750] pg/mL, p=0.04).

Table 3. Echocardiography parameters of included patients

Parameter		Total (n=22)	Non-survivors (n=3)	Survivors (n=19)	p. value
		Median (IQR)			
On Admission	EF (%)	71 (67 to 73)	67.5 (67 to 68)	72 (67 to 74)	0.37
	LVEDD (mm)	32 (25 to 39)	26.65 (19.3 to 34)	32 (25 to 40)	0.40
	Z score	-0.3 (-1.4 to 0.39)	-2.03 (-2.1 to -1.96)	-0.25 (-1.1 to 0.73)	0.07
Day 3	EF(%)	70 (66 to 74)	68.5 (67 to 70)	72 (64 to 74)	0.59
	LVEDD (mm)	31 (26 to 40)	22.5 (19 to 26)	33 (26 to 43)	0.11
	Z score	-0.2 (-0.91 to 0.51)	-3.51 (-4.74 to -2.3)	-0.01 (-0.63 to 0.55)	0.02

Echocardiography parameters of non-survivors and survivors were comparable on admission. None of the patients presented with a decreased ejection fraction characterized as EF <55% at the time of procedure. On day 3 of admission, median LVEDD Z-score of non-survivors was lower than survivors (-3.51 [IQR -4.74 to -2.3] vs. -0.01 [IQR -0.63 to 0.55), p=0.023) and mean LVESD Z-score of non-survivors was lower (-2.3 [IQR -2.9 to -1.71] vs. 0.43 [-0.37 to 0.8], p=0.03). There were no significant differences in bioimpedance analysis (see Table 4) and in the daily and cumulative fluid balance between survivors and non-survivors (see Table 5).

Table 4. Total blood water and absolute fluid overload of included patients

Parameter		Total (n=22)	Non-survivors (n=3)	Survivors (n=19)	P-value
		Median (IQR)			
On Admission	TBW (L)	17 (8.8 to 27.3)	16.15 (7.1 to 25.2)	17 (8.8 to 29)	0.55
	AFO (%)	-13.2 (-40.1 to 5.4)	0.95 (-16.6 to 18.5)	-13.2 (-43.3 to 5.4)	0.34
Day 3	TBW (L)	15.1 (9.7 to 29.6)	27.1 (8.9 to 45.3)	15.1 (9.7 to 29.6)	0.77
	AFO (%)	-5.3 (-13.8 to 3.2)	-5.3 (-13.8 to 3.2)	-1.5 (-13.8 to 10.1)	0.86

Table 5. Percent Fluid Overload of included patients

Parameter	Total (n=22)	Non-survivors (n=3)	Survivors (n=19)	P-value
	Median (IQR)			
Cumulative Fluid balance (mL)	1535 (940 to 2975)	2255 (1535 to 2975)	1500 (940 to 3320)	0.55
10% Fluid overload	0.95 (0.79 to 1.41)	1.59 (0.83 to 2.36)	0.95 (0.73 to 1.41)	0.63

Accounting for the different co-variates affecting survival, there were no significant independent associations between percent fluid overload, BNP, TBW, AFO, and LVEDD with mortality as the primary outcome (see Table 6).

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Table 6. Factors associated with mortality

Parameter	Hazard Ratio (95% CI)	P-value
% Fluid overload		
Cumulative Fluid balance	1.00 (0.98 to 1.01)	0.94
10% Fluid overload	1.42 (0.18 to 11.3)	0.74
BNP		
BNP admission	1.00 (0.98 to 1.01)	0.61
ΔBNP	1.00 (0.99 to 1.02)	0.38
TBW		
TBW on admission	0.99 (0.86 to 1.14)	0.86
TBW on Day 3	1.03 (0.94 to 1.12)	0.53
AFO		
AFO on admission	1.04 (0.96 to 1.14)	0.31
AFO on Day 3	1.01 (0.95 to 1.07)	0.82
LVEDD		
LVEDD on admission	0.96 (0.82 to 1.12)	0.58
LVEDD on Day 3	0.85 (0.64 to 1.14)	0.28

Diagnostic performances of BNP, TBW, AFO, and LVEDD in predicting clinical outcomes are shown in Table 7. BNP levels on admission above the cut-off has high sensitivity for vasopressor use and high specificity for mechanical ventilator (MV) use. ΔBNP above 5388.13 pg/ml and Day 3 LVEDD <22mm as the cut-off had high sensitivity for mortality.

All diagnostic examinations were directly correlated with cumulative fluid balance. ΔBNP levels directly displayed moderate strength of correlation (r=0.43, p=0.04) with cumulative fluid balance, while Day 3 TBW and LVEDD directly displayed strong strength of correlation (r=0.65, p=0.001; r=0.74, p<0.001).

Table 7. Diagnostic performance of BNP, TBW, AFO and LVEDD on clinical outcomes

Parameter	Cut off	Sensitivity	Specificity	PPV	NPV	AU-ROC
BNP on admission	(pg/mL)					
Mortality	≥670.34	66.67%	68.42%	25%	92.86%	0.61
Vasopressor use	>670.34	85.71%	86.67%	75%	92.86%	0.91
MV use	>1211.86	71.43%	86.67%	71.43%	86.67%	0.81
Length of stay >7	≥454.24	63.64%	72.73%	70%	66.67%	0.67
ΔBNP	(pg/mL)					
Mortality	≥5388.13	100%	94.74%	66.67%	100%	0.95
Vasopressor use	≥5388.13	50%	100%	100%	83.33%	0.50
MV use	≥361.87	57.14%	42.86%	33.33%	66.67%	0.53
Length of stay >7	≥450	63.64%	60%	63.64%	60%	0.52
TBW on admission	(L)					
Mortality	≤7.4	94.74%	50%	94.74%	50%	0.63
Vasopressor use	≤8.8	86.67%	50%	81.25%	60%	0.57
MV use	≤15.4	71.43%	71.43%	83.33%	55.56%	0.74
Length of stay >7	≤17	60%	54.55%	54.55%	60%	0.53
TBW on day 3	(L)					
Mortality	≤9.7	78.95%	50%	93.75%	20%	0.43
Vasopressor use	≤9.7	86.67%	50%	81.25%	60%	0.51
MV use	≤10.7	85.71%	57.14%	80%	66.67%	0.65
Length of stay >7	≤11.2	80%	45.45%	57.14%	71.43%	0.53
AFO on admission	(%)					
Mortality	≥18.5	50%	94.74%	50%	94.74%	0.71
Vasopressor use	≥-9.6	66.67%	60%	40%	81.82%	0.76
MV use	≥-30.4	100%	50%	50%	100%	0.71
Length of stay >7	≤-13.2	70%	63.64%	63.64%	70%	0.71
AFO on day 3	(%)					
Mortality	≤-13.6	73.68%	50%	93.33%	16.67%	0.54
Vasopressor use	≤-1.9	66.67%	66.67%	83.33%	55.56%	0.56
MV use	≥-2.9	71.43%	42.86%	38.26%	75%	0.52
Length of stay >7	≤-12.9	80%	45.45%	57.14%	71.43%	0.59
LVEDD on admission	(mm)					
Mortality	≤23	94.74%	50%	94.74%	50%	0.68
Vasopressor use	≤25	86.67%	50%	81.25%	60%	0.56
MV use	≤29	71.43%	71.43%	83.33%	55.56%	0.67
Length of stay >7	≤34	60%	72.73%	66.67%	66.67%	0.58
LVEDD on day 3	(mm)					
Mortality	<22	94.74%	50%	94.74%	50%	0.86
Vasopressor use	≤27	73.33%	66.67%	84.62%	50%	0.69
MV use	≤27	78.57%	71.43%	84.62%	62.5%	0.75
Length of stay >7	≤27	70%	45.45%	53.85%	62.5%	0.58

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Table 8. Correlation of Cumulative Fluid balance to ΔBNP, LVEDD, TBW and AFO

Parameter	Correlation coefficient	Level of association	P-value
ΔBNP	0.43	Directly moderate correlation	0.04
LVEDD on Day 3	0.65	Directly strong correlation	0.001
TBW on Day 3	0.74	Directly strong correlation	<0.001
AFO on Day 3	0.11	Directly weak correlation	0.56

ΔBNP, Day 3 TBW, Day 3 AFO, and Day 3 LVEDD values had no significant correlation with 10% fluid overload.

Table 9. Correlation of 10% fluid overload to ΔBNP, LVEDD, TBW and AFO

Parameter	Correlation coefficient	Level of association	P-value
ΔBNP	0.08	Directly weak correlation	0.72
LVEDD on Day 3	-0.33	Inversely moderate correlation	0.14
TBW on Day 3	-0.36	Inversely moderate correlation	0.11
AFO on Day 3	0.02	Directly weak correlation	0.92

DISCUSSION

Sepsis is one of the leading causes of mortality in the pediatric population. Point of care tests at the emergency department and subsequent monitoring may direct clinicians to make timely interventions to reduce morbidity and mortality, length of stay and improve healthcare costs.

We recruited pediatric patients who were admitted for sepsis at the emergency department, which validated that this pilot study was doable in the critical care setting. Moreover, we were able to monitor their progression in the hospital wards and intensive care unit without problems. Serum BNP determination is readily available in the laboratory of the hospital in which the study was conducted. BIA and point-of-care echocardiography were made available at the emergency department for the duration of the study.

This study was a milestone in the pediatric emergency department on the use of BNP, BIA and point-of-care echocardiography as these were all done in septic pediatric patients.

Serum BNP was included in the standard serum chemistry panel so no additional blood extraction was needed. Moreover, both BIA and point-of-care echocardiography were both non-invasive, quick procedures that did not add any discomfort for patients. BIA is portable, simple to perform, has a lower risk of error from inter-observer variability and is validated for use in children.[17] Point-of-care echocardiography may have inter-reader variability, however, it can be done accurately with proper training.[18] For this study, echocardiography was done by only one experienced cardiologist.

Mortality

Of the 22 recruited patients, non-survivors had severe infections compared to survivors and all patients needed fluid resuscitation and vasopressors. There was no difference between survivors and non-survivors in terms of overall cumulative fluid balance and fluid overload. This is possibly a consequence of judicious fluid therapy practiced in the emergency department and in the hospital wards which adhere to the Surviving Sepsis 2020 Guidelines by Weiss, et al. and the Maitland 2018 findings.[7,9]

This study confirms findings that BNP is elevated in pediatric sepsis and septic shock.[3-5] Median serum BNP levels on day 3 of admission were significantly higher in non-survivors compared with survivors. Subsequently, median ΔBNP levels measuring the difference between admission and Day 3 BNP were significantly higher in non-survivors compared with survivors. However, the BNP level was not a significant risk factor for mortality in pediatric sepsis.

In pediatric patients, increased levels of BNP can also be seen in congenital heart disease with left ventricular overload and cardiomyopathy.[19,20]

The non-survivors did not have significant fluid overload compared to survivors, however, Day 3 BNP values were significantly higher in expired patients, suggesting a different mechanism that is not related to myocardial ventricular stretch from fluid overload but possibly from underlying organ damage.[6,21] In some studies done in adults with sepsis and septic shock, elevated BNP levels have been attributed to cardiac dysfunction, or perhaps build up of inflammatory mediators and endotoxins.[22-26]

TBW and AFO measured by BIA independently were not significant risk factors for mortality in pediatric sepsis. It was surprising to note that all patients had negative AFO values for both survivors and non-survivors. Baseline echocardiography parameters were comparable in both survivors and non-survivors. None of the patients had systolic dysfunction both on admission and day 3 and all EF values were above 50%. Non-survivors had significantly lower diastolic blood pressure, lower Day 3 LVEDD, higher Day 3 BNP, yet with preserved EF. These data are also consistent with the bioimpedance analysis where there were negative AFO percentages, suggesting fluid deficit instead of fluid overload. There was significantly decreased albumin levels in non-survivors. We can infer that with decreased ECW values and decreased LVEDD and LVESD Z-scores, there was low circulating intravascular volume. However, given that BIA only measures ECW and is unable to distinguish between plasma volume and tissue edema components, echocardiography may be helpful to determine effective circulating intravascular volume.

EF was preserved in all patients and even in non-survivors, perhaps due to the use of vasopressors to augment cardiac output. However, there was decreased diastolic blood pressure with increased day 3 BNP levels which might suggest cardiac dysfunction with preserved EF. Studies to determine diastolic function of patients were beyond the scope of this study hence were not performed on patients.

Diastolic function is determined by measuring the ratio between the E wave (early diastolic filling phase) and A wave (atrial contraction) during echocardiography. It is suggested to pursue this study since systolic dysfunction may be foreshadowed or preceded by diastolic dysfunction.[16]

Fluid Overload

Of the three diagnostic tools tested, LVEDD and TBW had direct strong correlations with cumulative fluid balance. All three tests did not have any significant correlation with percent fluid overload and displayed poor accuracy in determining fluid overload. This could be due to the limited subjects in the study. There was a disparity in our results when compared with a similar study by Zhang, et al. in 2012 which looked into 18-80 year old adult patients with sepsis and BNP level & fluid overload in sepsis. Our study had increased BNP values in non-survivors in the absence of significant fluid overload, whereas increase in BNP values was attributed to fluid overload in the study by Zhang, et al.[11] A study by Hartemink, et al. in 2011, which recruited critically ill adult septic patients, implied that increased BNP levels may be indicative of fluid non-responsiveness, regardless of fluid status in critically ill septic patients.[25] As an aid for monitoring and decision-making, increasing BNP levels following fluid resuscitation may guide the clinician to veer away from infusing more fluids and steer towards use of inotropic support.[26]

Other Clinical Outcomes

BNP is a good biomarker for predicting vasopressor use, mechanical ventilator use, and mortality above the cut-off values mentioned. The TBW and AFO levels on admission and day 3 of hospitalization have AU-ROC levels below 0.80 which meant that the discrimination in predicting mortality, vasopressor use, mechanical ventilator use and length of stay of more than 7 days are not excellent.

This is consistent with the demonstrated comparable fluid status of both survivors and non-survivors. The results of this study showed that LVEDD on admission had no diagnostic value in predicting clinical outcomes. However, LVEDD taken on day 3 of admission has excellent diagnostic value in predicting mortality.

This study is limited by the number of patients recruited and may have introduced confounders such as differences in the severity of infection, lack of representativeness of different sources of infection and other unidentified factors. However, in the emergency room and in-patient settings, this would provide vital information to clinicians and might aid in decision-making and in the management of pediatric sepsis.

CONCLUSION

The rise in BNP levels appear to be independent of fluid status and is a good predictor of mortality. LVEDD and BIA are good estimates of cumulative fluid balance, but not as predictors of MV, vasopressor use, and mortality. The utility of these tests is limited to guide fluid therapy.

LIMITATIONS AND RECOMMENDATIONS

There are several limitations to the study. First, this is an observational pilot study and it focused on the feasibility of hypothesis testing. Second, there was an overall decrease in emergency room admissions due to low rates of admission and reduced admitting capacity in the pediatric wards and ICU. Further trials can be performed, such as a cohort study with increased number of participants or a randomized controlled trial utilizing BNP, BIA, or LVEDD to direct fluid administration in pediatric septic patients. Third, there are limitations in the availability of equipment for BIA and echocardiography in the study setting and these equipments are not readily available in the emergency department in all hospitals.

An area for further investigation is the correlation of serum BNP with diastolic dysfunction in pediatric septic patients using spectral doppler assessment. These non-invasive diagnostic tools might aid and augment clinical assessment of pediatric patients who are critically ill.

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ORIGINAL ARTICLE

RED CELL DISTRIBUTION WIDTH AND ITS ASSOCIATION WITH NEONATAL BACTEREMIA: A CASE-CONTROL STUDY

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ABSTRACT

Background: Bacteremia is a major cause of prolonged hospital stay and mortality in neonates and its early diagnosis remains a challenge to pediatricians. Red cell distribution width (RDW) is a component of a complete blood count test which is accessible and inexpensive and has been reported to be a possible diagnostic marker for neonatal bacteremia. This study determined the association of RDW with neonatal bacteremia in term and preterm neonates**.**

Methodology: This is a retrospective case-control study of 26 bacteremic neonates as cases and 104 non-bacteremic neonates, either symptomatic or with risk factors for bacteremia, as controls. Included newborns were seen between January 1, 2010 to September 30, 2021. Laboratory data obtained were CBC, C-reactive protein and blood culture.

Results: RDW values between bacteremic and non-bacteremic neonates were not significantly different. There was an association between RDW and neonatal bacteremia at an RDW level of $\geq$ 16.1, where the likelihood of bacteremia was three times higher compared with lower RDW values. Significantly lower levels of hemoglobin, hematocrit, RBC count, WBC count, platelet count, MCH and MCHC, and a higher CRP level were seen among bacteremic neonates compared to those who were not. The median RDW for both term and preterm neonates was close to 16, with a narrow inter-quartile range at 1 and 2 for controls and cases, respectively. The range (minimum to maximum) of RDW values of bacteremic preterm neonates was more variable than those of term neonates. Using RDW to detect bacteremia, it had an equivocal discriminatory power or AUC of 0.6056. We found insufficient evidence to demonstrate a correlation between RDW and other CBC parameters, except for MCHC. For MCHC, the results suggest a very weak and indirect correlation.

Conclusion: RDW was not significantly different between bacteremic and non-bacteremic neonates, but there was a suggested association between RDW and bacteremia at an RDW level of $\geq$ 16.1, at which level there was a 3-fold risk for bacteremia.

KEYWORDS: *Red Cell Distribution Width (RDW), Neonatal Bacteremia, Case-Control 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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INTRODUCTION

Bacteremia is a major cause of prolonged hospital stay and mortality in neonates. It can present with nonspecific signs and symptoms; thus, early diagnosis remains a challenge to pediatricians. Neonatal bacteremia is defined as a systemic inflammatory syndrome, in the presence of a growth in the blood culture, occurring within the first 28 days of life.[1] This can progress to various complications, such as severe sepsis, septic shock, multi-organ failure and death. In the evaluation of neonatal bacteremia, various hematologic markers are commonly used, such as a complete blood count (CBC), C-reactive protein (CRP), procalcitonin, and blood culture. However, blood culture, the gold standard, may take many hours to days to grow, with the identification of the organism taking even longer. Previous studies showed a positivity rate of blood cultures at a range of 25% to 54%.[2] Therefore, a rapid and practical means of predicting for bacteremia in a neonate would be invaluable for clinicians.

Red cell distribution width (RDW), a component of the CBC, measures the variability of the red blood cell size. It has been widely used to identify and differentiate between hematologic diseases, such as iron deficiency anemia and thalassemia, among others. Lippi, et al., reported that RDW increases in cases of infection.[3] RDW has been proven to predict outcomes of various illnesses in adults; however, its use among neonates has not been well-studied.

Using RDW as an initial screening test for neonatal bacteremia is proposed. This study's main objective is to determine the association between RDW and neonatal bacteremia among term and preterm neonates. Specifically, this study aims to compare the RDW of neonates based on age of gestation and blood culture results; determine the correlation between RDW with CRP and CBC indices; determine the optimal cut-off point and discriminatory power of RDW in predicting for bacteremia; and lastly, identify the organisms that cause bacteremia.

METHODOLOGY

This research utilized a retrospective, case-control study design among admitted neonates in a private tertiary hospital, from January 1, 2010 to September 30, 2021. A minimum sample size of 125 (25 cases and 100 controls) preterm and term neonates, with both CBC and blood culture done within the first 28 days of life were required for this study, based on a level of significance of 5%, a 1:4 ratio of cases to control, and an AUC of 0.938. This assumed that the AUC is significantly different from a null hypothesis value of 0.80 (good). The computation for sample size was based on the study of Deka, et al.[4]

Newborns admitted to the neonatal intensive care unit (NICU) or to the wards were identified using records review. Case patients were neonates, who had documented bacteremia on blood culture, within the first 28 days of life, with age of gestation (AOG) at term (>37 weeks AOG) or preterm (29 0/7 to 36 6/7 weeks AOG), delivered via spontaneous vaginal or caesarean section at the study institution, or outside of the institution as long as the neonate was transferred within 28 days of life. The CBC should have been taken on the same day that the blood culture was drawn, and the CRP within 48 hours from the time that the blood culture was obtained, prior to the start of empiric antibiotic therapy.

Neonates with the following conditions were excluded, based on studies that these conditions might have an effect on the RDW: (1) congenital malformations, (2) chromosomal abnormalities, (3) congenital infections due to the TORCH complex, (4) metabolic disease, (5) Rh or ABO incompatibility, (6) already on antibiotics in whom no blood culture was done, (7) had blood transfusion before the sepsis evaluation was done, and (8) perinatal asphyxia.[5-7]

After cases (bacteremic neonates) were identified, gestational-age-matched non-bacteremic controls were obtained by simple random sampling, with a 1:4 ratio.

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Neonatal bacteremia was defined as having a growth of a clinically significant bacterial organism in a neonate's blood culture. The controls were non-bacteremic neonates who were (1) culture-negative but symptomatic for possible infection, with any 1 of the following: temperature irregularity, cardiopulmonary issues [i.e., tachypnea, apnea, grunting, desaturations, retractions, tachycardia in the absence of cardiac disease, and cyanosis], feeding difficulties [i.e. poor suck, refusal to feed, feeding intolerance], early jaundice before the 24th hour of life; and (2) culture-negative asymptomatic patients, whose mothers had conditions that put their neonates at risk for bacteremia, such as maternal fever within one week from delivery, meconium-stained amniotic fluid, prolonged rupture of membranes for more than 18 hours, or maternal urinary tract infection within two weeks before delivery.

Descriptive statistics were used to summarize the general and clinical characteristics of the participants. Shapiro-Wilks test was used to determine the normality distribution, while Levene's test was used to test the homogeneity of variance of continuous variables. Continuous quantitative data were presented as mean and standard deviation (SD) when the distribution was normal, while median and range (minimum and maximum) were used when there was a non-Gaussian distribution. Continuous variables that satisfied the assumption of normality but violated the variance homogeneity were compared using Welch's test. If both assumptions were violated, the non-parametric Mann-Whitney U test was used. Categorical data were analyzed using Chi-square test. Fisher's exact test was used when the expected percentages in the cells were less than 5%.

The relationship of RDW with different laboratory parameters was tested using Spearman's correlation. The correlation coefficient interpretation is as follows: 0.0–0.2, very weak; 0.2–0.4, weak; 0.4–0.6, moderate; 0.6–0.8, strong; 0.8–1.0, very strong.

Receiver operating characteristic (ROC) curves were constructed to determine the optimal cut-off value of RDW in predicting neonatal bacteremia. Sensitivity, specificity, likelihood ratio and their 95% confidence intervals were computed. Youden's J index was defined for all points along the ROC curve, and the maximum value of the index was used as a criterion for selecting the best cut-off point. The null hypothesis was rejected at 0.05 α-level of significance. STATA version 15.0 (Stata Corp SE, College Station, TX, USA) was used for data analysis.

Ethical Considerations

This study was administered in accordance with the Good Clinical Practice (GCP) training, which were completed by the investigators. This study went through IRB approval. A waiver of informed consent was allowed, and granted by the IRB, as the conduct of the study entailed only a medical records review. The identities and confidentiality of study participants were preserved using anonymized case report forms. The authors have no potential conflicts of interest to disclose.

RESULTS

There were 130 neonates included in this study: 26 bacteremic cases, and 104 non-bacteremic controls (Table 1). Among 37 eligible cases, the following were excluded: incomplete chart (n=4), poor APGAR score (n=4), history of antibiotic use (n= 2), and history of blood transfusion prior to blood drawing (n=1), yielding the 26 cases (see Figure 1.) Among 120 controls, 104 were selected by simple random sampling.

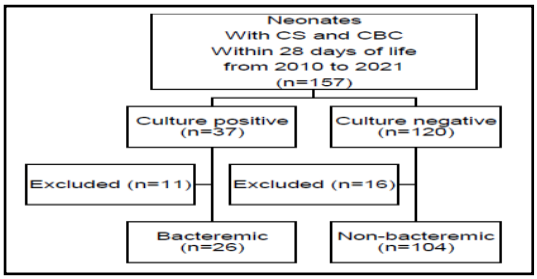

Figure 1. Methodology Flowchart

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Table 1. Neonatal characteristics, bacteremic versus non-bacteremic

Parameter	All (n=130)	Bacteremic (n=26)	Non-bacteremic (n=104)	p
	Median (Range); Frequency (%)			
Birthweight (grams)	2590 (795-4700)	2697.5 (1050-3600)	2570 (795-4700)	.903*
Sex				.722‡
Male	76 (58.46)	16 (61.54)	60 (57.69)	
Female	54 (41.54)	10 (38.46)	44 (42.31)	
APGAR	[n=121]		[n=97]	
1st min	9 (5-9)	9 (6-9)	9 (5-9)	.525*
5th min	9 (7-10)	9 (7-9)	9 (7-10)	.257‡
Delivery				.587‡
Cesarean section	81 (62.31)	15 (57.69)	66 (63.46)	
vaginal delivery	49 (37.69)	11 (42.31)	38 (36.54)	
Delivered				.593‡
Inborn	114 (87.69)	22 (84.62)	92 (88.46)	
Out born	16 (12.31)	4 (15.38)	12 (11.54)	
Indication for culture				<.001‡
Neonatal	79 (53.08)	23 (88.46)	46 (44.23)	
Perinatal	25 (19.23)	2 (7.69)	23 (22.12)	
Maternal	36 (27.69)	1 (3.85)	35 (33.65)	
Blood CS Day of life	1 (1-28)	4 (1-21)	1 (1-28)	<.001*
CBC day of life	1 (1-28)	4 (1-21)	1 (1-28)	<.001*
CRP day of life	1 (1-28); [n=126]	4 (1-21)	1 (1-28); [n=102]	<.001*

Statistical test used: * - Mann-Whitney U test; † - Fisher's Exact test; ‡ - Chi-square test

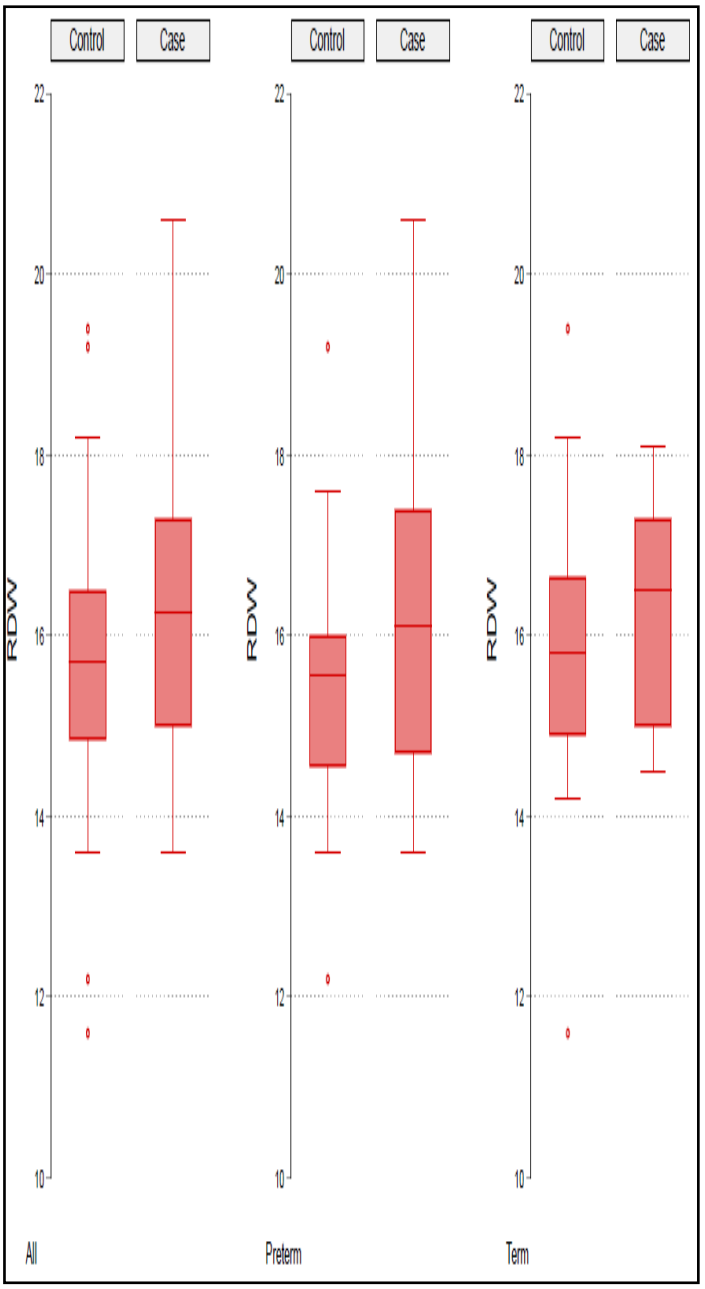

Figure 2. Boxplot of RDW between cases and controls; overall, preterm, and term

Overall, the median birth weight was 2.59 kilograms, 58% were male, 62% were delivered via caesarean section, and 12% were outborn. There were notable differences between the two groups in terms of indication for requesting for blood culture, 53% of which were due to neonatal causes. Blood culture, CBC and CRP were obtained at a significantly later day in the bacteremic group at a median of day 4, versus a median of day 1 for the control group.

The median RDW for both term and preterm neonates was close to 16, with a narrow inter-quartile range at 1 and 2 for controls and cases, respectively. The range (minimum to maximum) of RDW values for bacteremic preterm neonates was more variable than those of the term neonates, as demonstrated by the symmetric whiskers in the boxplot of term neonates.

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Table 2. CBC and CRP results of neonates, bacteremic versus non-bacteremic

Parameter	All (n=130)	Bacteremic (n=26)	Non-bacteremic (n=104)	*p*
	Median (Range); Mean ± SD; Frequency (%)			
RDW	15.75 (11.6-20.6)	16.25 (13.6-20.6)	15.7 (11.6-19.4)	.096*
Hemoglobin (g/L)	17.01 ± 2.9	14.81 ± 3.48	17.56 ± 2.46	**<.001**
Hematocrit	48.1 ± 7.89	42.5 ± 9.73	49.5 ± 6.71	**.002**
RBC (x 10^12/L)	4.76 ± 0.79	4.27 ± 0.98	4.89 ± 0.69	**.005**
WBC (10^9/L)	15.89 (1.51-48.06)	11.035 (1.51-35.31)	17.37 (4.85-48.06)	**.007***
Segmenter	61.5 (14-85)	59 (14-85)	62 (23-85)	.382*
Lymphocyte	27 (6-80)	26 (10-80)	27 (6-64)	.942*
Monocyte	10 (1-26)	10.5 (1-18)	10 (2-26)	.886*
Eosinophil	1 (0-9)	0.5 (0-4)	1 (0-9)	.118*
MCH (pg)	35.6 (27.7-41.6)	34.9 (27.7-41)	35.8 (30.1-41.6)	**.008***
MCHC	100.7 (81.1-192.4)	99.25 (81.1-119.7)	101.05 (88-192.4)	**.031***
MCV	35.33 ± 1.12	34.82 ± 1.17	35.46 ± 1.08	.139
Platelet	286500 (10000-2900000)	205000 (10000-521000)	304000 (33000-2900000)	**<.001***
CRP (mg/L)	2.6 (0.09-231.61)	17.995 (0.1-231.61)	1.85 (0.09-175.17)	**.002***
≤5	71 (56.35)	9 (37.5)	62 (60.78)	
>5	55 (43.65)	15 (62.5)	40 (39.22)	

Statistical test used: If with asterisk (*), Mann-Whitney U test. Otherwise, Welch's test.

There were significant differences between the two groups in the following: hemoglobin, hematocrit, RBC count, WBC count, MCH, MCHC and platelet count which were lower, and CRP which was higher among those with bacteremia versus non-bacteremia.

The median RDW values were not significantly different between the two groups.

Table 3. Blood CS growth results among neonates

Organism		Frequency	Proportion (%)
Gram positive	***Streptococcus agalactiae***	6	23
	Oxacillin-resistant *Staphylococcus epidermidis*	3	11.5
	Staphylococcus aureus	1	4
	Staphylococcus saprophyticus	1	4
	Micrococcus luteus	1	4
	Streptococcus sanguinis	1	4
Gram negative	***Escherichia coli***	3	11.5
	Klebsiella pneumoniae	2	7.7
	Pseudomonas stutzeri	2	7.7
	Serratia marcescens	2	7.7
	Salmonella enteritidis	1	4
	Acinetobacter baumanii complex	1	4
	Citrobacter koseri	1	4
	Enterobacter aerogenes	1	4

The most common blood isolates were *Streptococcus agalactiae* and oxacillin-resistant *staphylococcus epidermidis* for the gram-positive organisms, and *Escherichia coli* for the gram-negative organisms.

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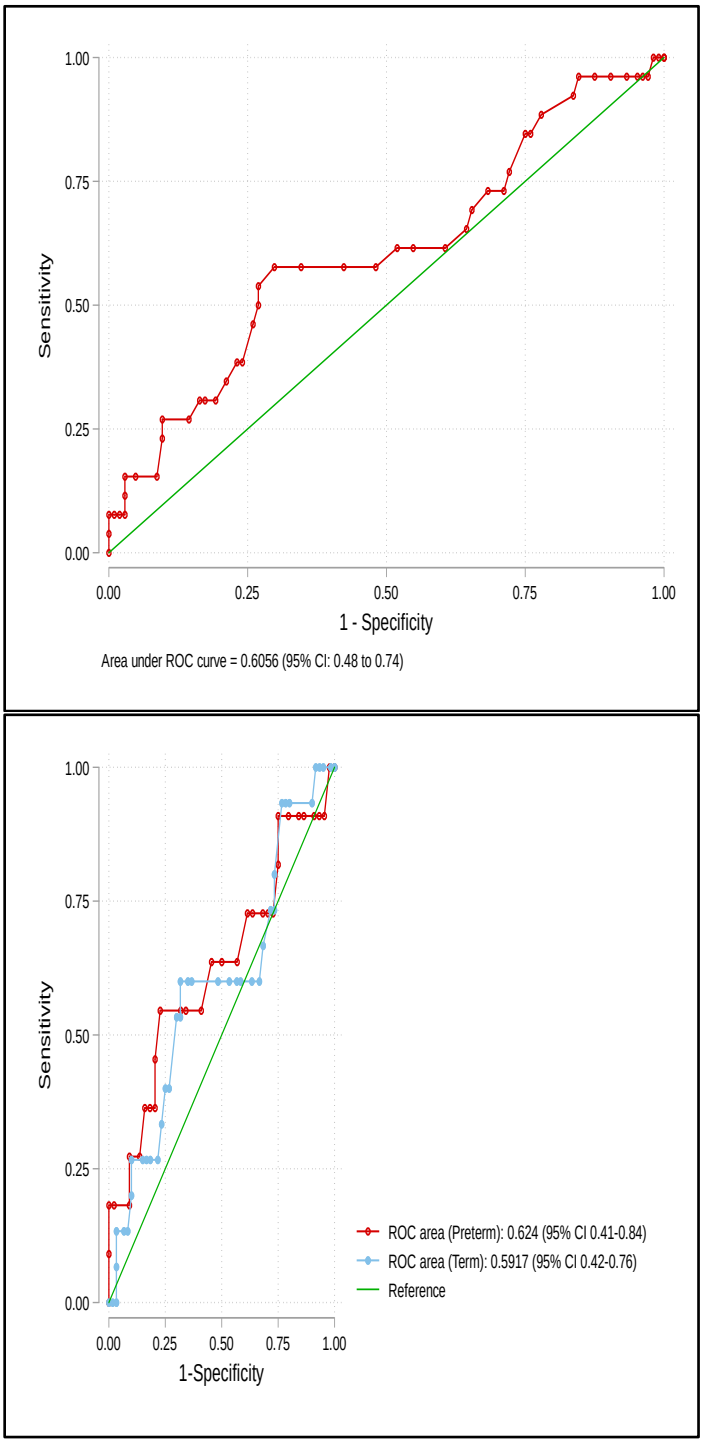

Figure 3. Receiver operating characteristic curve of RDW in predicting bacteremia

Using RDW to detect bacteremia, it had an equivocal discriminatory power or AUC of 0.6056 and 95% CI of 0.48 to 0.74.

Table 4. Diagnostic performance measure of RDW at different cutoff scores

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-	Youden's J index
(>= 15)	76.92%	27.88%	37.69%	1.0667	0.8276	4.80%
(>= 15.1)	73.08%	28.85%	37.69%	1.027	0.9333	1.93%
(>= 15.2)	73.08%	31.73%	40.00%	1.0704	0.8485	4.81%
(>= 15.3)	69.23%	34.62%	41.54%	1.0588	0.8889	3.85%
(>= 15.4)	65.38%	35.58%	41.54%	1.0149	0.973	0.96%
(>= 15.5)	61.54%	39.42%	43.85%	1.0159	0.9756	0.96%
(>= 15.6)	61.54%	45.19%	48.46%	1.1228	0.8511	6.73%
(>= 15.7)	61.54%	48.08%	50.77%	1.1852	0.8	9.62%
(>= 15.8)	57.69%	51.92%	53.08%	1.2	0.8148	9.61%
(>= 15.9)	57.69%	57.69%	57.69%	1.3636	0.7333	15.38%
(>= 16)	57.69%	65.38%	63.85%	1.6667	0.6471	23.07%
(>= 16.1)	57.69%	70.19%	67.69%	1.9355	0.6027	27.88%
(>= 16.2)	53.85%	73.08%	69.23%	2	0.6316	26.93%
(>= 16.3)	50.00%	73.08%	68.46%	1.8571	0.6842	23.08%
(>= 16.5)	46.15%	74.04%	68.46%	1.7778	0.7273	20.19%
(>= 16.6)	38.46%	75.96%	68.46%	1.6	0.8101	14.42%
(>= 16.7)	38.46%	76.92%	69.23%	1.6667	0.8	15.38%
(>= 16.8)	34.62%	78.85%	70.00%	1.6364	0.8293	13.47%
(>= 16.9)	30.77%	80.77%	70.77%	1.6	0.8571	11.54%
(>= 17)	30.77%	82.69%	72.31%	1.7778	0.8372	13.46%

Maximal cutpoint for both term and preterm neonates were based on the highest Youden's J index to maximize both specificity and sensitivity. The cut point with the highest Youden's J index was established at an RDW level of ≥16.1 (sensitivity 58%, specificity 70%, LR+ 1.94, LR- 0.60 and Youden's J index at 28%).

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Table 5. Association of RDW to bacteremia

Parameter		Odds Ratio (95% CI)	*p*
Overall (n=130)	RDW as continuous variable	1.403 (1.03-1.92)	**.034**
	RDW ≥ 16.1	3.211 (1.33-7.77)	**.010**
	RDW ≥ 16.1 *adjusted by birthweight*	3.238 (1.33-7.90)	**.010**
Preterm (n=55)	RDW as continuous variable	1.475 (0.97-2.25)	.070
	RDW ≥ 16.1	4.08 (1.03-16.23)	**.046**
	RDW ≥ 16.1 *adjusted by birthweight*	4.663 (1.11-19.58)	**.035**
Term (n=75)	RDW as continuous variable	1.313 (0.81-2.11)	.264
	RDW ≥ 16.2	3.237 (1.007-10.40)	**.049**
	RDW ≥ 16.2 *adjusted by birthweight*	3.325 (1.02-10.80)	**.046**

Our results suggest an association between RDW and bacteremia; overall, every unit increase of RDW corresponds with an increased odds of bacteremia by 1.4 times (95% CI 1.03-1.92, p = 0.034). Neonates with RDW ≥ 16.1 are three times as likely to have bacteremia, compared to those with lower RDW values, even after adjusting for birthweight. A similar association was seen even after the neonates were stratified by gestational age, into preterm and term groups.

Table 6.Correlation between RDW and laboratory values

Parameter	Correlation Coefficient	Interpretation	p
Hemoglobin (g/L)	0.084	Direct, very weak	.340
Hematocrit	0.129	Direct, very weak	.143
RBC (x 10^12/L)	0.138	Direct, very weak	.118
WBC (10^9/L)	0.068	Direct, very weak	.441
Segmenter	0.115	Direct, very weak	.191
Lymphocyte	-0.152	Indirect, very weak	.084
MCH (pg)	-0.098	Indirect, very weak	267
MCHC	-0.185	Indirect, very weak	.035
MCV	0.009	Direct, very weak	.922
Platelet	-0.074	Indirect, very weak	.405
CRP	0.167	Direct, very weak	.063

We found insufficient evidence to demonstrate a correlation between RDW and other CBC parameters, except for MCHC. For MCHC, the results suggest a very weak and indirect correlation (p = 0.035).

Table 7. Subgroup analysis for bacteremic neonates (n=26)

Parameter	Nonsurvivor (n=6)	Survivor (n=20)	cOR (95% CI)	*p*
RDW	15.65 (14.6-17.1)	16.4 (13.6-20.6)	0.767 (0.41-1.43)	.405
<16.1	3 (50)	8 (40)	Reference	-
≥ 16.1	3 (50)	12 (60)	0.68 (0.12-3.79)	.660

We found insufficient evidence to demonstrate an association between RDW and mortality among bacteremic neonates.

DISCUSSION

Neonatal bacteremia remains a diagnostic challenge to pediatricians. It has a high mortality rate, so that early diagnosis and appropriate treatment are critical. As previously mentioned, blood culture is the gold standard in diagnosing neonatal bacteremia. However, studies have shown that blood cultures have a low positivity yield, and the isolation and identification of an organism takes time.[2] Hence, another parameter for predicting bacteremia in a neonate is invaluable for pediatricians.

Red cell distribution width is part of a routine CBC test, which is readily available and cost-effective. Lanzkowsky wrote that RDW and mean corpuscular volume (MCV) are mainly used to determine the etiology of anemia.[6] Higher RDW values indicate an increase in the variations of RBC volume.[6] Jianping Chen, et al. found that aside from RDW's use as a tool to differentiate between various types of anemia, it can be increased during inflammation and oxidative stress.[8]

Although the mechanism of this increase in RDW during bacteremia is unknown, it has been proposed that an inflammatory process affects red cell production, as may occur in neonatal bacteremia.[9]

In our study, red cell distribution width values among term and preterm neonates, as well as those with bacteremia (16.2) and non-bacteremic controls (15.7), were not significantly different. These results are unlike that reported by Tonbul, et al., who prospectively studied RDW levels of 1,596 healthy newborns on the first day of life, and found that levels differed between term (16.6) and preterm newborns (17.9).[10] In the same study, it was speculated that increased erythropoiesis occurs in early gestational ages (GA), and their results showed that preterm neonates at 32-34 weeks GA had higher RDW values, compared to those of term neonates (37-42 weeks GA).[10] A negative correlation between RDW and GA may explain the broad range of RDW values in the bacteremic preterm neonate group, in contrast to the symmetric whiskers seen in the term neonates (Figure 2).[11]

A prospective observational study by Deka, et al. showed significantly different RDW values on day 1 of life, between the 50 septic neonates (18.6) and 50 well newborns (16.2).[4] Our study results may have varied from the above studies due to differences in population size, as the controls they used were healthy newborns, while our study used symptomatic newborns with no blood culture isolate; disease prevalence, and timing of blood sampling. Another possible reason for our findings as being different from the above studies may be the selection of cut-off levels for RDW. When the Youden J Index was applied to our study results to measure the RDW's ability to determine a balance between sensitivity and specificity, we found RDW level of ≥16.1 to be the optimal value to yield the highest J index. Other investigators may have used cut-off points based on a preference for either a more specific or sensitive test, instead of finding a good a balance between sensitivity and specificity.

This study found a significant association between RDW and neonatal bacteremia when an RDW of ≥ 16.1 was used as a cut-off point, at which a neonate was three times more likely to have bacteremia, compared to one with a lower RDW value, even after adjusting for birthweight, and after stratifying by gestational age. One study showed that an increased RDW is reflective of an inflammatory process triggered by hormones such as noradrenaline and angiotensin, which stimulate the production and proliferation of cells by erythrogenin (EPO), with the end-result of an increased RDW.[8] Ellahony, et al. also reported that in a septic patient, oxidative stress is increased, resulting in a decrease in the lifespan of circulating red blood cells (RBCs) which stimulate erythroid tissue to produce and release new RBCs from the bone marrow.[12]

Guo and Sun also reported an association between RDW and sepsis, but RDW was not found to be the sole predictor of neonatal sepsis based on the ROC analysis.[13] Guo's study showed that an elevated baseline RDW (17.9) in preterm infants was associated with sepsis (aOR 4.68).[13] As they followed the changes in the RDW during the hospital stay, they found a better association between RDW and sepsis, such that the ROC curve analysis of RDW at baseline, along with the RDW through the length of the hospital stay, showed an ROC curve analysis of 0.81; the sensitivity and specificity were 78.2 and 72.5%, respectively.[13] Our ROC analysis, on the other hand, showed an AUC of 0.605, which indicates RDW to be a poor predictor for neonatal bacteremia. An improvement on this result may be possible, if dynamic changes in RDW are recorded over the course of the hospitalization for neonates who may later develop bacteremia.

Our study found significantly higher C-reactive protein (CRP) levels and lower WBC and platelet counts among bacteremic neonates versus those who weren't. These findings were similar to findings in a review by Da Silva, et al., where CRP was shown to be a good diagnostic measure for neonatal sepsis with a sensitivity of 58-100%, and an NPV of 86-100%.[14]

Lippi, et al. reported CRP to have an AUC of 0.88, which indicates it to be a good diagnostic test for neonatal sepsis.[3] Thus, CRP was established as a specific diagnostic marker for neonatal bacteremia; however, CRP levels only begin to increase after 6 to 8 hours of infection, so that the level may be falsely test negative if done earlier.[14] CRP test is also expensive and not readily available in resource-limited settings, hence, its routine use locally may not be possible.

In our study, significantly lower platelet levels were seen among bacteremic neonates, which agrees with a local study of 100 NICU neonates by Mayuga, et al., where thrombocytopenia was significantly more common among septic babies, but with a sensitivity of 35% and negative predictive value (NPV) of 87%.[14,15] Hence, using platelet count as a sole diagnostic marker for bacteremia is not recommended and should be used in relation with other diagnostic parameters.

In our study, WBC count was notably lower in the bacteremic versus the non-bacteremic group. However, the median WBC count in the bacteremic group was still within normal limits for preterm and term neonates.[6] In the study by Mayuga, et al., no significant association between WBC and neonatal sepsis was reported.[15] Da Silva, et al. also reported that very high or very low WBC counts as sepsis indicators have a wide range of sensitivity at 17% to 90%, and specificity of 31% to 100%.[14] Most often, bacteremic babies will not present with marked leukocytosis nor leukopenia, and values may also be affected by other causes (e.g., metabolic factors, stress, etc.). Thus, using WBC count alone as a diagnostic marker for neonatal bacteremia is not recommended but may be used in conjunction with other diagnostic parameters.

Blood culture, CBC and CRP were obtained earlier in the non-bacteremic neonates (day 1) as compared to bacteremic neonates (day 4). Majority (55.8%) of the tests were requested due to neonatal and maternal reasons.

This early timing for the sepsis work-up is not unexpected as this is often done as a result of maternal risk factors and the early tachypnea commonly seen soon after birth, which may be due to a variety of reasons. Among the bacteremic neonates, however, the blood cultures and CBCs were done on the 4th day of life, often due to a clinical setback or observation in the neonate that may not have been evident at birth. The timing of these tests could have affected the results obtained in our study.

Our study showed MCH and MCHC to be significantly lower among bacteremic neonates. To the best of our knowledge, these findings have not been previously reported. Piagnerelli, et al. reported a decrease in the hematocrit, hemoglobin and RBC count among septic neonates; however, they found no association or significant differences for MCHC or MCH between septic and non-septic babies.[16] We report more gram-positive than gram-negative organisms in this study. In a local study by Meliton, gram-negative sepsis was more common in the study institution.[17] However, in our study, many gram-negative bacteremic cases were not included due to the inclusion and exclusion criteria (i.e., history of early antibiotic use, history of blood transfusion, and lack of a corresponding control group). Nevertheless, it is notable that there were six cases of *Streptococcus agalactiae* in our study. Among the 366 neonatal bacteremia in five local studies, there was only one previous report of a *Streptococcus agalactiae* blood culture growth, with that sole case coming from this study institution.[17-21]

In our study, a significant and positive correlation between RDW and MCHC in the neonatal bacteremia group was observed. This was in contrast to the study by Cosar, et al. which found a significant correlation between RDW and CRP.[4,22] In another retrospective study, data from 500 septic term neonates were obtained and compared RDW values with other diagnostic parameters for sepsis.[12] The study showed a positive correlation between RDW and CRP, WBC count, and a negative correlation between RDW and hemoglobin and platelet count.[12]

Our results may have varied from previous studies due to differences in the study population, disease prevalence and timing of blood sampling. Our study found no significant difference between RDW levels seen among bacteremic neonates who survived, versus those who died. This is in contrast to a prospective study that showed RDW levels of 251 septic neonates (19.9%) to be significantly higher than those of healthy controls (18.9%).[23] In another prospective study, 50 septic neonates were compared to a control group composed of healthy neonates; their results showed that an elevated RDW was associated with severe sepsis, septic shock and a higher mortality rate in the ICU.[24] The mechanism as to how an elevated RDW is associated with an increased severity of illness remains unknown, but factors such as augmented inflammation, leading to organ dysfunction, have been speculated.[23]

Our findings may have also varied from previous studies due to differences in the study population, wherein they included clinically and laboratory diagnosed septic neonates as cases, and healthy neonates as controls; while in our study, we included bacteremic neonates as cases and symptomatic non-bacteremic neonates as controls. An improvement in our findings may have been possible if the RDW values were correlated with severity of the disease (e.g., subgrouping cases as septic and septic shock); and if RDW were dynamically measured over time, from the baseline levels, through the different stages of bacteremia and sepsis.[12]

Being a retrospective study, a limitation of this study is that we could only test for an association between RDW and neonatal bacteremia, and no causal relationship could be made. The insufficient evidence to demonstrate a correlation between RDW and neonatal bacteremia, as well as between RDW with other factors, may be associated with a low prevalence of neonatal bacteremia in the study population, the selected cut-off points for RDW, and the choice of control group.

Another limitation in this study is that there is no serial monitoring of RDW levels of bacteremic patients after the administration of antibiotics was done. Our study was conducted in a single tertiary hospital; hence, results may not be generalized to the rest of the country.

CONCLUSION AND RECOMMENDATIONS

Early diagnosis of neonatal bacteremia is essential for clinicians to be able to provide prompt and appropriate intervention for bacteremic neonates. In this study, RDW, which is a part of a routine CBC test and is readily available, showed an association with neonatal bacteremia at an RDW level of $\geq$ 16.1 at which there was a three-fold risk for neonatal bacteremia. However, this study found that RDW was not significantly different between bacteremic and non-bacteremic neonates. Lastly, this study showed significantly lower levels of hemoglobin, hematocrit, RBC count, WBC count, platelet count, MCH and MCHC, and a higher CRP among bacteremic neonates versus non-bacteremic neonates.

We recommend a prospective cohort study with a larger population in future studies to be able to accurately evaluate RDW as diagnostic marker for neonatal bacteremia. Also, in future prospective cohort studies, the utility of MCH and MCHC as indicators for neonatal bacteremia may also be studied.

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ORIGINAL ARTICLE

CLINICO-EPIDEMIOLOGIC FEATURES AND OUTCOME OF INFECTIOUS AND IMMUNE-MEDIATED PEDIATRIC ENCEPHALITIS

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ABSTRACT

Introduction: The etiology of encephalitis involves an enormous range and can be classified as infectious or immune-mediated. There are several factors influencing its prognosis and has been associated with significant morbidity and mortality. This study aims to evaluate the clinico-epidemiologic characteristics and outcomes of infectious and immune-mediated encephalitis among pediatric patients.

Methodology: Retrospective descriptive cross-sectional study that included patients aged 6 months to 17 years old with encephalitis in a tertiary hospital between January 2010 to December 2020.

Results: A total of 23 cases were reviewed and 60.87% were infectious while that of immune-mediated was 39.13%. Among those with identified infectious cause, *Mycoplasma pneumonia* was the most common (28.57%). Infectious encephalitis was more common among younger males (35.71%) while immune-mediated affected female adolescents more (55.56%). The most common neurologic manifestation was altered mental status and/or behavioral changes. Treatment such as antibiotics (78.26%), anticonvulsant therapy (78.26%), and steroids (43.48%) were given. All immune-mediated cases received steroids. More than half of patients had complete recovery (56.52%).

Conclusion: Pediatric encephalitis should be considered among patients with neurologic dysfunction with or without systemic involvement. Behavioral changes in an apparently well child should prompt clinicians to consider anti-NMDAR encephalitis, especially if viral studies are negative and with no other known cause. Viruses remain to be the most common etiology, but other possible causes should be highly considered such as anti-NMDAR and Mycoplasma. A normal CSF analysis, imaging and/or encephalography (EEG) may not totally exclude encephalitis. Prognosis is relatively good hence an early diagnosis and initiation of appropriate management is important.

KEYWORDS: *Encephalitis, Infectious Encephalitis, Viral Encephalitis, Mycoplasma, Immune-mediated Encephalitis*

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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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INTRODUCTION

Acute encephalitis is the acute inflammatory process which involves the brain parenchyma associated with symptoms of neurologic dysfunction along with systemic symptoms.[1] In the year 2008, Acute Encephalitis Syndrome (AES) was coined by the World Health Organization (WHO), which referred to the acute-onset of fever and presence of change in mental status (including signs and symptoms such as confusion, disorientation, delirium or coma) and/or new-onset of seizures (excluding simple febrile seizures) in a person of any age at any time of the year.[2,3] The reported worldwide incidence varies, relatively ranging from 3.5 to 7.4 cases per 100,000 patient-years. It affects all ages but compared to adults, incidence tends to be higher in the pediatric population, with more than 16 cases per 100,000 patient-years.[4,5] In the Philippines, the Epidemiologic Bureau of the Department of Health under the Philippine Integrated Disease Surveillance and Response (PIDSR) system established the Acute Meningitis-Encephalitis Syndrome (AMES) Surveillance, which officially started in 2015. Based on its latest data, a total of 1664 AMES cases were reported from January 1 to May 25, 2019, wherein majority were males (58%) and mostly were children less than 5 years of age (49%).[6,7]

Etiology of encephalitis involves an enormous range and can be classified as infectious, para-infectious, autoimmune, and/or of unknown cause. Among all the possible infectious causes, viruses remained to be the most common.[8] Cases of primarily immune mediated or autoimmune in nature have been recognized as well, which manifests with a broad clinical spectrum. Acute encephalitis has been associated with significant morbidity and mortality, with outcomes ranging from full recovery to death. Several studies on pediatric encephalitis reported mortality rate of less than 10%, but over 50% of these patients have significant neurologic and behavioral sequelae.[1] The accurate determination of its prognosis remains elusive.

Currently, majority of published studies on pediatric encephalitis were focused mainly on acute viral encephalitis, being it the most common. There is minimal availability of studies that covers the clinical profile and outcomes of both infectious and immune mediated cases, especially in the local setting. It is important to take into consideration other possible etiologies, the different factors associated to its occurrence, as well as their presentation depending on the cause. This will then help in early detection and diagnosis, leading to a more directed approach in management and prevention of development of complications. Hence, additional data will be of significant help.

This study aimed to evaluate the clinico-epidemiologic characteristics of pediatric encephalitis patients admitted in an urban tertiary hospital from January 2010 to December 2020. The specific objectives were: 1) to determine the proportion of acute encephalitis attributed as infectious and immune-mediated; 2) to characterize the cases of acute encephalitis in terms of etiology, age, sex, nutritional status, presenting systemic and neurologic manifestations, duration of symptoms prior to admission, diagnostic work-ups, length of hospital stay, and medical management; and 3) to classify the outcomes of these patients at the time of discharge as to complete or partial recovery, and mortality.

METHODOLOGY

This was a retrospective descriptive cross-sectional study of subjects aged 6 months to 17 years old admitted in an urban tertiary hospital between January 1, 2010 to December 31, 2020, with a final diagnosis of acute encephalitis regardless of its etiology, and/or with the following ICD 10 codes:

- A83 (mosquito-borne viral encephalitis)
- A84 (tick-borne encephalitis)
- A85 (other viral encephalitis, not elsewhere classified)
- A86 (unspecified viral encephalitis)
- B00.4 (herpes viral encephalitis)

- B01.1 (varicella encephalitis, myelitis and encephalomyelitis)
- B10.01 (human herpes virus 6 encephalitis)
- B02.0 (zoster encephalitis)
- G04.0 (acute disseminated encephalitis and encephalomyelitis)
- G04.81 (other encephalitis and encephalomyelitis)
- G04.9 (encephalitis and encephalomyelitis, unspecified)

Patients with final diagnoses of acute meningoencephalitis and those with other known neurologic conditions were excluded. A total enumeration of cases was done.

Upon the approval of the Makati Medical Center Institutional Review Board (IRB), a list of eligible patients was obtained from the medical records, admission census of the department of Pediatrics during the stated years, as well as from the records of pediatric infectious disease specialists and neurologists. A full medical chart review of eligible subjects was done and retrieved via the ArchiveOne database and electronic medical records (EMR) system. A patient data sheet was used for each eligible subject in acquiring the required information.

Descriptive statistics was used to summarize the general and clinical characteristics of the participants. Continuous data which follows the normal distribution were summarized using mean and standard deviation while non-Gaussian variables were reported as median and range. Categorical variables were reported as frequency and proportion. Missing values were not imputed. STATA version 15.0 (StataCorp SE, College Station, TX, USA) was used for data analysis.

Operational Definition of Terms

1. Acute Encephalitis – acute onset of any changes in mental status (such as confusion, disorientation, coma, inability to talk, increase in irritability, somnolence, or abnormal behavior greater than that seen with usual febrile illness), and/or new onset of seizures (excluding simple febrile seizures), with or without acute onset or a recent history of fever.
2. Etiology – primary cause identified, based on ancillaries done, and classified as either infectious or immune-mediated
   2a. Infectious – includes all viral, bacterial, fungal, and parasitic causes
   2b. Immune mediated – may be autoimmune in nature, e.g., anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, acute disseminated encephalomyelitis
      2b.1 Laboratory confirmed anti-NMDAR encephalitis – patients with anti-NMDAR antibody detected on CSF
      2b.2 Possible anti-NMDAR encephalitis – patients who were still diagnosed with anti-NMDAR encephalitis, with no detection of CSF anti-NMDAR antibody done or with negative results but still presented with either or combination of the following: rapid onset of abnormal behavior, psychiatric symptoms, cognitive or speech dysfunction, seizures, dyskinesias or movement disorders, autonomic dysfunction or with ovarian tumors detected
3. Nutritional status – based on subject's body mass index (weight in kilograms divided by height in meters squared) on admission
4. Hospital stay – length of the patient's stay in the hospital in terms of number of days from the date of admission until the date of discharge
5. Outcome – clinical state of the patient at the time of discharge
   5a. Complete recovery – complete resolution of presenting symptoms
   5b. Partial recovery – partial resolution of presenting symptoms or those still with neurologic deficits or neurologic sequelae
   5c. Mortality

Ethical Considerations

This study was conducted upon the approval of the Makati Medical Center Institutional Review Board (IRB).

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Patient confidentiality and anonymity was strictly observed throughout the entire duration of the study in compliance with the Data Privacy Act of 2012 (Republic Act 10173). A waiver of informed consent was requested and granted by the IRB as the study was done via chart review only. There was no direct contact involved with eligible subjects. No disclosure was done by the authors, nor any potential conflict of interest identified.

RESULTS

A total of 23 patients admitted in an urban tertiary hospital from January 2010 to December 2020 were diagnosed with encephalitis. All etiologies were included and further classified as infectious or immune-mediated.

Table 1. Infectious Etiology of Pediatric Encephalitis

Identified Infectious Etiology	Frequency (n=14)	%	
		All (23)	Infectious (14)
Unspecified viral	4	17.39	28.57
Mycoplasma	4	17.39	28.57
Dengue	2	8.70	14.29
Varicella	1	4.35	7.14
Herpes Simplex Virus (HSV)	1	4.35	7.14
Measles	1	4.35	7.14
Enterovirus	1	4.35	7.14

Table 2. Immune-mediated Pediatric Encephalitis

Identified Immune-mediated Etiology	Frequency (n=9)	%	
		All (23)	Immune mediated (9)
Anti-NMDA receptor encephalitis	8	34.78	88.89
• Possible	5	21.74	55.56
• Laboratory confirmed	3	13.04	33.33
Autoimmune (Unspecified)	1	4.35	11.11

Fourteen patients were classified as infectious (60.87%) and nine were of immune-mediated etiology (39.13%). Encephalitis with a viral etiology occurred in the majority (10 in 14) of the cases reviewed and four of which had no specific cause identified but with CSF findings suggestive of viral encephalitis (e.g., normal to elevated WBC count, normal to elevated protein, normal CSF/serum glucose ratio) and bacterial cultures were negative. However, among all infectious cases with an identified causative agent, *M. pneumoniae* was the determined cause in 4 of the 14 cases (28.57%). Table 2 shows the cases of immune-mediated encephalitis and eight out of nine were managed as anti-N-methyl D aspartate receptor (anti-NMDAR) encephalitis – five of which were considered as possible cases while three cases were laboratory confirmed with anti-NMDAR antibody detected on their CSF.

Table 3. Age and Sex Distribution of Pediatric Encephalitis Patients

Parameter	All (n=23)	Classification of etiology	
		Infectious (n=14)	Immune-mediated (n=9)
	Median (Range); Frequency (%)		
Age (years)	12 (1–17)	9.5 (1–17)	13 (4–15)
1-5	8 (34.78)	5 (35.71)	3 (33.33)
6-10	3 (13.04)	2 (14.29)	1 (11.11)
11-15	9 (39.13)	4 (28.57)	5 (55.56)
16-17	3 (13.04)	3 (21.43)	0 (0)
Sex			
Male	14 (60.87)	10 (71.43)	4 (44.44)
Female	9 (39.13)	4 (28.57)	5 (55.56)

Overall, affected patients were from 1 to 17 years old, with the median age of 12 years old. Majority belongs to the 11-15 age group (39.13%) and followed by the 1-5 years age group (34.78%). Sixty-one percent were males, and they were mostly of the infectious type (71.43%). Infectious encephalitis was distributed among children aged 1-5 years old (35.71%) followed by the 11-15 years old age group (28.57%). On the other hand, immune-mediated encephalitis was observed to be more common among adolescents (11-15 years old) at 56% with slight female preponderance (55.56%).

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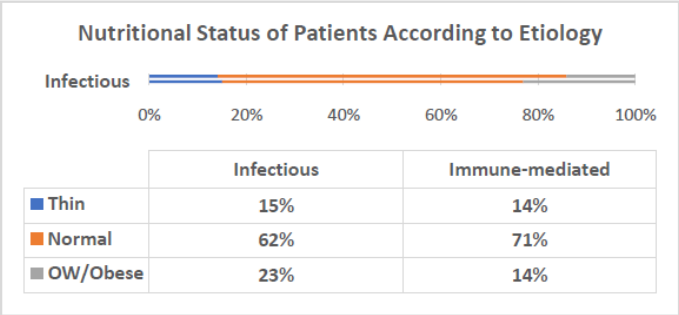
Table 4. Nutritional Status of Pediatric Encephalitis Patients



	Infectious	Immune-mediated
Thin	15%	14%
Normal	62%	71%
OW/Obese	23%	14%

The nutritional status of the patients was based on their body mass index (BMI) and interpreted in correlation with age. Normal BMI was observed in 62% and 71% of children with infectious and immune-mediated encephalitis, respectively. Twenty-three percent of children with infectious encephalitis were classified as either overweight or obese.

Table 5. Neurologic and Systemic Manifestations of Pediatric Encephalitis Patients

Manifestations	All (n=23)	Classification of etiology	
		Infectious (n=14)	Immune-mediated (n=9)
	Frequency (%)		
Neurologic manifestations	**23 (100)**	**14 (100)**	**9 (100)**
Altered mental status/ behavioral changes	17 (73.91)	8 (57.14)	9 (100)
Seizures	16 (69.57)	10 (71.43)	6 (66.67)
Headache	9 (39.13)	5 (35.71)	4 (44.44)
Dyskinesia (orofacial, limb)	3 (13.04)	0 (0)	3 (33.33)
Insomnia	2 (8.69)	0 (0)	2 (22.22)
Gen. body weakness	2 (8.69)	1 (7.14)	1 (11.11)
Systemic manifestations	**20 (86.96)**	**14 (100)**	**6 (66.67)**
Fever	18 (78.26)	13 (92.86)	5 (55.56)
Vomiting	10 (43.48)	8 (57.14)	2 (22.22)
Respiratory symptoms	9 (39.13)	6 (42.86)	3 (33.33)
Rashes	4 (17.39)	4 (28.57)	0 (0)
Abdominal pain	2 (8.7)	2 (14.29)	0 (0)
Loose stools	2 (8.7)	2 (14.29)	0 (0)

Table 5 shows the frequency of the neurologic, as well as systemic manifestations of pediatric encephalitis observed in this study. The most common neurologic manifestation was altered mental status and/or behavioral changes (73.91%). All patients with immune-mediated encephalitis presented with behavioral changes. Seizures were seen in almost 70% of patients, and this was noted in majority of the infectious cases (71.43%).

Common systemic manifestations were fever (78.26%), vomiting (43.48%), and respiratory symptoms (39.13%). All patients with the infectious type and more than half of the immune-mediated cases (6 out of 9) presented with systemic symptoms. Fever remained to be the most common on both groups. Two anti-NMDAR encephalitis patients had adnexal tumors detected upon further work up during admission.

The duration of symptoms prior to admission ranges from less than a day (18 hours) to 270 days, with a median duration of symptoms prior to admission was eight days. Patients of the infectious type had a median duration of six days of symptoms prior to admission while those of the immune-mediated type had thirty days.

Table 6. CSF Analysis of Pediatric Encephalitis Patients

Parameter	All	Classification of etiology	
		Infectious	Immune-mediated
	Frequency (%)		
WBC count	[n=21]	[n=12]	[n=9]
Normal	12 (57.14)	8 (66.67)	4 (44.44)
High	9 (42.86)	4 (33.33)	5 (55.56)
Lymphocyte predominance	4 (44.44)	2 (50)	2 (40)
Segmenter predominance	2 (22.22)	1 (25)	1 (20)
Unspecified	3 (33.33)	1 (25)	2 (40)
Glucose	[n=20]	[n=11]	[n=9]
Normal	15 (75)	9 (81.82)	6 (66.67)
Low	4 (20)	1 (9.09)	3 (33.33)
Slightly low	1 (5)	1 (9.09)	0 (0)
Protein	[n=20]	[n=11]	[n=9]
Normal	13 (65)	7 (63.64)	6 (66.67)
High	4 (20)	3 (27.27)	1 (11.11)
Low	3 (15)	1 (9.09)	2 (22.22)
Culture/Viral Studies			
HSV 1&2 Positive	1 (6.67)	1 (12.50)	0 (0)
Enterovirus Positive	1 (14.29)	1 (20)	0 (0)
Antibodies (PCR)			
Anti NMDA (+)	3 (13.04)	0 (0)	3 (33.33)
Dengue IgG (+), IgM (-)	1 (4.35)	1 (7.14)	0 (0)

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Out of the twenty-three subjects, only twenty-one had CSF analysis done. Those two patients who did not have lumbar tap had contraindications such as disseminated cutaneous lesions even on puncture site (Varicella) and hemodynamic instability with high risk for bleeding and coagulopathy (Dengue shock syndrome). As seen in Table 6, WBC count was normal in more than half of the patients (57.14%). Among the infectious group, pleocytosis was only observed in four patients who had Herpes simplex virus (HSV), enterovirus, dengue and one unidentified viral etiology. Fifty-six percent of the immune-mediated encephalitis had elevated WBC count. There was no significant shift in the levels of CSF glucose and protein for both groups and were normal at 75% and 65%, respectively.

Among those with specified causes, three infectious cases were determined via CSF viral studies, particularly HSV, Enterovirus (viral DNA/RNA PCR) and Dengue (antibody) while three subjects were confirmed to be anti-NMDA receptor encephalitis by the presence of anti-NMDAR antibodies in their CSF samples. Infectious causes and metabolic disturbances were ruled out among those with immune-mediated cases prior to diagnosis.

Table 7. Serology, Neuroimaging and Electroencephalography of Pediatric Encephalitis Patients

Diagnostics	All	Classification of etiology	
		Infectious	Immune-mediated
	Frequency (%)		
Serology			
Dengue NS1 Antigen (+)	1 (4.35)	1 (7.14)	0 (0)
Dengue IgM & IgG Antibody (+)	1 (4.35)	1 (7.14)	0 (0)
Mycoplasma IgM Antibody (+)	4 (17.39)	4 (28.57)	0 (0)
Neuroimaging			
CT scan	[n=6]	[n=4]	[n=2]
Normal	5 (83.33)	3 (75)	2 (100)
Pertinent findings	1 (16.67)	1 (25)	0 (0)
MRI	[n=19]	[n=11]	[n=8]
Normal	5 (26.32)	3 (27.27)	2 (25)
Pertinent findings	14 (73.68)	8 (72.73)	6 (75)
Electroencephalography	[n=17]	[n=9]	[n=8]
Normal	4 (23.53)	3 (33.33)	1 (12.50)
Abnormal	13 (76.47)	6 (66.67)	7 (87.50)

The remaining identified cases tested positive for serum Mycoplasma IgM (17.39%) and Dengue NS1 antigen (4.35%). The patient who had Dengue antibody detected on CSF was also positive with serum Dengue antibodies (IgM and IgG).

In terms of neuroimaging done, 83.33% had normal plain cranial CT scan while among those who had MRI of the brain, 73.68% had intracranial changes such as diffuse leptomeningeal enhancement of the cerebral hemispheres, diffuse cortical thickening, ill-defined diffuse symmetric abnormal signals in the bilateral cerebral white matter on T2W and FLAIR sequence, nonspecific non-enhancing punctate FLAIR hyperintensities in the right frontal white matter, bilateral ventricular dilatation, etc. Among those seventeen patients who had electroencephalography (EEG) done, abnormal results were observed in 13 patients (76.47%). Among those with immune-mediated encephalitis, 87.5% of them showed diffuse slowing of background activity, specifically in the theta-delta range.

Table 8. Medical Management of Pediatric Encephalitis Patients

Medical Management	All (n=23)	Classification of etiology	
		Infectious (n=14)	Immune-mediated (n=9)
	Frequency (%)		
Antibiotics	18 (78.26)	14 (100)	4 (44.44)
Anticonvulsant therapy	18 (78.26)	11 (78.57)	7 (77.78)
Steroids	10 (43.48)	1 (7.14)	9 (100)
Antiviral therapy	5 (21.74)	5 (35.71)	0 (0)
IVIG	5 (21.74)	0 (0)	5 (55.56)
Immunosuppressant	2 (8.7)	0 (0)	2 (22.22)
Monoclonal antibodies	1 (4.35)	0 (0)	1 (11.11)
Others (anti-psychotics, tranquilizers)	8 (34.78)	4 (28.57)	4 (44.44)

The most common medical treatments given for pediatric encephalitis were antibiotics (78.26%), anticonvulsant therapy (78.26%), and steroids (43.48%). Acyclovir was given in five patients (21.74%) upon the establishment of the diagnosis of a viral etiology. All of the patients with immune-mediated encephalitis were managed with steroids (high dose methylprednisolone for 3-5 days) and 55.56% also received intravenous immunoglobulin (IVIG).

Table 9. Length of hospital stay and Outcome of Pediatric Encephalitis Patients

Parameter	All (n=23)	Classification of etiology	
		Infectious (n=14)	Immune-mediated (n=9)
	Median (Range); Frequency (%)		
Length of hospital stay (days)	13 (4 – 79)	12 (4 – 79)	17 (6 – 41)
Outcome at time of discharge			
Complete recovery	13 (56.52)	11 (78.57)	2 (22.22)
Partial recovery	9 (39.13)	3 (21.43)	6 (66.67)
Mortality	1 (4.35)	0 (0)	1 (11.11)

The overall median duration of hospital stay was 13 days (4 to 79 days), 12 days (4 to 79 days) in infectious type and 17 days (6 to 41 days) in immune-mediated type. Complete recovery was seen in more than half of all patients (56.52%). Among those with the infectious etiology, complete recovery was seen in 78.57%. Partial recovery, defined as those with partial resolution of presenting symptoms or those still with neurologic deficits or neurologic sequelae (such as improving motor strength of extremities, minimal orofacial and/or limb dyskinesia) at the time of discharge, was noted in nine patients overall (39.13%) and six (66.67%) of which were of the immune-mediated type. However, two of these patients were transferred to another institution in the middle of their treatment. There was one mortality, who was diagnosed with an immune-mediated acute encephalitis.

DISCUSSION

This retrospective study determined the clinico-epidemiologic profile of pediatric encephalitis patients in an urban tertiary hospital. More than half of the patients had an infectious etiology, and among which, 28.57% still remained to be of unknown specific viral cause.

Identified etiologies included *Mycoplasma pneumoniae* (n=4, 28.57%), Dengue virus (n=2, 14.29%), and one case each of HSV, varicella, measles and enterovirus. On the other hand, 39.13% were classified as immune-mediated encephalitis, and eight out of these nine subjects (88.89%) were managed as anti-NMDAR encephalitis. Although the majority of the immune-mediated encephalitis patients were not confirmed cases with the presence of CSF anti-NMDA receptor antibody, (test was not available in earlier years), three cases were found to have anti- NMDA receptor antibody in the CSF.

In general, the patients affected in this study ranged from 1 to 17 years old, with a median age of 12 years, and mainly involved two age groups: 1-5 years old (34.78%) and 11-15 years old (39.13%). A plurality of them were males (60.87%). Similar to a local study on acute viral encephalitis among pediatric patients in a tertiary government hospital by Alcaraz, et. al in 2016, wherein bulk of the cases were noted in the 1-4 years age group with male predominance, the infectious encephalitis subjects in this study were mostly males (71.43%) aged 1-5 years old (35.71%) and 11-15 years old (28.57%).[9] On the contrary, immune-mediated encephalitis were observed more commonly among adolescents aged 11-15 years old (55.56%), with a slight female preponderance (55.56%). In a study done in Texas in 2020, male children were noted to more likely have infectious encephalitis, whereas female children present with an autoimmune etiology (58% vs. 34%). Also, the proportion of autoimmune cases relative to the infectious type increases with age.[10]

Infectious encephalitis patients had a relatively shorter median duration of symptoms prior to admission (6 days) as compared to the immune-mediated group (30 days). This may be due to the finding that patients with the infectious type usually presented with both systemic and neurologic symptoms almost always simultaneously prompting a more immediate consult.

On the other hand, the immune-mediated cases also presented with nonspecific but mostly mild systemic manifestations such as fever, vomiting and respiratory symptoms, described to be the prodromal phase in cases of anti-NMDAR encephalitis by Peery, et. al.[11]

The most prominent neurologic manifestation among these patients was the acute or subacute onset of behavioral changes in an apparently well child such as aggressiveness, violent behaviors, restlessness, hallucinations and insomnia. Due to the psychotic symptoms, three of these patients had psychiatric consult initially prior to the work up for encephalitis. This could have been one of the reasons for the delay in the admission and diagnosis. Hence, it is important to rule out organic pathology first prior to considering psychiatric disorders.

Several mechanisms of injury of the central nervous system were proposed to explain the onset of these neurologic symptoms, depending on its etiology. Parenchymal destruction, including direct neuronal and glial invasion with apoptosis, as well as mechanical and vascular injuries, such as vascular occlusion leading to infarction and secondary effects of cerebral edema, were associated with cases of direct infections to the central nervous system (CNS) as well as para-infectious processes. On the other hand, immune-mediated mechanisms, such as cytotoxic antibodies causing apoptosis and impaired neuronal function and cytokine effects, are observed in autoimmune encephalitis.[8]

Clinically, infectious and immune-mediated encephalitis have a substantial overlap in presentation. As based on the International Encephalitis Consortium's diagnostic criteria for encephalitis of presumed infectious or autoimmune etiology, all the subjects included in this study presented with neurologic dysfunction, such as altered mental status, new onset of seizures and/or focal neurologic symptoms, for at least 24 hours, with no alternative cause identified.[12] Altered mental status and/or behavioral changes was the most common CNS manifestation (73.91%). All immune-mediated encephalitis patients presented with behavioral changes.

Majority of the infectious cases (71.43%) manifested with seizures – mostly were characterized as generalized tonic-clonic, but focal seizures were also noted. One patient with dengue encephalitis also presented as status epilepticus.

Fever was still the most common systemic symptom observed overall, as well as for either group. Some physical findings could help in providing clues in the identification of the specific etiology. The characteristics of the generalized cutaneous lesions present in four patients were distinctive to their respective infectious cause – papulovesicular lesions seen on the subject who had fulminant varicella with encephalitis, petechial rashes in one case of dengue encephalitis, maculopapular rashes with cephalocaudal distribution in the case of measles encephalitis, and macular rashes on the patient who had enteroviral encephalitis. There were no other lesions observed for the remaining infectious causes or for those who had the immune-mediated type.

CSF analysis was nonspecific in this study in terms of presence of pleocytosis and alterations in the levels of glucose and protein, hence, a normal CSF WBC count, glucose and protein levels may not totally rule out encephalitis. In a study on viral encephalitis by Chaudhuri, it was pointed that although CSF abnormalities may support the diagnosis, some changes may be nonspecific and may seem to be not helpful in determining the specific etiology. Also, it is important to emphasize the importance of observing proper handling, transport and storage of the CSF samples to be used, as well as the timing of the lumbar puncture, as these may affect the results as well.[13]

Serologic testing for serum antigen and antibodies, in correlation with the clinical presentation, has been very helpful in the etiologic identification among the subjects in this study. All the cases of Mycoplasma encephalitis were diagnosed with the evidence of a positive serum IgM (enzyme immunoassay) during the course of the illness.

Due to the low yield of positive CSF PCR results for *Mycoplasma pneumoniae,* Christie, et al. defined *M. pneumoniae*-associated encephalitis as any patient with the presence of acute *M. pneumoniae* infection by a positive IgM, a significant rise in IgG titers between acute and convalescent specimens, or a positive respiratory or CSF PCR.[14]

Neuroimaging can be a helpful tool in the diagnosis of pediatric encephalitis and to exclude other possible neurologic conditions. MRI is more sensitive and provides more details. Six out of twenty-three patients had CT scan done and five of which (83.33%) were normal. MRI was done in 19 patients and 14 (73.68%) had pertinent findings, however, mostly were non-specific. There were no specific imaging findings identified that were correlated to their respective etiology. Three subjects had both neuroimaging done and their CT scans were all normal but had significant findings on MRI – one case of autoimmune encephalitis had abnormal enhancements along both cerebral sulci, sylvian fissures, suprasellar cistern and prepontine cistern; second case is a confirmed case of anti-NMDAR encephalitis with focal encephalitis on the right posterior temporal and adjacent parieto-occipital area; and the last case was a case of Mycoplasma associated encephalitis which showed some spectroscopic signs of slight neuronal loss in both medial temporal lobes. In cases wherein intracranial infections such as encephalitis are highly suspected, cranial MRI with or without contrast would be a reasonable first-line imaging since it will provide more detailed findings. However, Fraley, et al. pointed out that CT scan without contrast is recommended as a first line study among pediatric patients presenting with acute change in mental status and suspected intracranial infections since this can promptly exclude other acute neurosurgical emergencies.[16] If further evaluation is needed and neurologic deficits seems to be unexplained by CT scan, MRI would be a useful tool.

Certain patterns in neuroimaging may also be helpful in differentiating etiologies of encephalitis, although these may not be specific and exclusive, hence, it is still important that interpretation should always be done in correlation with each patient's history and clinical presentation.[16]

Among those patients wherein an electroencephalogram (EEG) was done, abnormal results were seen in 66.67% of infectious cases and 87.5% of the immune-mediated type. Majority showed diffuse slowing of background activity, specifically in the theta-delta range among the immune-mediated cases as well as involvement of multiple lobes. This was also comparable with the EEG findings of anti-NMDAR encephalitis as described by Peery, et al.[11] Although EEG is a sensitive and an accessible diagnostic tool for the evaluation of CNS function, most patients with encephalitis will have abnormal results and most of the abnormalities noted are non-specific. Therefore, it would be reasonable to seek advice from pediatric neurology specialists regarding the use of EEG for a particular patient.[16]

Anti-NMDAR encephalitis

Anti-NMDAR encephalitis is an autoimmune disease mediated by antibodies against the GluN1 subunit of the NMDA receptor, characterized by a complex neuropsychiatric syndrome.[17] Eight out of nine subjects with immune-mediated encephalitis in this study were managed as anti-NMDAR encephalitis, with three cases confirmed with the detection of anti-NMDAR antibodies in their CSF. Graus, et al. emphasizes that the absence of auto-antibodies does not totally rule out an immune-mediated process and a positive test may not always imply an accurate diagnosis.[15] Behavioral changes were the most prominent presentation observed among all classified as immune-mediated during the time of admission.

Almost all showed psychotic symptoms, such as auditory and visual hallucinations, aggressive episodes, violent behaviors, flighty speech, and either excessive nonsense talking or decreased verbal output. Majority of these patients initially presented with inability to focus and concentrate, e.g., in school activities, confusion, restlessness and insomnia prior to the psychotic symptoms. One confirmed anti-NMDAR encephalitis subject from the younger age group (4-year-old female) was described to have behavioral regression to a 1-year old, with no verbal output and regard, as well as bladder and bowel incontinence, with slight central "atrophic" changes in the brain and spectroscopic findings of minimal "neuronal loss" in medial temporal lobes seen on the cranial MRI. Orofacial and limb dyskinesia were also observed in three patients, and two of which were confirmed cases. Facial dyskinesias and abnormal limb movements are frequently seen in cases of anti-NMDAR encephalitis and may also serve as vital clues in the recognition of the disease, particularly if associated with other symptoms such as behavioral changes.[17] Peery, et al. elaborated that anti-NMDAR encephalitis, in its fulminant form, manifests with a prodromal phase which was characterized by nonspecific systemic symptoms. This is then followed by other phases – psychotic (emotional and behavioral disturbances, psychosis, delusions, hallucinations, decreased cognitive skills, difficulty speaking, and agitation) and/or seizure phase (commonly generalized tonic-clonic in character), unresponsive phase (may seem to be mute or akinetic), and hyperkinetic phase.[11] In all of these cases, infectious causes and metabolic disturbances were all ruled out before the diagnosis that is immune-mediated in nature was made.

Previous studies emphasized the association of an underlying ovarian tumor among female patients with anti-NMDAR encephalitis.

In this study, two anti-NMDAR cases, one of which was laboratory confirmed, also had adnexal tumors – a right ovarian hemangioma on biopsy after exploratory laparotomy and oophorectomy in a 13-year old subject, while the other was considered to be an ovarian teratoma in nature in a 14-year old patient, based on its characteristics on whole abdominal CT scan, however biopsy for confirmation was not done since she was transferred to another institution for continuation of management.

Dalmau, et al. pointed out that even though the presence of tumors, specifically those expressing NMDA receptors, precipitates the breaking of immune tolerance, there still seem to be other immunologic triggers that are involved.[18] The presence of an underlying tumor is not a requirement in the clinical presentation especially in the pediatric age group. Furthermore, tumor association appears to be inversely related to age and tends to be more common among adult cases.[11] However, screening for adnexal masses in suspected cases of anti-NMDAR encephalitis particularly in older children and adolescents may assist in establishing the diagnosis.

***Mycoplasma pneumoniae* encephalitis**

Mycoplasma pneumoniae is a known respiratory pathogen, however extrapulmonary complications are not that rare as well, occurring between 5-10% of hospitalized patients. The incidence of *Mycoplasma pneumoniae*-associated encephalitis is predominantly in the pediatric age group.[14] The age of the affected patients in this study ranged from 1 to 13 years old, with no gender predominance. Among those with identified infectious etiology in this study, *Mycoplasma pneumoniae* was the most common at 28.57%, whom all tested positive for serum Mycoplasma IgM. All these four patients presented with seizures responsive to anti-convulsant medications, such as diazepam, levetiracetam and phenobarbital.

Although respiratory symptoms are the most common presentation of typical *M. pneumoniae* infections and that the respiratory tract seems to be the most common entry site, systemic symptoms observed among these patients were non-specific – with fever and gastrointestinal symptoms seen in three patients, and respiratory symptoms noted only in two cases. Interestingly, this finding was consistent with other studies, in that respiratory symptoms tend to be less common in neuro-invasive cases of Mycoplasma infections.[14] There was also no other extrapulmonary (e.g., mucocutaneous) manifestations observed among these patients.

There were no specific changes found on neuroimaging and EEG that were common among all the cases. Cranial MRI showed diffuse cortical thickening with increased signal intensity on multiple lobes, intense gyri form restricted diffusion signals and cortical swelling with T2W/FLAIR hyperintense signals, and slight neuronal loss.

EEG changes include poorly organized bilateral theta-delta slowing of background activity and slowing with sharp epileptiform activities. One patient had normal MRI and EEG. The most common medical treatment given to the subjects were broad spectrum antibiotics (78.26%), such as third generation cephalosporins (ceftriaxone), which was given empirically mainly because of the overlap clinically of encephalitis with bacterial meningitis. Macrolides, like azithromycin and clarithromycin, were given to all the patients diagnosed with *Mycoplasma pneumoniae*-associated encephalitis. Anticonvulsant therapy (78.26%) was given to all patients who presented with seizures and majority were well-controlled. The therapeutic goal is the modulation of the body's immune response.[16] All patients with immune-mediated encephalitis were managed with steroids, specifically high dose methylprednisolone and 55.56% also received intravenous immunoglobulin (IVIG). Due to the behavioral disturbances such as agitation and aggressive episodes seen in some patients, they were also given anti-psychotics and tranquilizers (35%).

The overall median duration of hospital stay was 13 days (4 to 79 days) and was observed to be shorter (12 days) among the infectious type compared to the immune-mediated cases (17 days). Prognosis was relatively good as observed in this study with more than half of the subjects had complete recovery prior to discharge (56.52%). In terms of outcomes, majority of the infectious cases in this study had complete recovery. There were nine patients (39.13%) who had partial resolution of neurologic symptoms and six of them were classified as immune-mediated.

Fraley, et al. emphasized that in autoimmune cases, the recovery time may be prolonged and may take weeks from the time of clinical presentation to signs of improvement.[16] The case of HSV encephalitis developed central respiratory failure as a complication, with tracheostomy done eventually. The patient was on rehabilitation therapy upon discharge. The patient with acute enteroviral encephalitis had upper and lower motor deficits, who was improving with physical and occupational therapy, however was transferred to another institution. There was one mortality noted in this study who had an immune-mediated type of encephalitis. The said patient expired due to nosocomial complications.

CONCLUSION

Encephalitis should be considered among patients who present with acute onset of neurologic symptoms such as seizures, alteration in mental status, with or without systemic symptoms. Behavioral changes in an apparently well child, such as clinical symptoms of aggressiveness, violent behaviors, restlessness, hallucinations, and insomnia, should prompt clinicians to consider encephalitis, specifically anti-NMDAR encephalitis. This is particularly important if the viral studies are negative and there is no other determined cause to explain the behaviors. It is also imperative to rule out organic pathology first prior to considering psychiatric disorders.

Although viral etiologic agents remain to be the most common cause of encephalitis, other possible etiologies should be highly considered, such as *Mycoplasma pneumoniae* and immune-mediated causes, with anti-NMDAR encephalitis being the most common. Infectious encephalitis was observed to be more common among males in the younger age group. Immune-mediated encephalitis was noted to affect female adolescents more.

A complete work-up such as CSF analysis, culture/viral studies, serologic testing, neuroimaging and electroencephalogram are of significant help in establishing the diagnosis of encephalitis and more importantly, in the determination of its etiology. However, a normal CSF analysis, imaging and/or EEG may not totally exclude encephalitis. Cranial MRI is more helpful in the detection of changes in the brain. Prognosis is relatively good, however, full recovery among immune-mediated encephalitis patients may take time. A prompt diagnosis and early initiation of appropriate management leads to a good outcome and further complications and permanent neurologic sequelae may be avoided.

RECOMMENDATIONS

A larger population of pediatric encephalitis, covering both infectious and immune-mediated type, or a multi-center study are recommended for future studies to further describe its clinical and epidemiologic profile. Geographic location, travel history, ethnicity, as well as immunization history may be included as factors to be reviewed among these patients and evaluate if these may contribute to etiology identification.

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ORIGINAL ARTICLE

THE 2013-2015 NATIONWIDE PREVALENCE SURVEY OF SOIL-TRANSMITTED HELMINTHS (STH) AND SCHISTOSOMIASIS AMONG SCHOOL-AGE CHILDREN IN PUBLIC SCHOOLS IN THE PHILIPPINES

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ABSTRACT

Objectives: The Department of Health (DOH) aims to reduce the prevalence of intestinal parasitism and proportion of heavy intensity of infection in the country by 2022. Among the interventions is school-based mass drug administration (MDA). Regular assessment of MDA gives guidance to the DOH. The aim of this survey was to determine the prevalence of soil transmitted helminthiasis and schistosomiasis among public school children ages 5 to 16 years old.

Methodology: A cross-sectional, school-based study using multi-stage stratified cluster sampling was conducted from 2013 to 2015, covering the National Capital Region (NCR), and all provinces, except Maguindanao and Sulu. Stool samples were examined using the duplicate Kato Katz (KK).

Results: Of the 26,171 school children with stool samples examined, 7,440 (28.4%) were infected with at least one soil-transmitted helminth (STH). Infections among male students were significantly higher than female students (31.0% versus 26.0%). Heavy, moderate, and light intensity of infections were 3.2%, 29.0% and 67.7%, respectively. STH cumulative prevalence per province ranged between 0.5% and 89.5%. Schistosomiasis infections were detected in known non-endemic provinces: Ilocos Norte, Biliran, Tawi-Tawi, Basilan, and Dinagat Islands. Majority (68%) of the infections were with single parasites but as many as five parasites were detected in one child. Infections with heterophyids were also observed.

Conclusion: While the national prevalence of schistosomiasis was less than 1.0%, the cumulative prevalence of soil-transmitted helminthiasis among school-aged children was higher than the global figure of 24.0%.

KEYWORDS: *Soil-transmitted Helminthiasis, Schistosomiasis, School-aged Children, Prevalence, Intensity of Infections, Philippines*

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INTRODUCTION

Parasitic infections, particularly soil transmitted helminthiasis (STH) and schistosomiasis are among the most important public health problems around the world and both are recognized as Neglected Tropical Diseases (NTD).[1,2] The transmission of these infections is enhanced by poor living conditions, including inadequate sanitary facilities, improper human waste disposal, insufficient or unreliable water supply, poor knowledge of hygienic practices and substandard dwelling conditions.[3,4] Previous studies have shown high cumulative prevalence of STH infection ranging from 33.2% to 67.4%.[5-7] A 2008 study revealed 54% (1,820/3,373) of students were positive for any STH infection with 23.1% heavy-intensity infection.[8] *Schistosomiasis japonicum* causes serious, long term health problems and even death if left untreated. A schistosomiasis focal survey by the Department of Health in 2017 reported a national prevalence of 4.68%.[9]

The primary intervention of DOH to control the transmission and reduce the morbidity of these infections is administering preventive chemotherapy with albendazole for STH and praziquantel for schistosomiasis. In 2007, the Department of Health-Integrated Helminth Control Program (DOH-IHCP) started the nationwide mass deworming program (mass drug administration or MDA) in collaboration with the Department of Education (DepEd). The program covers school children ages 6-12 in all public elementary schools. A biannual deworming happens every January and July, with the purpose of reducing the prevalence to less than 30% after 3 years.[10] To monitor the impact of MDA, the World Health Organization (WHO) recommends surveys every 3-5 years. The data gathered could guide program implementers in prioritizing strategic actions to reach its objective of reducing the morbidity and mortality of STH infections, as well as *Schistosoma japonicum* infections.[11,12]

In 2013, the Department of Health Infectious Disease Office (DOH-IDO) commissioned the Research Institute for Tropical Medicine (RITM) to carry out a nationwide parasite survey. This study aimed to assess the current burden of soil transmitted helminths infections in every province by determining the prevalence and the intensity of parasitic infection among public school children ages 5-16 years old and to update the prevalence and burden of infection of *Schistosoma japonicum* in schistosoma-endemic areas.

METHODOLOGY

Sampling design

A multi-stage, cluster sampling design was applied. The 84 provinces (each of the four districts of the National Capital Region (NCR) was counted as a province) were classified as either schistosomiasis endemic (SE) or non-schistosomiasis endemic (non-SE) based on historical data provided by the DOH's Schistosomiasis Control and Elimination Program where primary and secondary public schools were selected (see Table 1). In the SE provinces, we purposely selected schools in barangays that reported schistosomiasis. Where there was more than one schistosomiasis endemic barangay, random selection was done among those barangays with the probability of selection proportional to the size of the number of students in a class. This approach was also used in the selection of schools and grade levels in non-SE provinces.

Table 1. List of the known 28 schistosomiasis endemic provinces

Agusan del Norte	Misamis Oriental
Agusan del Sur	Negros Occidental
Bohol	Northern Samar
Bukidnon	North Cotabato
Cagayan	Oriental Mindoro
Compostela Valley	Sorsogon
Davao del Norte	South Cotabato
Davao Oriental	Sultan Kudarat
Davao del Sur	Surigao del Norte
Eastern Samar	Surigao del Sur
Lanao del Norte	Western Samar
Lanao del Sur	Zamboanga del Norte
Leyte	Zamboanga del Sur
Maguindanao	Zamboanga Sibugay

To assess prevalence and intensity of STH and schistosomiasis infections, the WHO recommends examining 200-250 individuals from each ecologically homogeneous area.[13] Because the schistosomiasis prevalence is much lower than STH, sample size requirements for school children surveyed in SE provinces were arbitrarily doubled to increase probability of finding schistosomiasis cases. Thus, 250 school children from each of NSE provinces and 500 school children from each SE were targeted. Adjusting for an expected compliance rate of 70% for submitting stool samples, 36,000 students were targeted for enrolment to ensure the sample size of 28,000 will be reached.[14] To ensure students from the desired age groups were included, classes or sections from kindergarten to Grade 10 were regarded as sampling clusters. In each province, three class sections were selected from Grade 3, and one class section each from kindergarten to Grade 2 and Grade 4 to Grade 10, respectively.

Included in the study were students of either sex, aged 5 to 16 years, who had not taken any antihelminthic three months prior to stool collection, had a signed written parental consent, and had a signed written assent for children between 12-16 years. Students who had acute illnesses and those who could not provide suitable stool samples were excluded.

Organizing the Survey

Meetings were held between officials from the DOH-Infectious Disease Office (DOH-IDO) and Department of Education-Bureau of Learner Support Services (DepED-BLSS) to discuss the survey objectives and design and the logistic and operational support needed. The DOH-IDO endorsed the study to its regional offices and to the local government units (LGUs) through a Department Memorandum. A training of trainers was rolled out where teams from the DepED and DOH regional offices and their respective divisions at the provincial level were oriented on the objectives and procedures of the survey.

Medical technologists hired on a fulltime basis underwent intensive training in Kato Katz procedure. Those who failed to reach the required proficiency level of 100% underwent re-training until they passed the assessment.

Conducting the Survey

Parent-teacher association (PTA) meetings were held in each of the selected schools where trained teachers and school nurses oriented the parents or guardians and students on the nature and purpose of the study. Depending on their availability, either the district nurse or teacher obtained the written informed consent and assent from parents and students, respectively. At the school and during a pre-set schedule, pilot-tested data collection forms were used by the trained DepEd nurses and teachers to collect the following information: student's name, date of birth, age, sex, and the date of the last intake of deworming drug. Data were verified for completeness before the distribution of the stool collection kit to the students. Forms were sent to the designated laboratory in each province by the Barangay Health Workers (BHW) on the agreed date of specimen collection. Stool collection kits were provided to students who were trained on the proper stool collection, transport, labelling, and disposal of wastes. The students collected single stool samples at home and submitted them to the school nurse prior to the start of their classes. Students were given 4 days to submit their stool samples. All samples collected for the day were transported to the designated laboratory for processing and examination.

Processing and Examination of Stools

Duplicate smears were prepared using the 41.7mg Kato-Katz template for each sample. In a systematic manner, smears were examined using a compound light microscope within 24 hours.

The egg per gram for each species of STH was calculated by multiplying the egg count results to a constant factor (24) to classify the intensity of infections according to the WHO Guidelines. Results were recorded in a microscopy worksheet and transcribed in the individual case record form.

Ten percent of the total slides prepared were randomly selected each day for re-examination in a blinded manner by the validator microscopist. During the first two years, slides selected for quality control were sent by courier to RITM. However, by the third year of the survey, the selected slides were examined by the validator within 24 hours after the first reading.

Data Management and Analysis

Case report forms were completed, and data verified prior to double encoding in a data entry system developed using Microsoft Access 2013. Students with missing information (e.g., age and gender) were not included in the analysis. Students who were either below 5 years old or above 16 years old were excluded from the analysis due to their age being outside the recommended age for primary or secondary school. Statistical analyses were performed using Stata Version 13. Analysis of the data was according to age group (5-7 years, 8-9 years, 10-12 years and 13-16 years) and not on the grade level as indicated in the sampling design. The consideration was that there were children not within the assumed age-group of a specific grade level (e.g., a 10 year-old child in kindergarten). Parasitological parameters obtained were cumulative prevalence and intensity of STH infections. Intensities of infections with each STH species were reported in eggs per gram (EPG) and classified as light, moderate, or heavy according to the WHO classification by species (see Table 2). In addition, geometric mean egg counts (GMEC) were also computed for each helminth species.

The intensity of infection for the cumulative prevalence of STH was defined as follows: heavy-intensity infection: infected with at least one parasite at high intensity and all other parasite present at moderate or light intensity; moderate intensity infection: infected with at least one parasite at moderate-intensity and all other parasite species present at moderate or light intensity; light intensity infection: all parasite species present at light intensity.

Table 2. Thresholds of intensity of infection by STH species (geometric mean egg count, or GMEC, per gram of stool as examined by Kato-Katz method)

Species	Light	Moderate	Heavy
A. lumbricoides	1 - 4,999	5, 000 - 49,999	≥ 50,000
T. trichiura	1 - 999	1,000 - 9,999	≥ 10,000
Hookworm	1 - 1,999	2,000 - 3,999	≥ 4,000

The cumulative prevalence and species-specific prevalence were expressed in percentages. The cumulative prevalence was computed as the total number of children found positive for any of the STH parasite species divided by the total number of children examined and multiplied by 100. Computation for the species-specific prevalence was computed from the total number of students infected with specific species of STH and *S. japonicum* divided by the total number of children examined and multiplied by 100. The intensity of infection is expressed in eggs per gram of feces (EPG) and was computed[15] as follows:

Eggs per gram (EPG) feces = 1 egg X 24

Mean EPG was calculated as a geometric mean. Chi-square test was performed to determine the association of age group and sex with prevalence with the level of significance set at 0.05.

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Ethics Committee Approval

The study was granted approval by the RITM Institutional Review Board with approval number 2013-26. Written parental/guardian consent was obtained for all students. Written assent was also obtained from children 12 to 16 years old. Following information in the participant information sheet, the results of the stool examination were submitted to the school nurse for proper management. Parents and children were not directly informed of the results. Participant identification was limited to authorized research staff. The school nurses were provided a list of children who required treatment of their intestinal parasitic infections.

The Department of Health funded the survey. All authors declare no conflict of interest.

RESULTS

The prevalence survey was conducted from 2013-2015 in 82 of the 84 provinces in the country. Due to security concerns and logistical issues, the provinces of Sulu and Maguindanao were not surveyed. A total of 44,877 students were listed from randomly selected class levels of the 27/28 SE provinces (21,095 students), 55/56 non-SE provinces (23,782 students) including the 4 districts of the National Capital Region (NCR). Of the students that were selected, 27,352 (62.0%) students gave their assent to participate and, thus, were enrolled. However, only 58.3% (26,171) had the written consent of their parents. This is shown in Figure 1.

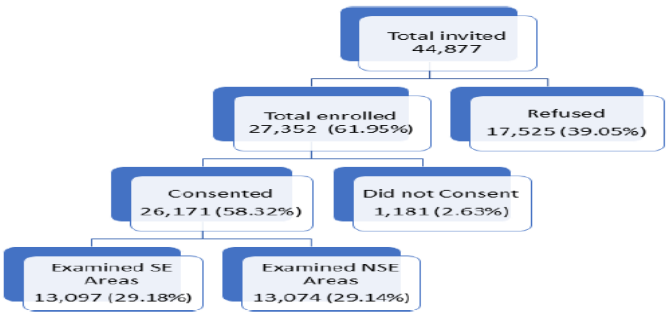

Figure 1. Breakdown of students invited to participate, number enrolled, number with parental consent and number who were from schistosomiasis endemic and non-endemic provinces

There was an equal proportion of students from SE provinces (29.2%) and non-SE provinces (29.1%). Almost half of the students were male (49.6%); as expected because of the sampling procedures, half were 8-9 years old. Table 3 illustrates the distribution by sex and age groups among schistosomiasis and non-schistosomiasis endemic provinces.

Table 3. Enrolled students by non-schistosomiasis endemic (NSE) and schistosomiasis-endemic (SE) provinces

Province Classification	Sex			Age Group			
	Male (%)	Female (%)	TOTAL	5-7 (%)	8-9 (%)	10-16 (%)	Total
NSE	6,312 (49.1)	6,533 (50.9)	12,845	3,342 (25.6)	6,811 (52.2)	2,888 (22.1)	13,041
SE	6,673 (50.1)	6,653 (49.9)	13,326	2,409 (18.4)	5,989 (45.9)	4,662 (35.7)	13, 060
TOTAL	12,985 (49.6)	13,186 (50.4)	26,171	5,751 (22.0)	12,800 (49.0)	7,550 (28.9)	26,101*

*Discrepancy in total number due to missing data on age.

Most provinces did not achieve the targeted sample size for that province; however, after computing for this study's power, not achieving the required sample size had no significant effect (see Supplementary Table 1). Although the sample size was computed according to whether a province was endemic for schistosomiasis or not, the cumulative prevalence and STH species prevalence are not presented following these categories.

STH Cumulative Prevalence and Range of Prevalence by Species

Overall, 28.4% (n=7,440) of students were infected with any of the three soil transmitted helminths: *Ascaris lumbricoides*, *Trichuris trichiura,* and hookworm. Infections were predominantly of light intensity (67.7%), followed by moderate (29.0%) and heavy (3.2%) intensities. The STH cumulative prevalence ranged from 0.5% (Ilocos Norte) to 89.5% (Sorsogon). Only one of the 279 students examined in Ilocos Norte had an intestinal parasite (*T. trichiura*).

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The most common STH parasite detected was *T. trichiura* (19.7%, n=5,159) followed by *A. lumbricoides* (17.4%; n=4,560); and hookworm (0.55%, n=144). The prevalence of *T. trichiura* was greater than that of *A. lumbricoides* in 60% of the provinces and ranged from 0.5% to 81.8%. The highest EPG was observed in *A. lumbricoides* infections (2,361.8) followed by *T. trichiura* (230.5), and hookworm (102.8).

The cumulative prevalence for STH and range of prevalence (0%, >0-<1%, ≥1-10%, ≥10-<20%, ≥20-<50% and ≥50%) by parasite species among the provinces are shown in Figures 2a-2d. The cumulative prevalence of the STH by province and intensity of infection are given in Supplementary Table 2. The mean prevalence of STH among the four districts in the National Capital Region (NCR) was 21.8%. District 1 (Manila) had the highest prevalence followed by District 2 (Mandaluyong, Marikina, Pasig, Quezon City, San Juan), District 3 (Caloocan, Malabon, Navotas, Valenzuela), and District 4 (Las Piñas, Makati, Muntinlupa, Paranaque, Pasay, Pateros, Taguig). Except for Ilocos Norte, *A. lumbricoides* infection was detected in all provinces. The provinces with the highest prevalence were Sorsogon (68.1%) and Masbate (56.4%). The prevalence of this parasite ranged from 1 to below 10% in Abra, Antique, Apayao, Batanes, Benguet, Bohol, Bukidnon, Bulacan, Cagayan, Camiguin, Compostela Valley, Davao del Norte, Davao del Sur, Guimaras, Isabela, Ifugao, Kalinga, Mountain Province, Negros Oriental, Quirino, and Siquijor. Twenty-eight provinces recorded a prevalence between 10% to <20%, and the remaining 25 provinces had a prevalence ranging between 20% to <50% (see Figure 2b). Provinces with more than 50% prevalence of *T. trichiura* were Catanduanes, Masbate, Northern Samar, and Sorsogon (Figure 2c). Twenty-seven provinces had prevalence ranging from 20% to <50%, 20 provinces had prevalence of 10% to <20%, and 27 provinces had prevalence of less than 10%. Prevalence of hookworm was lowest among the three soil-transmitted helminths.

Hookworm was not detected in 48 provinces and in the National Capital Region (NCR). Hookworm prevalence of <4.0% was observed in 30 provinces, mostly in Mindanao and Visayas islands; few cases were detected in Luzon Island (Figure 2d). The highest prevalence was recorded in Zamboanga del Sur, Sarangani, North Cotabato, Agusan Del Sur, and Zamboanga Sibugay.

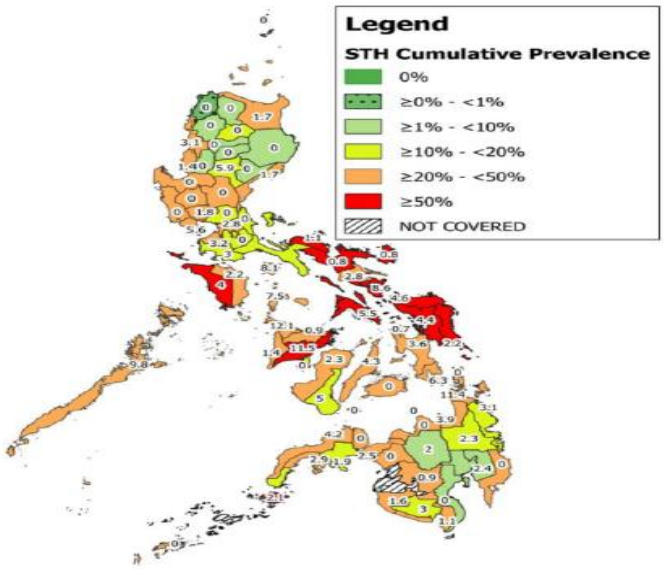

Figure 2a. Map of the Philippines with cumulative prevalence of soil-transmitted helminth (STH) infections in province surveyed

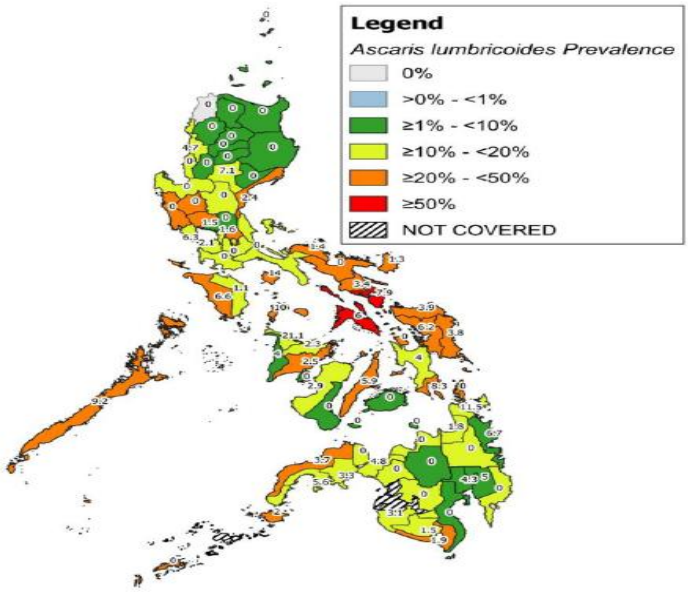

Figure 2b. Map of the Philippines with prevalence of *A. lumbricoides* infections in provinces surveyed

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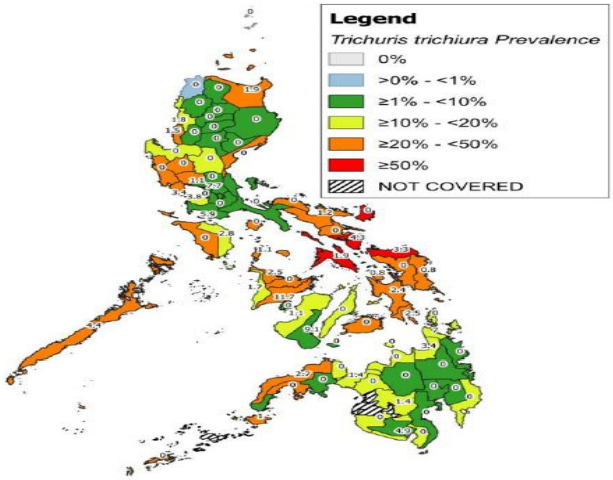

Figure 2c. Map of the Philippines with prevalence of *T. trichiura* infections in provinces surveyed

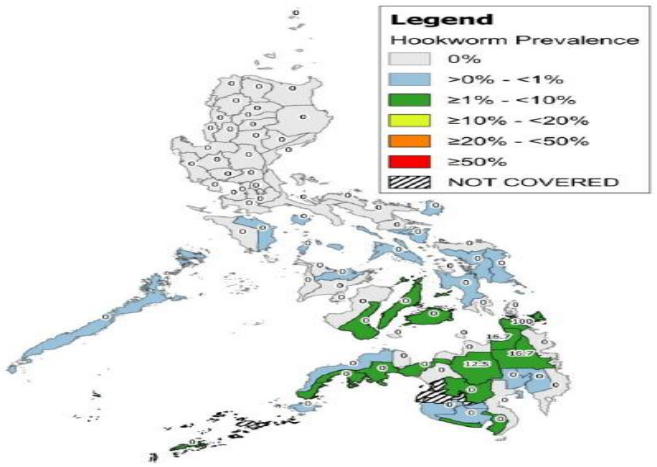

Figure 2d. Map of the Philippines with prevalence of hookworm infections in provinces surveyed

Table 4. Combination of infection with multiple parasites

Combination of multiple parasites	No. (%)	Combination of multiple parasites	No. (%)
Single parasite infection		**Dual parasite infection**	
Trichuris trichiura	2,713 (10.366)	Hookworm + *H. nana*	1 (0.004)
Ascaris lumbricoides	2,117 (8.089)	*S. japonicum* + Heterophyid	1 (0.004)
Schistosoma japonicum	111 (0.424)	*E. vermicularis* + Heterophyid	1 (0.004)
Heterophyid	97 (0.371)	Subtotal	2,434 (9.300)
Enterobius vermicularis	90 (0.344)	**Triple parasite infection**	
Hookworm	68 (0.260)	*A. lumbricoides* + *T. trichiura* + *S. japonicum*	47 (0.180)
Hymenolepis nana	1 (0.004)	*A. lumbricoides* + *T. trichiura* + *E. vermicularis*	23 (0.088)
E. histolytica	1 (0.004)	*A. lumbricoides* + *T. trichiura* + Hookworm	13 (0.050)
Subtotal	5,198 (19.862)	*A. lumbricoides* + *T. trichiura* + Heterophyid	8 (0.031)
Dual parasite infection		*A. lumbricoides* + Hookworm + *S. japonicum*	5 (0.019)
A. lumbricoides + *T. trichiura*	2,249 (8.593)	*A. lumbricoides* + *T. trichiura* + *H. nana*	1 (0.004)
T. trichiura + *S. japonicum*	33 (0.126)	*A. lumbricoides* + Hookworm + Heterophyid	1 (0.004)
A. lumbricoides + *S. japonicum*	23 (0.088)	*T. trichiura* + Hookworm + Heterophyid	1 (0.004)
A. lumbricoides + Hookworm	22 (0.084)	*A. lumbricoides* + *S. japonicum* + *E. vermicularis*	1 (0.004)
T. trichiura + Heterophyid	22 (.0.084)	*A. lumbricoides* + *E. vermicularis* + Heterophyid	1 (0.004)
A. lumbricoides + *E. vermicularis*	21 (0.080)	*T. trichiura* + *E. vermicularis* + Heterophyid	1 (0.004)
T. trichiura + Hookworm infection	21 (0.080)	Subtotal	102 (0.390)
A. lumbricoides + Heterophyid	17 (0.065)	**Quadruple parasite infection**	
T. trichiura + *E. vermicularis*	17 (0.065)	*A. lumbricoides* + *T. trichiura* + Hookworm + *S. japonicum*	7 (0.027)
S. japonicum + *E. vermicularis*	2 (0.008)	*A. lumbricoides* + *T. trichiura* + *S. japonicum* + Heterophyid	1 (0.004)
Hookworm + Heterophyid	2 (0.008)	**Quintuplet parasite infection**	
A. lumbricoides + *H. nana*	1 (0.004)	*A. lumbricoides* + *T. trichiura* + Hookworm + *S. japonicum* + *E. vermicularis*	1 (0.004)
Hookworm + *S. japonicum*	1 (0.004)	**No parasite infection**	18,731 (71.572)

Infections with more than one parasite, and with food-borne and other intestinal parasites

Twenty percent of the examined school children were infected with a single parasite, the most common of which was *T. trichiura* followed by *A. lumbricoides*.

Infection with two parasites was observed in 9.3% of the school children examined and over 90% were co-infections with *A. lumbricoides* and *T. trichiura* (Table 4).

Almost 68% of the infections were with one parasite and 32% were with two or more parasites.

The provinces where more than 10% of the school children had infections with these two parasites were Catanduanes (25.2%), Eastern Samar (19.4%), Masbate (45.3%), Occidental Mindoro (15.3%), Palawan (24.7%), (Sorsogon (60.1%), Surigao del Norte (16.1%), Tawi-Tawi (15.2%), Western Samar (29.4%) and Zamboanga del Norte (16.8%). Three hundred fourteen school children (1.2%) were observed to be infected with food-borne and other intestinal parasites. The most common was *Enterobius vermicularis* (n=158, 0.60%), followed by heterophyids (n=154, 0.59%), and *Hymenolepis nana* (n=3, 0.01%). *Enterobius vermicularis*, and heterophyids were detected in school children from various provinces in Mindanao, Visayas, and Luzon. *H. nana* was observed in Tawi-Tawi (n=2) and Lanao del Norte (n=1).

Intensity of Infection

Ascaris lumbricoides

Heavy-intensity infection was found in 3.2% (n=166) of the school children positive with *A. lumbricoides*. Aklan had the highest proportion of heavy-intensity infections (21.1%) followed by Marinduque (14.0%), Surigao del Norte (11.5%), and Romblon (10.0%). Twenty-nine percent of all of the school children had moderate intensity of infection with this parasite. Iloilo, Bataan, Camarines Norte, Surigao del Norte and Dinagat Islands had the highest number of moderate intensity of infections with this roundworm. The proportion of moderate intensity of infection between 20% to <50% was observed in 50 provinces, while 11 provinces had less than 20% moderate intensity infection. The infections in Batanes, Siquijor, Ifugao, Benguet, and Mountain Province were of light intensity.

In the highly-urbanized NCR, the prevalence of *A. lumbricoides* was 24.4% in the First District, 14.4% in the Third District, 13.2% in the Second District, and 10.6% in the Fourth District. The proportion of heavy intensity of infection was 4.5% in District 1 and 8.3% in District 3.

More than half of infected students with moderate-intensity infection were observed in Districts 1 (50.8%) and 3 (54.2%), while 24.7% was recorded in District 2 and 33.3% in District 4. The prevalence and intensity of infection with *A. lumbricoides* in the province by regions is shown in Supplementary Table 3.

Trichuris trichiura

Across all provinces, *T. trichiura* infections were predominantly of light intensity (80.88%). In decreasing order, the provinces with the highest proportion of heavy-intensity infection were Iloilo, Negros Oriental, Rizal, Surigao del Norte (7.0%), and Batangas. The NCR districts had a prevalence between 4.2% and 8.0% and were light-intensity infections. Supplementary Table 4 shows the prevalence and intensity of infection with *T. trichiura* in the province by regions.

Hookworm

No infection with hookworm was observed in 21 provinces in Regions 1, 2, 3, 4A, four districts of NCR and CAR. It was detected in one school child in Capiz (region 6). Hookworm was prevalent in all but eight of the 21 provinces in Mindanao and 90% of the infections were light-intensity. Although the overall number of infected children was very low, moderate and heavy-intensity infections were observed in Zamboanga del Sur, Agusan del Norte, Agusan del Sur, Surigao del Norte and Bukidnon. Supplementary Table 5 shows the prevalence and intensity of infection with hookworms in the province by regions.

***Schistosoma japonicum* Prevalence and Intensity of Infection**

The overall prevalence of schistosomiasis among the school children was 0.94% (233/26,171) and ranged from 0.0% to 10.0%. While 73% of these infections were low intensity, 8.8% and 17.2% were heavy and moderate intensity of infection, respectively.

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In decreasing order, the highest prevalence was observed in Northern Samar, Agusan del Norte, Sorsogon, Bukidnon, North Cotabato, Agusan del Sur, Davao del Sur, and Lanao del Sur. *S. japonicum* infection was not detected among the school children in two known endemic areas: Bohol and Compostela Valley. The parasite, however, was detected in a child from each of these non-SE provinces: Ilocos Norte, Biliran, Tawi-tawi, Basilan, and Dinagat Islands. Please see Figure 3 and Supplementary Table 6.

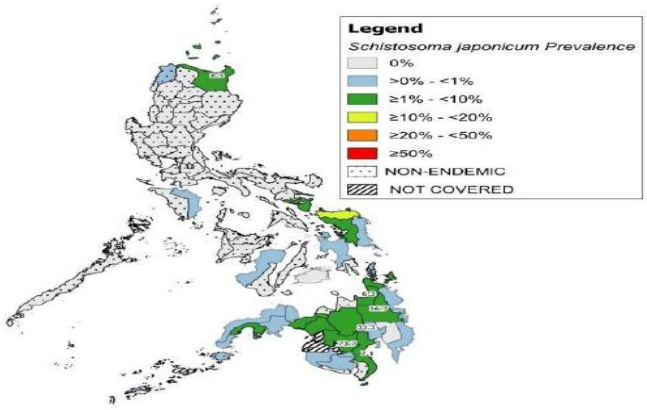

Figure 3. Map of the Philippines with prevalence of S. japonicum infections in provinces surveyed

Prevalence by Age Group and Sex

The cumulative prevalence of the parasites was observed to decrease by increasing age groups. Except for children between the ages of 5 to 7 years, male children had significantly higher cumulative prevalence rates than female children. The distribution of infections of the parasite species by sex and age groups are illustrated in Figure 4. The prevalence of *A. lumbricoides* across the three younger age groups was comparable and was observed to be lower in the oldest age groups. Especially among male children, infections with *T. trichiura* increased by age group but dropped significantly in the 13 to 16 year old. For these two parasites, male school children had significantly higher infections rates than female children, except for the youngest age group. Hookworm infection, on the other hand, was significantly higher among the two older age groups and infection significantly higher among male children. For *S. japonicum*, the prevalence of infection increased with age. Although infection in males were higher than female children, these were not significant.

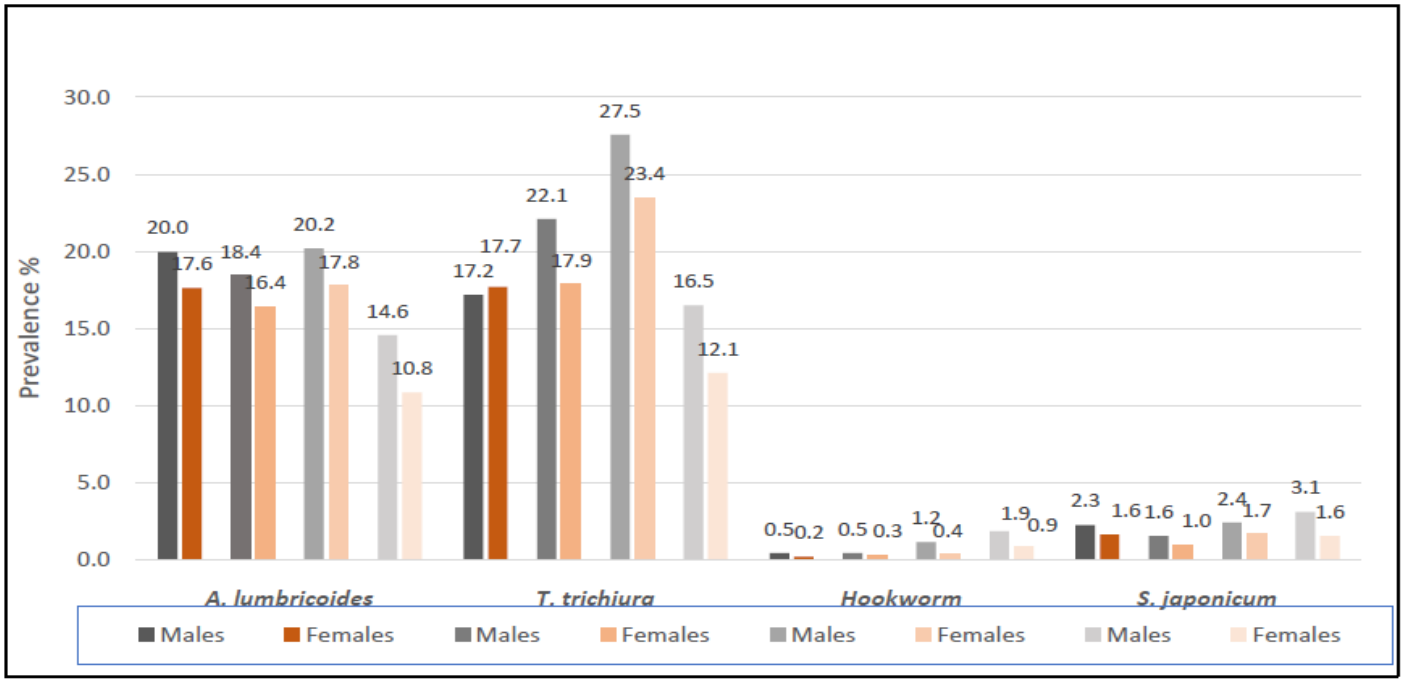

Figure 4. Distribution of age-groups and sex-specific STH and schistosomiasis prevalence in school-age children in the Philippines (2013-2015)

DISCUSSION

The purpose of this nationwide survey was to determine the prevalence of STH and schistosomiasis, and intensity of these infections among school-aged children between 5 to 16 years old. The cumulative STH prevalence and the percent of heavy-intensity infection observed were lower than those reported in 2009**:** 28% vs. 54% and 3.3% vs. 23.1%, respectively.[8] The provinces surveyed in that study were Bulacan and Camarines Sur in Luzon, Negros Occidental and Leyte in Visayas, and Compostela Valley and Surigao del Norte in Mindanao. Those provinces were selected as representative for the region where they belong and not the country in general, whereas in this survey, each province has been represented. The low prevalence and percent of moderate and heavy-intensity infections found in this survey may be attributed to the bi-annual mass drug administration (MDA) of single-dose albendazole 400 mg and praziquantel consistently implemented by the DOH for more than 10 years. Data from the STH National Program shows MDA using albendazole among school-aged children had a coverage that ranged from 42% to 61% from 2011 to 2015 (pers. comm. Palasi W., 2021). Majority of the infections among the school children were with single parasites; however, there were a considerable number of students with two or more parasitic infections. A study in Leyte in 2005 revealed that children with light-intensity infections with single parasites had significantly reduced hemoglobin (Hb) levels compared to children without parasitic infections and this reduction in Hb increased among children with three or four parasitic infections.[16]

We believe that the prevalence of hookworm in this survey was underestimated. Hookworm was the most prevalent intestinal parasite in a survey of 19,000 (17.0%) school children in Benin.[17] Among 478 school children in Cagayan Valley, the prevalence was 2.72%.[18]

From surveys for schistosomiasis among households in selected provinces in Luzon and in Maguindanao, the prevalence of hookworm was 4.6% and 0.3%, respectively.[18] In the first study, stools were examined for hookworm eggs within 60 minutes after the slide was prepared, while in the second, within two hours after collection. In the later study, the authors explained that the delay in examining the stools might have contributed to the low prevalence observed for hookworms. For this survey, in addition to Kato-Katz's low sensitivity in detecting hookworm, the delay in examining of the stools and conditions under which they were transported may have contributed to the overall low hookworm prevalence observed.

The overall prevalence of *S. japonicum* infections (0.89%) and percent of heavy-intensity infection (4.68%) in this survey was lower than the 2.5% national prevalence reported by the Schistosomiasis active surveillance in 2008.[19] Unfortunately, no documented formal investigations (e.g., presence of infected vectors) were made regarding the detection of schistosomiasis infected school children in non-SE provinces. The detection of heterophyids among school children in 33 provinces (mainly in Mindanao) and *H. nana* in four provinces also in Mindanao, brings attention to the dire neglect of these parasitic infections which have already been reported locally in the past.[20,21]

The required number of school children enrolled in the survey was twice that of school children from NSE. In addition, only schistosomiasis endemic municipalities and barangays were purposely included in the sampling frame. This created a bias to increase the probability of detecting schistosomiasis; hence, the findings of the study may not be compared with the previous national prevalence study by Leonardo and colleagues.[19] However, the survey estimated the prevalence of schistosomiasis in endemic areas and can be used to gauge the interventions of the Schistosomiasis Control and Elimination Program (SCEP).

The study also attempted to apply the WHO sampling design to estimate STH and schistosomiasis prevalence in other age groups similar to previous studies.[11] Status of the provinces' schistosomiasis endemicity and grade level (as proxy indicator of age) were the stratifying variables used. Ninety-three percent of the targeted 28,000 specimens were collected in this survey. WHO criteria states that 250 would be needed to estimate the STH and/or schistosomiasis prevalence in an area.

CONCLUSION

Despite the decades of mass drug administration and WASH, STH and schistosomiasis continue to be important infections in school-aged children in public schools of the Philippines. The survey recorded a decrease in the overall prevalence of STHs and schistosomiasis as compared to previous local studies. However, the STH cumulative prevalence (28.4%), and moderate and heavy intensity of infection (29.0% and 3.2%, respectively) are above the Department of Health targets of STH cumulative prevalence of below 20%, and moderate and heavy intensity of infection below 2%. Though resource-intensive, implementing a national prevalence survey for STH and schistosomiasis is a much-needed assessment of the impact of the Department of Health's interventions to reduce the burden of these infections. This survey has identified provinces that may be selected as sentinel sites for regular prevalence surveys.

CHALLENGES

The duration of the national prevalence survey was originally planned for one year. A few events caused it to extend to three years. The September 2013 armed conflict in Zamboanga City prevented any activity in the region. In 2015, security concerns prevented survey staff from collecting samples in Sulu and Maguindanao. Eastern Visayas (Region VIII) was devastated by Typhoon Yolanda in November 2013.

Sample collection stalled a few times due to financial and logistical setbacks. It was only in 2015 that a sizable budget was secured and allowed hiring of full-time medical technologist to perform stool examination. Changes to the schedule of the MDAs also affected the timeline of sample collections. The limited number of personnel handling a high volume of samples made it difficult to have samples examined within 30 minutes of preparation. Other methods such as FLOTAC or examining three stool samples by Kato-Katz could result in more accurate results but would entail higher expense and workload for survey personnel. Requesting for three stool samples from participants, as opposed to only one, could also result in a decrease or inconsistency in participation rate.

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DECLARATIONS

Availability of Data and Materials

The datasets used and analyzed during this study are not publicly available due to the inclusion of identifying information on individuals but are available from the corresponding author on reasonable request and approval from relevant ethics committees.

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Supplementary Table 1. Computation of Power

Study parameters:

alpha = 0.0500
N = 26,171
delta = 0.0140 (maximum allowable error)
p0 = 0.2800 (cumulative incidence from study)
pa = 0.2940

Estimated power:

power = 0.9988

Supplementary Table 2. Cumulative prevalence of STH infections by province, 2013-2015.

Region	Province	No. of students examined	Cumulative prevalence (%)	Intensity of infection (%)		
				Light	Moderate	Heavy
1	ILOCOS NORTE	203	1 (0.5)	1 (100.0)	0 (0.0)	0 (0.0)
	ILOCOS SUR	279	64 (22.9)	37 (57.8)	25 (39.0)	2 (3.1)
	LA UNION	231	70 (30.3)	55 (78.6)	14 (20.0)	1 (1.4)
	PANGASINAN	179	36 (20.1)	27 (75.0)	9 (25.0)	0 (0.0)
	Total	892	171 (19.2)	120 (7.0)	48 (28.1)	3 (1.8)
2	BATANES	155	4 (2.6)	4 (100.0)	0 (0.0)	0 (0.0)
	CAGAYAN*	493	120 (24.3)	84 (70.0)	34 (28.3)	2 (1.7)
	ISABELA	282	22 (7.8)	19 (86.4)	3 (13.6)	0 (0.0)
	NUEVA VIZCAYA	131	17 (13.0)	13 (76.5)	3 (17.6)	1 (5.9)
	QUIRINO	307	15 (4.9)	13 (86.7)	2 (13.3)	0 (0.0)
	Total	1,368	178 (13.0)	133 (74.7)	42 (23.6)	3 (1.7)
3	AURORA	174	60 (34.5)	44 (73.3)	15 (25.0)	1 (1.7)
	BATAAN	142	36 (25.4)	22 (61.1)	12 (33.3)	2 (5.6)
	BULACAN	215	30 (14.0)	26 (86.7)	4 (13.3)	0 (0.0)
	NUEVA ECIJA	228	52 (22.8)	35 (67.3)	17 (32.7)	0 (0.0)
	PAMPANGA	234	113 (48.3)	77 (68.1)	34 (30.1)	2 (1.8)
	TARLAC	195	81 (41.5)	58 (71.6)	23 (28.4)	0 (0.0)
	ZAMBALES	140	59 (42.1)	55 (93.2)	4 (6.8)	0 (0.0)
	Total	1,328	431 (32.5)	317 (73.5)	109 (25.3)	5 (1.2)
4A	BATANGAS	244	33 (13.5)	19 (57.6)	13 (39.4)	1 (3.0)
	CAVITE	260	63 (24.2)	36 (57.1)	25 (39.7)	2 (3.2)
	LAGUNA	188	33 (17.6)	20 (60.6)	13 (39.4)	0 (0.0)
	QUEZON	204	35 (17.2)	30 (85.7)	5 (14.3)	0 (0.0)
	RIZAL	255	71 (27.8)	52 (73.2)	17 (23.9)	2 (2.8)
	Total	1,151	235 (20.4)	157 (66.8)	73 (31.1)	5 (2.1)
4B	MARINDUQUE	215	86 (40.0)	61 (70.9)	18 (20.9)	7 (8.1)
	OCCIDENTAL MINDORO	222	126 (56.8)	83 (65.9)	38 (30.2)	5 (4.0)
	ORIENTAL MINDORO	481	135 (28.1)	93 (68.9)	39 (28.9)	3 (2.2)
	PALAWAN	275	133 (48.4)	68 (51.1)	52 (39.1)	13 (9.8)
	ROMBLON	259	107 (41.3)	64 (59.8)	35 (32.7)	8 (7.5)
	Total	1,452	587 (40.4)	369 (62.9)	182 (31.0)	36 (6.1)
5	ALBAY	241	106 (44.0)	71 (67.0)	32 (30.2)	3 (2.8)
	CAMARINES NORTE	154	88 (57.1)	42 (47.7)	45 (51.1)	1 (1.1)
	CAMARINES SUR	255	133 (52.2)	75 (56.4)	57 (42.9)	1 (0.8)
	CATANDUANES	202	128 (63.4)	63 (49.2)	64 (50.0)	1 (0.8)
	MASBATE	236	183 (77.5)	87 (47.5)	86 (47.0)	10 (5.5)
	SORSOGON	429	384 (89.5)	183 (47.7)	168 (43.8)	33 (8.6)
	Total	1,517	1,022 (67.4)	521 (51.0)	452 (44.2)	49 (4.8)
6	AKLAN	316	107 (33.9)	67 (62.6)	27 (25.2)	13 (12.1)
	ANTIQUE	315	74 (23.5)	60 (81.1)	13 (17.6)	1 (1.4)

Region	Province	No. of students examined	Cumulative prevalence (%)	Intensity of infection (%)		
				Light	Moderate	Heavy
	CAPIZ	260	107 (41.2)	74 (69.2)	32 (29.9)	1 (0.9)
	GUIMARAS	283	35 (12.4)	31 (88.6)	4 (11.4)	0 (0.0)
	ILOILO	255	130 (51.0)	51 (39.2)	64 (49.2)	15 (11.5)
	NEGROS OCCIDENTAL	619	133 (21.5)	112 (84.2)	18 (13.5)	3 (2.3)
	Total	2,048	586 (28.6)	395 (67.4)	158 (27.0)	33 (5.6)
7	BOHOL	657	160 (24.4)	155 (96.9)	5 (3.1)	0 (0.0)
	CEBU	366	138 (37.7)	97 (70.3)	35 (25.4)	6 (4.3)
	NEGROS ORIENTAL	327	40 (12.2)	37 (92.5)	1 (2.5)	2 (5.0)
	SIQUIJOR	303	11 (3.6)	9 (81.8)	2 (18.2)	0 (0.0)
	Total	1,653	349 (21.1)	298 (85.4)	43 (12.3)	8 (2.3)
8	BILIRAN	295	139 (47.1)	88 (63.3)	50 (36.0)	1 (0.7)
	EASTERN SAMAR	506	273 (54)	202 (74.0)	65 (23.8)	6 (2.2)
	LEYTE	443	165 (37.2)	130 (78.8)	29 (17.6)	6 (3.6)
	NORTHERN SAMAR	589	434 (73.7)	208 (47.9)	206 (47.5)	20 (4.6)
	SOUTHERN LEYTE	264	112 (42.4)	69 (61.6)	36 (32.1)	7 (6.3)
	WESTERN SAMAR	445	298 (67.0)	173 (58.1)	112 (37.6)	13 (4.4)
	Total	2,542	1,421 (55.9)	870 (61.2)	498 (35.0)	53 (3.7)
9	ZAMBOANGA DEL NORTE	546	190 (34.8)	107 (56.3)	75 (39.5)	8 (4.2)
	ZAMBOANGA DEL SUR	597	107 (17.9)	90 (84.1)	15 (14.0)	2 (1.9)
	ZAMBOANGA SIBUGAY	481	140 (29.1)	114 (81.4)	22 (15.7)	4 (2.9)
	Total	1,624	437 (26.9)	311 (71.2)	112 (25.6)	14 (3.2)
10	BUKIDNON	522	50 (9.6)	42 (84.0)	7 (14.0)	1 (2.0)
	CAMIGUIN	231	36 (15.6)	29 (80.6)	7 (19.4)	0 (0.0)
	LANAO DEL NORTE	426	118 (27.7)	92 (78.0)	23 (19.5)	3 (2.5)
	MISAMIS OCCIDENTAL	365	89 (24.4)	66 (74.2)	23 (25.8)	0 (0.0)
	MISAMIS ORIENTAL	265	71 (26.8)	53 (74.6)	18 (25.4)	0 (0.0)
	Total	1,809	364 (20.1)	282 (77.5)	78 (21.4)	4 (1.1)
11	COMPOSTELA VALLEY	550	41 (7.5)	39 (95.1)	1 (2.4)	1 (2.4)
	DAVAO DEL NORTE	527	47 (8.9)	42 (89.4)	4 (8.5)	1 (2.1)
	DAVAO DEL SUR	461	40 (8.7)	33 (82.5)	7 (17.5)	0 (0.0)
	DAVAO ORIENTAL	541	121 (22.4)	118 (97.5)	3 (2.5)	0 (0.0)
	Total	2,079	249 (12.0)	232 (93.2)	15 (6.0)	2 (0.8)
12	NORTH COTABATO	551	114 (20.7)	91 (79.8)	22 (19.3)	1 (0.9)
	SARANGANI	265	87 (32.8)	72 (82.8)	14 (16.1)	1 (1.1)
	SOUTH COTABATO	558	99 (17.7)	82 (82.8)	14 (14.1)	3 (3.0)
	SULTAN KUDARAT	508	123 (24.2)	99 (80.5)	22 (17.9)	2 (1.6)
	Total	1,882	423 (22.5)	344 (81.3)	72 (17.0)	7 (1.7)
CARAGA	AGUSAN DEL NORTE	369	97 (26.3)	67 (69.1)	26 (26.8)	4 (4.1)
	AGUSAN DEL SUR	216	43 (19.9)	31 (72.1)	11 (25.6)	1 (2.3)
	DINAGAT ISLANDS	224	69 (30.8)	35 (50.7)	34 (49.3)	0 (0.0)
	SURIGAO DEL NORTE	337	69 (20.5)	31 (44.9)	30 (43.5)	8 (11.6)
	SURIGAO DEL SUR	279	32 (11.5)	25 (78.1)	6 (18.8)	1 (3.1)
	Total	1,425	310 (21.8)	189 (61.0)	107 (34.5)	14 (4.5)
NCR	NCR 1ST DISTRICT	250	75 (30.0)	43 (57.3)	32 (42.7)	0 (0.0)
	NCR 2ND DISTRICT	167	31 (18.6)	24 (77.4)	6 (19.4)	1 (3.2)
	NCR 3RD DISTRICT	167	31 (18.6)	16 (51.6)	13 (41.9)	2 (6.5)
	NCR 4TH DISTRICT	141	21 (14.9)	15 (71.4)	6 (28.6)	0 (0.0)
	Total	725	158 (21.8)	98 (62.0)	57 (3.2)	3 (1.9)
CAR	ABRA	252	11 (4.4)	9 (81.8)	2 (18.2)	0 (0.0)

Region	Province	No. of students examined	Cumulative prevalence (%)	Intensity of infection (%)		
				Light	Moderate	Heavy
	APAYAO	307	22 (7.2)	19 (86.4)	3 (13.6)	0 (0.0)
	BENGUET	230	8 (3.5)	8 (100.0)	0 (0.0)	0 (0.0)
	IFUGAO	282	22 (7.8)	21 (95.5)	1 (4.5)	0 (0.0)
	KALINGA	275	38 (13.8)	34 (89.5)	4 (10.5)	0 (0.0)
	MOUNTAIN PROVINCE	292	16 (5.5)	14 (87.5)	2 (12.5)	0 (0.0)
	Total	1,638	117 (7.1)	105 (89.7)	12 (10.3)	0 (0.0)
ARMM	BASILAN	240	143 (59.6)	91 (63.6)	49 (34.3)	3 (2.1)
	LANAO DEL SUR	601	149 (24.8)	124 (83.2)	25 (16.8)	0 (0.0)
	TAWI-TAWI	197	96 (48.7)	74 (77.1)	22 (22.9)	0 (0.0)
	Total	1,038	388 (37.4)	289 (74.5)	96 (24.7)	3 (0.8)
Total		**26,171**	**7,426 (28.4)**	**5,030 (67.7)**	**2,154 (29.0)**	**242 (3.2)**

Supplementary Table 3. *Ascaris lumbricoides* prevalence and intensity of infection by province

Region	Province	No. of students examined	*A. lumbricoides* prevalence		Intensity of infection (%)		
			No. (%)	95% CI	Light	Moderate	Heavy
1	ILOCOS NORTE	203	0	0.0.0-0.0.0	0	0	0
	ILOCOS SUR	279	43 (15.4)	11.6-20.2	20 (46.5)	21 (48.8)	2 (4.7)
	LA UNION	231	25 (10.8)	7.4-15.6	18 (72.0)	7 (28.0)	0
	PANGASINAN	179	24 (13.4)	9.1-19.3	15 (62.5)	9 (37.5)	0
	Total	892	92 (10.3)	8.5-12.5	53 (57.6)	37 (40.2)	2 (2.2)
2	BATANES	155	3 (1.9)	0.6-5.9	3 (100.0)	0	0
	CAGAYAN*	493	36 (7.3)	5.3-10	24 (66.7)	12 (33.3)	0
	ISABELA	282	18 (6.4)	4.0-9.9	15 (83.3)	3 (16.7)	0
	NUEVA VIZCAYA	131	14 (10.7)	6.4-17.3	10 (71.4)	3 (21.4)	1 (7.1)
	QUIRINO	307	11 (3.6)	2.0-6.4	9 (81.8)	2 (18.2)	0
	Total	1,368	82 (6.0)	4.9-7.4	61 (74.4)	20 (24.4)	1 (1.2)
3	AURORA	174	41 (23.6)	17.8-30.5	26 (63.4)	14 (34.1)	1 (2.4)
	BATAAN	142	16 (11.3)	7.0-17.7	4 (25.0)	11 (68.8)	1 (6.3)
	BULACAN	215	21 (9.8)	6.4-14.6	20 (95.2)	1 (4.8)	0
	NUEVA ECIJA	228	38 (16.7)	12.3-22.1	24 (63.2)	14 (36.8)	0
	PAMPANGA	234	68 (29.1)	23.6-35.2	37 (54.4)	30 (44.1)	1 (1.5)
	TARLAC	195	55 (28.2)	22.3-35.0	36 (65.5)	19 (34.5)	0
	ZAMBALES	140	32 (22.9)	16.6-30.6	29 (90.6)	3 (9.4)	0
	Total	1,328	271 (20.4)	18.3-22.7	176 (64.9)	92 (33.9)	3 (1.1)
4A	BATANGAS	244	26 (10.7)	7.3-15.2	14 (53.8)	12 (46.2)	0
	CAVITE	260	48 (18.5)	14.2-23.7	23 (47.9)	24 (50.0)	1 (2.1)
	LAGUNA	188	26 (13.8)	9.6-19.6	15 (57.7)	11 (42.3)	0
	QUEZON	204	21 (10.3)	6.8-15.3	16 (76.2)	5 (23.8)	0
	RIZAL	255	64 (25.1)	20.1-30.8	47 (73.4)	16 (25.0)	1 (1.6)
	Total	1,151	185 (16.1)	14.1-18.3	115 (62.2)	68 (36.8)	2 (1.1)
4B	MARINDUQUE	215	50 (23.3)	18.1-29.4	30 (60.0)	13 (26.0)	7 (14.0)
	OCCIDENTAL MINDORO	222	76 (34.2)	28.2-40.8	42 (55.3)	29 (38.2)	5 (6.6)
	ORIENTAL MINDORO	481	92 (19.1)	15.8-22.9	56 (60.9)	35 (38.0)	1 (1.1)
	PALAWAN	275	87 (31.6)	26.4-37.4	30 (34.5)	49 (56.3)	8 (9.2)
	ROMBLON	259	70 (27.0)	21.9-32.8	29 (41.4)	34 (48.6)	7 (10.0)
	Total	1,452	375 (25.8)	23.6-28.1	187 (49.9)	160 (42.7)	28 (7.5)
5	ALBAY	241	87 (36.1)	30.2-42.4	54 (62.1)	30 (34.5)	3 (3.4)
	CAMARINES NORTE	154	72 (46.8)	38.9-54.7	28 (38.9)	43 (59.7)	1 (1.4)

Region	Province	No. of students examined	*A. lumbricoides* prevalence		Intensity of infection (%)		
			No. (%)	95% CI	Light	Moderate	Heavy
	CAMARINES SUR	255	102 (40.0)	34.1-46.2	50 (49.0)	52 (51.0)	0
	CATANDUANES	202	78 (38.6)	32.1-45.6	37 (47.4)	40 (51.3)	1 (1.3)
	MASBATE	236	133 (56.4)	49.9-62.6	56 (42.1)	69 (51.9)	8 (6.0)
	SORSOGON	429	292 (68.1)	63.5-72.3	119 (40.8)	150 (51.4)	23 (7.9)
	Total	1,517	764 (50.4)	47.8-52.9	344 (45.0)	384 (50.3)	36 (4.7)
6	AKLAN	316	57 (18)	14.2-22.7	26 (45.6)	19 (33.3)	12 (21.1)
	ANTIQUE	315	25 (7.9)	5.4-11.5	16 (64.0)	8 (32)	1 (4.0)
	CAPIZ	260	43 (16.5)	12.5-21.6	25 (58.1)	17 (39.5)	1 (2.3)
	GUIMARAS	283	16 (5.7)	3.5-9.1	12 (75.0)	4 (25.0)	0
	ILOILO	255	80 (31.4)	25.9-37.4	15 (18.8)	63 (78.8)	2 (2.5)
	NEGROS OCCIDENTAL	619	68 (11.0)	8.7-13.7	51 (75.0)	15 (22.1)	2 (2.9)
	Total	2,048	289 (14.1)	12.7-15.7	145 (50.2)	126 (43.6)	18 (6.2)
7	BOHOL	657	16 (2.4)	1.5-3.9	14 (87.5)	2 (12.5)	0
	CEBU	366	102 (27.9)	23.5-32.7	64 (62.7)	32 (31.4)	6 (5.9)
	NEGROS ORIENTAL	327	18 (5.5)	3.5-8.6	17 (94.4)	1 (5.6)	0
	SIQUIJOR	303	3 (1.0)	0.3-3.0	3 (100.0)	0	0
	Total	1,653	139 (8.4)	7.2-9.8	98 (70.5)	35 (25.2)	6 (4.3)
8	BILIRAN	295	68 (23.1)	18.6-28.2	36 (52.9)	32 (47.1)	0
	EASTERN SAMAR	506	132 (26.1)	22.4-30.1	84 (63.6)	43 (32.6)	5 (3.8)
	LEYTE	443	75 (16.9)	13.7-20.7	51 (68.0)	21 (28.0)	3 (4.0)
	NORTHERN SAMAR	589	280 (47.5)	43.5-51.6	117 (41.8)	152 (54.3)	11 (3.9)
	SOUTHERN LEYTE	264	60 (22.7)	18.0-28.2	24 (40.0)	31 (51.7)	5 (8.3)
	WESTERN SAMAR	445	210 (47.2)	42.6-51.9	96 (45.7)	101 (48.1)	13 (6.2)
	Total	2,542	825 (32.5)	30.7-34.3	408 (49.5)	380 (46.1)	37 (4.5)
9	ZAMBOANGA DEL NORTE	546	135 (24.7)	21.3-28.5	72 (53.3)	58 (43.0)	5 (3.7)
	ZAMBOANGA DEL SUR	597	61 (10.2)	8.0-12.9	45 (73.8)	14 (23.0)	2 (3.3)
	ZAMBOANGA SIBUGAY	481	71 (14.8)	11.9-18.2	50 (70.4)	17 (23.9)	4 (5.6)
	Total	1,624	267 (16.4)	14.7-18.3	167 (62.5)	89 (33.3)	11 (4.1)
10	BUKIDNON	522	37 (7.1)	5.2-9.6	29 (78.4)	8 (21.6)	0
	CAMIGUIN	231	22 (9.5)	6.3-14.1	17 (77.3)	5 (22.7)	0
	LANAO DEL NORTE	426	62 (14.6)	11.5-18.2	38 (61.3)	21 (33.9)	3 (4.8)
	MISAMIS OCCIDENTAL	365	54 (14.8)	11.5-18.8	37 (69.8)	16 (30.2)	0
	MISAMIS ORIENTAL	265	39 (14.7)	10.9-19.5	24 (61.5)	15 (38.5)	0
	Total	1,809	214 (11.8)	10.4-13.4	145 (68.1)	65 (30.5)	3 (1.4)
11	COMPOSTELA VALLEY	550	20 (3.6)	2.4-5.6	18 (90.0)	1 (5.0)	1 (5.0)
	DAVAO DEL NORTE	527	23 (4.4)	2.9-6.5	19 (82.6)	3 (13.0)	1 (4.3)
	DAVAO DEL SUR	461	22 (4.8)	3.2-7.2	16 (72.7)	6 (27.3)	0
	DAVAO ORIENTAL	541	78 (14.4)	11.7-17.6	76 (97.4)	2 (2.6)	0
	Total	2,079	143 (6.9)	5.9-8.1	129 (90.2)	12 (8.4)	2 (1.4)
12	NORTH COTABATO	551	68 (12.3)	9.8-15.4	48 (70.6)	20 (29.4)	0
	SARANGANI	265	68 (12.2)	9.7-15.2	53 (77.9)	14 (20.6)	1 (1.5)
	SOUTH COTABATO	558	54 (20.4)	15.9-25.7	41 (75.9)	12 (22.2)	1 (1.9)
	SULTAN KUDARAT	508	65 (12.8)	10.2-16.0	44 (67.7)	19 (29.2)	2 (3.1)
	Total	1,882	255 (13.5)	12.1-15.2	186 (72.9)	65 (25.5)	4 (1.6)
CARAGA	AGUSAN DEL NORTE	369	57 (15.4)	12.1-19.5	35 (61.4)	21 (36.8)	1 (1.8)
	AGUSAN DEL SUR	216	34 (15.7)	11.4-21.3	23 (67.6)	11 (32.4)	0
	DINAGAT ISLANDS	224	54 (24.1)	18.9-30.2	22 (40.7)	32 (59.3)	0
	SURIGAO DEL NORTE	337	52 (15.4)	11.9-19.7	15 (28.8)	31 (59.6)	6 (11.5)

Region	Province	No. of students examined	*A. lumbricoides* prevalence		Intensity of infection (%)		
			No. (%)	95% CI	Light	Moderate	Heavy
	SURIGAO DEL SUR	279	15 (5.4)	3.3-8.8	11 (73.3)	3 (20.0)	1 (6.7)
	Total	1,425	212 (14.9)	13.1-16.8	106 (50.0)	98 (46.2)	8 (3.8)
NCR	NCR 1ST DISTRICT	250	61 (24.4)	19.4-30.1	30 (49.2)	31 (50.8)	0
	NCR 2ND DISTRICT	167	22 (13.2)	8.8-19.3	16 (72.7)	5 (22.7)	1 (4.5)
	NCR 3RD DISTRICT	167	24 (14.4)	9.8-20.6	9 (37.5)	13 (54.2)	2 (8.3)
	NCR 4TH DISTRICT	141	15 (10.6)	6.5-17.0	10 (66.7)	5 (33.3)	0
	Total	725	122 (16.8)	14.3-19.7	65 (53.3)	54 (44.3)	3 (2.5)
CAR	ABRA	252	7 (2.8)	1.3-5.7	5 (71.4)	2 (28.6)	0
	APAYAO	307	11 (3.6)	2-6.4.0	9 (81.8)	2 (18.2)	0
	BENGUET	230	5 (2.2)	0.9-5.1	5 (100.0)	0	0
	IFUGAO	282	14 (5.0)	3.0-8.2	14 (100.0)	0	0
	KALINGA	275	18 (6.5)	4.2-10.2	14 (77.8)	4 (22.2)	0
	MOUNTAIN PROVINCE	292	3 (1.0)	0.3-3.2	3 (100.0)	0	0
	Total	1,638	58 (3.5)	2.7-4.6	50 (86.2)	8 (13.8)	0
ARMM	BASILAN	240	102 (42.5)	36.4-48.9	54 (52.9)	46 (45.1)	2 (2.0)
	LANAO DEL SUR	601	108 (18.0)	15.1-21.3	87 (80.6)	21 (19.4)	0
	TAWI-TAWI	197	57 (28.9)	23.0-35.7	43 (75.4)	14 (24.6)	0
	Total	1,038	267 (25.7)	23.2-28.5	184 (68.9)	81 (30.3)	2 (0.7)
Overall		**26,171**	**4,560 (17.4)**	**16.97-17.89**	**2,619 (57.4)**	**1,774 (38.9)**	**166 (3.6)**

Supplementary Table 4. ***Trichuris trichiura*** **prevalence and intensity of infection per province**

Region	Province	No. of students examined	*T. trichiura* prevalence		Intensity of infection (%)		
			No. (%)	95% CI	Light	Moderate	Heavy
1	ILOCOS NORTE	203	1 (0.5)	0.1-3.5	1 (100.0)	0 (0.0)	0 (0.0)
	ILOCOS SUR	279	55 (19.7)	15.4-24.8	41 (74.5)	13 (23.6)	1 (1.8)
	LA UNION	231	65 (28.1)	22.7-34.3	53 (81.5)	11 (16.9)	1 (1.5)
	PANGASINAN	179	20 (11.2)	7.3-16.7	20 (100.0)	0 (0.0)	0 (0.0)
	Total	892	141 (15.8)	13.6-18.4	115 (81.6)	24 (17)	2 (1.4)
2	BATANES	155	1 (0.6)	0.1-4.5	1 (100.0)	0 (0.0)	0 (0.0)
	CAGAYAN*	493	107 (21.7)	18.3-25.6	80 (74.8)	25 (23.4)	2 (1.9)
	ISABELA	282	8 (2.8)	1.4-5.6	8 (100.0)	0 (0.0)	0 (0.0)
	NUEVA VIZCAYA	131	6 (4.6)	2.1-9.9	5 (83.3)	1 (16.7)	0 (0.0)
	QUIRINO	307	7 (2.3)	1.1-4.7	7 (100.0)	0 (0.0)	0 (0.0)
	Total	1,368	129 (9.4)	8.0-11.1	101 (78.3)	26 (20.2)	2 (1.6)
3	AURORA	174	37 (21.3)	15.8-28.0	36 (97.3)	1 (2.7)	0 (0.0)
	BATAAN	142	29 (20.4)	14.5-27.9	25 (86.2)	3 (10.3)	1 (3.4)
	BULACAN	215	11 (5.1)	2.8-9.0	8 (72.7)	3 (27.3)	0 (0.0)
	NUEVA ECIJA	228	24 (10.5)	7.1-15.3	19 (79.2)	5 (20.8)	0 (0.0)
	PAMPANGA	234	88 (37.6)	31.6-44.0	79 (89.8)	8 (9.1)	1 (1.1)
	TARLAC	195	55 (28.2)	22.3-35.0	50 (90.9)	5 (9.1)	0 (0.0)
	ZAMBALES	140	41 (29.3)	22.3-37.4	40 (97.6)	1 (2.4)	0 (0.0)
	Total	1,328	285 (21.5)	19.3-23.8	257 (90.2)	26 (9.1)	2 (0.7)
4A	BATANGAS	244	17 (7.0)	4.4-11.0	13 (76.5)	3 (17.6)	1 (5.9)
	CAVITE	260	26 (10.0)	6.9-14.3	22 (84.6)	3 (11.5)	1 (3.8)
	LAGUNA	188	13 (6.9)	4.0-11.6	11 (84.6)	2 (15.4)	0 (0.0)
	QUEZON	204	18 (8.8)	5.6-13.6	18 (100.0)	0 (0.0)	0 (0.0)
	RIZAL	255	13 (5.1)	3.0-8.6	10 (76.9)	2 (15.4)	1 (7.7)
	Total	1,151	87 (7.6)	6.2-9.2	74 (85.1)	10 (11.5)	3 (3.4)

Region	Province	No. of students examined	*T. trichiura* prevalence		Intensity of infection (%)		
			No. (%)	95% CI	Light	Moderate	Heavy
4B	MARINDUQUE	215	61 (28.4)	22.7-34.8	49 (80.3)	12 (19.7)	0 (0.0)
	OCCIDENTAL MINDORO	222	84 (37.8)	31.7-44.4	70 (83.3)	14 (16.7)	0 (0.0)
	ORIENTAL MINDORO	481	72 (15.0)	12.0-18.5	65 (90.3)	5 (6.9)	2 (2.8)
	PALAWAN	275	113 (41.1)	35.4-47.0	85 (75.2)	23 (20.4)	5 (4.4)
	ROMBLON	259	87 (33.6)	28.1-39.6	83 (95.4)	3 (3.4)	1 (1.1)
	Total	1,452	417 (28.7)	26.4-31.1	352 (84.4)	57 (13.7)	8 (1.9)
5	ALBAY	241	62 (25.7)	20.6-31.7	57 (91.9)	5 (8.1)	0 (0.0)
	CAMARINES NORTE	154	101 (50.0)	43.1-56.9	56 (55.4)	45 (44.6)	0 (0.0)
	CAMARINES SUR	255	48 (31.2)	24.3-39.0	39 (81.3)	9 (18.8)	0 (0.0)
	CATANDUANES	202	86 (33.7)	28.2-39.8	71 (82.6)	14 (16.3)	1 (1.2)
	MASBATE	236	157 (66.5)	60.2-72.3	117 (74.5)	37 (23.6)	3 (1.9)
	SORSOGON	429	351 (81.8)	77.9-85.2	238 (67.8)	98 (27.9)	15 (4.3)
	Total	1,517	805 (53.1)	50.5-55.6	578 (71.8)	208 (25.8)	19 (2.4)
6	AKLAN	316	79 (25.0)	20.5-30.1	57 (72.2)	20 (25.3)	2 (2.5)
	ANTIQUE	315	58 (18.4)	14.5-23.1	51 (87.9)	6 (10.3)	1 (1.7)
	CAPIZ	260	97 (37.3)	31.6-43.4	76 (78.4)	21 (21.6)	0 (0.0)
	GUIMARAS	283	22 (7.8)	5.2-11.6	22 (100.0)	0 (0.0)	0 (0.0)
	ILOILO	255	120 (47.1)	41.0-53.2	68 (56.7)	38 (31.7)	14 (11.7)
	NEGROS OCCIDENTAL	619	87 (14.1)	11.5-17.0	82 (94.3)	4 (4.6)	1 (1.1)
	Total	2,048	463 (22.6)	20.8-24.5	356 (76.9)	89 (19.2)	18 (3.9)
7	BOHOL	657	147 (22.4)	19.3-25.7	144 (98.0)	3 (2.0)	0 (0.0)
	CEBU	366	60 (16.4)	12.9-20.6	55 (91.7)	5 (8.3)	0 (0.0)
	NEGROS ORIENTAL	327	22 (6.7)	4.5-10	20 (90.9)	0 (0.0)	2 (9.1)
	SIQUIJOR	303	8 (2.6)	1.3-5.2	6 (75.0)	2 (25.0)	0 (0.0)
	Total	1,653	237 (14.3)	12.7-16.1	225 (94.9)	10 (4.2)	2 (0.8)
8	BILIRAN	295	119 (40.3)	34.9-46.1	85 (71.4)	33 (27.7)	1 (0.8)
	EASTERN SAMAR	506	238 (47.0)	42.7-51.4	195 (81.9)	41 (17.2)	2 (0.8)
	LEYTE	443	126 (28.4)	24.4-32.8	108 (85.7)	15 (11.9)	3 (2.4)
	NORTHERN SAMAR	589	80 (30.3)	25.0-36.2	67 (83.8)	11 (13.8)	2 (2.5)
	SOUTHERN LEYTE	264	361 (61.3)	57.3-65.2	218 (60.4)	131 (36.3)	12 (3.3)
	WESTERN SAMAR	445	221 (49.7)	45.0-54.3	191 (86.4)	30 (13.6)	0 (0.0)
	Total	2,542	1,145 (45)	43.1-47.0	864 (75.5)	261 (22.8)	20 (1.7)
9	ZAMBOANGA DEL NORTE	546	147 (26.9)	23.4-30.8	98 (66.7)	45 (30.6)	4 (2.7)
	ZAMBOANGA DEL SUR	597	50 (8.4)	6.4-10.9	49 (98.0)	1 (2.0)	0 (0.0)
	ZAMBOANGA SIBUGAY	481	100 (20.8)	17.4-24.7	90 (90.0)	10 (10.0)	0 (0.0)
	Total	1,624	297 (18.3)	16.5-20.2	237 (79.8)	56 (18.9)	4 (1.3)
10	BUKIDNON	522	12 (2.3)	1.3-4.0	12 (100.0)	0 (0.0)	0 (0.0)
	CAMIGUIN	231	26 (11.3)	7.8-16.1	21 (91.3)	2 (8.7)	0 (0.0)
	LANAO DEL NORTE	426	71 (16.7)	13.4-20.5	66 (95.7)	2 (2.9)	1 (1.4)
	MISAMIS OCCIDENTAL	365	65 (17.8)	14.2-22.1	53 (84.1)	10 (15.9)	0 (0.0)
	MISAMIS ORIENTAL	265	48 (18.1)	13.9-23.3	39 (86.7)	6 (13.3)	0 (0.0)
	Total	1,809	222 (12.3)	10.8-13.9	191 (90.1)	20 (9.4)	1 (0.5)
11	COMPOSTELA VALLEY	550	21 (3.8)	2.5-5.8	21 (100.0)	0 (0.0)	0 (0.0)
	DAVAO DEL NORTE	527	23 (4.4)	2.9-6.5	22 (95.7)	1 (4.3)	0 (0.0)
	DAVAO DEL SUR	461	25 (5.4)	3.7-7.9	24 (96.0)	1 (4.0)	0 (0.0)
	DAVAO ORIENTAL	541	62 (11.5)	9.0-14.4	61 (98.4)	1 (1.6)	0 (0.0)
	Total	2,079	131 (6.3)	5.3-7.4	128 (97.7)	3 (2.3)	0 (0.0)
12	NORTH COTABATO	551	69 (12.5)	10.0-15.6	63 (91.3)	5 (7.2)	1 (1.4)
	SARANGANI	265	41 (7.3)	5.5-9.8	36 (87.8)	3 (7.3)	2 (4.9)

Region	Province	No. of students examined	*T. trichiura* prevalence		Intensity of infection (%)		
			No. (%)	95% CI	Light	Moderate	Heavy
	SOUTH COTABATO	558	50 (18.9)	14.6-24.1	47 (94.0)	3 (6.0)	0 (0.0)
	SULTAN KUDARAT	508	74 (14.6)	11.8-17.9	70 (94.6)	4 (5.4)	0 (0.0)
	Total	1,882	234 (12.4)	11.0-14.0	216 (92.3)	15 (6.4)	3 (1.3)
CARAGA	AGUSAN DEL NORTE	369	65 (17.6)	14.0-21.9	46 (79.3)	10 (17.2)	2 (3.4)
	AGUSAN DEL SUR	216	19 (8.8)	5.7-13.4	18 (100.0)	0 (0.0)	0 (0.0)
	DINAGAT ISLANDS	224	29 (12.9)	9.1-18.1	26 (92.9)	2 (7.1)	0 (0.0)
	SURIGAO DEL NORTE	337	59 (17.5)	13.8-22.0	34 (59.6)	19 (33.3)	4 (7.0)
	SURIGAO DEL SUR	279	27 (9.7)	6.7-13.8	22 (81.5)	5 (18.5)	0 (0.0)
	Total	1,425	199 (14)	12.3-15.9	146 (77.7)	36 (19.1)	6 (3.2)
NCR	NCR 1ST DISTRICT	250	20 (8.0)	5.2-12.1	19 (95.0)	1 (5.0)	0 (0.0)
	NCR 2ND DISTRICT	167	12 (7.2)	4.1-12.3	11 (91.7)	1 (8.3)	0 (0.0)
	NCR 3RD DISTRICT	167	7 (4.2)	2.0-8.6	7 (100.0)	0 (0.0)	0 (0.0)
	NCR 4TH DISTRICT	141	9 (6.4)	3.3-11.9	8 (88.9)	1 (11.1)	0 (0.0)
	Total	725	48 (6.6)	5.0-8.7	45 (93.8)	3 (6.3)	0 (0.0)
CAR	ABRA	252	6 (2.4)	1.1-5.2	6 (100.0)	0 (0.0)	0 (0.0)
	APAYAO	307	13 (4.2)	2.5-7.2	12 (92.3)	1 (7.7)	0 (0.0)
	BENGUET	230	3 (1.3)	0.4-4.0	3 (100.0)	0 (0.0)	0 (0.0)
	IFUGAO	282	10 (3.5)	1.9-6.5	9 (90.0)	1 (10)	0 (0.0)
	KALINGA	275	27 (9.8)	6.8-14.0	26 (96.3)	1 (3.7)	0 (0.0)
	MOUNTAIN PROVINCE	292	15 (5.1)	3.1-8.4	13 (86.7)	2 (13.3)	0 (0.0)
	Total	1,638	74 (4.5)	3.6-5.6	69 (93.2)	5 (6.8)	0 (0.0)
ARMM	BASILAN	240	100 (41.7)	35.6-48.1	88 (88.0)	11 (11.0)	1 (1.0)
	LANAO DEL SUR	601	75 (12.5)	10.1-15.4	70 (93.3)	5 (6.7)	0 (0.0)
	TAWI-TAWI	197	70 (35.5)	29.1-42.5	57 (81.4)	13 (18.6)	0 (0.0)
	Total	1,038	245 (23.6)	21.1-26.3	215 (87.8)	29 (11.8)	1 (0.4)
Overall		**26,171**	**5,159 (19.7)**	**19.2-20.2**	**4,169 (81.1)**	**878 (17.1)**	**91 (1.8)**

Supplementary Table 5. Hookworm prevalence and intensity of infection per province*

Region/s	Province	No. of students examined	Hookworm prevalence		Intensity of infection (%)		
			No. (%)	95% CI	Light	Moderate	High
4B	MARINDUQUE	215	1 (0.5)	0.1-3.3	1 (100.0)	0 (0.0)	0 (0.0)
	OCCIDENTAL MINDORO	222	0 (0.0)	--	--	--	--
	ORIENTAL MINDORO	481	1 (0.2)	0.0-1.5	1 (100.0)	0 (0.0)	0 (0.0)
	PALAWAN	275	2 (0.7)	0.2-2.9	2 (100.0)	0 (0.0)	0 (0.0)
	ROMBLON	259	1 (0.4)	0.1-2.7	1 (100.0)	0 (0.0)	0 (0.0)
	Total	1,452	5 (0.3)	0.1-0.8	5 (100.0)	0 (0.0)	0 (0.0)
5	ALBAY	241	0 (0.0)	--	--	--	--
	CAMARINES NORTE	154	1 (0.5)	0.1-3.5	1 (100.0)	0 (0.0)	0 (0.0)
	CAMARINES SUR	255	0 (0.0)	--	--	--	--
	CATANDUANES	202	0 (0.0)	--	--	--	--
	MASBATE	236	1 (0.4)	0.1-3.0	1 (100.0)	0 (0.0)	0 (0.0)
	SORSOGON	429	2 (0.5)	0.1-1.9	2 (100.0)	0 (0.0)	0 (0.0)
	Total	1,517	4 (0.3)	0.1-0.7	4 (100.0)	0 (0.0)	0 (0.0)
6	AKLAN	316	0 (0.0)	--	--	--	--
	ANTIQUE	315	0 (0.0)	--	--	--	--
	CAPIZ	260	1 (0.4)	0.1-2.7	1 (100.0)	0 (0.0)	0 (0.0)

Region/s	Province	No. of students examined	Hookworm prevalence		Intensity of infection (%)		
			No. (%)	95% CI	Light	Moderate	High
	GUIMARAS	283	0 (0.0)	--	--	--	--
	ILOILO	255	0 (0.0)	--	--	--	--
	NEGROS OCCIDENTAL	619	0 (0.0)	--	--	--	--
	Total	2,048	1 (0.1)	0.0-0.4	1 (100.0)	0 (0.0)	0 (0.0)
7	BOHOL	657	7 (1.1)	0.5-2.2	7 (100.0)	0 (0.0)	0 (0.0)
	CEBU	366	6 (1.6)	0.7-3.6	6 (100.0)	0 (0.0)	0 (0.0)
	NEGROS ORIENTAL	327	4 (1.2)	0.5-3.2	4 (100.0)	0 (0.0)	0 (0.0)
	SIQUIJOR	303	0 (0.0)	--	--	--	--
	Total	1,653	17 (1.0)	0.6-1.6	17 (100.0)	0 (0.0)	0 (0.0)
8	BILIRAN	295	0 (0.0)	--	--	--	--
	EASTERN SAMAR	506	4 (0.8)	0.3-2.1	4 (100.0)	0 (0.0)	0 (0.0)
	LEYTE	443	2 (0.5)	0.1-1.8	2 (100.0)	0 (0.0)	0 (0.0)
	NORTHERN SAMAR	589	0 (0.0)	--	--	--	--
	SOUTHERN LEYTE	264	0 (0.0)	--	--	--	--
	WESTERN SAMAR	445	2 (0.4)	0.1-1.8	2 (100.0)	0 (0.0)	0 (0.0)
	Total	2,542	8 (0.3)	0.2-0.6	8 (100.0)	0 (0.0)	0 (0.0)
9	ZAMBOANGA DEL NORTE	546	2 (0.4)	0.1-1.5	2 (100.0)	0 (0.0)	0 (0.0)
	ZAMBOANGA DEL SUR	597	24 (4.0)	2.7-5.9	23 (96.0)	1 (4.2)	0 (0.0)
	ZAMBOANGA SIBUGAY	481	10 (2.1)	1.1-3.8	10 (100.0)	0 (0.0)	0 (0.0)
	Total	1,624	36 (2.2)	1.6-3.1	35 (97.0)	1 (2.8)	0 (0.0)
10	BUKIDNON	522	9 (2.0)	1.0-3.0	7 (87.5)	0 (0.0)	1 (12.5)
	CAMIGUIN	231	0 (0.0)	--	--	--	--
	LANAO DEL NORTE	426	9 (2.0)	1.0-4.0	9 (100.0)	0 (0.0)	0 (0.0)
	MISAMIS OCCIDENTAL	365	0 (0.0)	--	--	--	--
	MISAMIS ORIENTAL	265	0 (0.0)	--	--	--	--
	Total	1,809	18 (1.0)	1.0-2.0	16 (94.1)	0 (0.0)	1 (5.9)
11	COMPOSTELA VALLEY	550	1 (0.2)	0.0-1.3	1 (100.0)	0 (0.0)	0 (0.0)
	DAVAO DEL NORTE	527	2 (0.4)	0.1-1.5	2 (100.0)	0 (0.0)	0 (0.0)
	DAVAO DEL SUR	461	0 (0.0)	--	--	--	--
	DAVAO ORIENTAL	541	0 (0.0)	--	--	--	--
	Total	2,079	3 (0.1)	0.0-0.4	3 (100.0)	0 (0.0)	0 (0.0)
12	NORTH COTABATO	551	16 (2.9)	1.8-4.7	16 (100.0)	0 (0.0)	0 (0.0)
	SARANGANI	265	5 (0.9)	0.4-2.1	5 (100.0)	0 (0.0)	0 (0.0)
	SOUTH COTABATO	558	8 (3.0)	1.5-5.9	8 (100.0)	0 (0.0)	0 (0.0)
	SULTAN KUDARAT	508	4 (0.8)	0.3-2.1	4 (100.0)	0 (0.0)	0 (0.0)
	Total	1,882	33 (1.8)	1.2-2.5	33 (100.0)	0 (0.0)	0 (0.0)
CARAGA	AGUSAN DEL NORTE	369	6 (2.0)	1.0-4.0	5 (83.3)	0 (0.0)	1 (16.7)
	AGUSAN DEL SUR	216	6 (3.0)	1.0-6.0	4 (66.7)	1 (16.7)	1 (16.7)
	DINAGAT ISLANDS	224	0 (0.0)	--	--	--	--
	SURIGAO DEL NORTE	337	2 (1.0)	0.0-2.0	0 (0.0)	0 (0.0)	2 (100.0)
	SURIGAO DEL SUR	279	0 (0.0)	--	--	--	--
	Total	1,425	14 (1.0)	1.0-2.0	9 (64.3)	1 (7.1)	4 (28.6)
ARMM	BASILAN	240	1 (0.4)	0.1-2.9	1 (100.0)	0 (0.0)	0 (0.0)
	LANAO DEL SUR	601	0 (0.0)	--	--	--	--
	TAWI-TAWI	197	4 (2.0)	0.8-5.3	4 (100.0)	0 (0.0)	0 (0.0)
	Total	1,038	5 (0.5)	0.2-1.2	5 (100.0)	0 (0.0)	0 (0.0)
Overall		**26,171**	144 (0.6)	0.5-0.7	136 (95.1)	2 (1.4)	5 (3.5)

*No hookworm parasite detected among the school children in the provinces of Regions 1, 2, 3, 4A, NCR, CARAGA and CAR.

Supplementary Table 6. *Schistosoma japonicum* prevalence and intensity of infection per province*

Region	Province	No. of students examined	*S. japonicum* prevalence		Intensity of infection (%)		
			No. (%)	95% CI	Light	Moderate	Heavy
1	ILOCOS NORTE	203	1 (0.5)	0.1-3.5	1 (2.0)	0 (0.0)	0 (0.0)
	ILOCOS SUR	279	0 (0.0)	--	--	--	--
	LA UNION	231	0 (0.0)	--	--	--	--
	PANGASINAN	179	0 (0.0)	--	--	--	--
	Total	892	1 (0.1)	0.0-0.8	1 (2.0)	0 (0.0)	0 (0.0)
2	BATANES	155	0 (0.0)	--	--	--	--
	CAGAYAN*	493	12 (2.4)	1.4-4.2	10 (22.0)	1 (8.3)	1 (8.3)
	ISABELA	282	0 (0.0)	--	--	--	--
	NUEVA VIZCAYA	131	0 (0.0)	--	--	--	--
	QUIRINO	307	0 (0.0)	--	--	--	--
	Total	1,368	12 (0.9)	0.5-1.5	10 (22.0)	1 (8.3)	1 (8.3)
4B	MARINDUQUE	215	0 (0.0)	--	--	--	--
	OCCIDENTAL MINDORO	222	0 (0.0)	--	--	--	--
	ORIENTAL MINDORO*	481	1 (0.2)	0.0-1.5	1 (100.0)	0 (0.0)	0 (0.0)
	PALAWAN	275	0 (0.0)	--	--	--	--
	ROMBLON	259	0 (0.0)	--	--	--	--
	Total	1,452	1 (0.1)	0.0-0.5	1 (100.0)	0 (0.0)	0 (0.0)
5	ALBAY	241	0 (0.0)	--	--	--	--
	CAMARINES NORTE	154	0 (0.0)	--	--	--	--
	CAMARINES SUR	255	0 (0.0)	--	--	--	--
	CATANDUANES	202	0 (0.0)	--	--	--	--
	MASBATE	236	0 (0.0)	--	--	--	--
	SORSOGON*	429	17 (4.0)	2.5-6.3	14 (31.0)	3 (17.6)	0 (0.0)
	Total	1,517	17 (1.1)	0.7-1.8	14 (31.0)	3 (17.6)	0 (0.0)
6	AKLAN	316	0 (0.0)	--	--	--	--
	ANTIQUE	315	0 (0.0)	--	--	--	--
	CAPIZ	260	0 (0.0)	--	--	--	--
	GUIMARAS	283	0 (0.0)	--	--	--	--
	ILOILO	255	0 (0.0)	--	--	--	--
	NEGROS OCCIDENTAL*	619	2 (0.3)	0.1-1.3	1 (50.0)	1 (50.0)	0 (0.0)
	Total	2,048	2 (0.1)	0.0-0.4	1 (50.0)	1 (50.0)	0 (0.0)
8	BILIRAN	295	1 (0.3)	0.1-2.4	1 (100.0)	0 (0.0)	0 (0.0)
	EASTERN SAMAR*	506	1 (0.2)	0.0-1.4	1 (100.0)	0 (0.0)	0 (0.0)
	LEYTE*	443	2 (0.5)	0.1-1.8	0 (0.0)	1 (50.0)	1 (50.0)
	NORTHERN SAMAR*	589	59 (10.0)	7.8-12.7	47 (79.7)	12 (20.3)	0 (0.0)
	SOUTHERN LEYTE	264	0 (0.0)	--	--	--	--
	WESTERN SAMAR*	445	6 (1.4)	0.6-3.0	4 (66.7)	2 (33.3)	0 (0.0)
	Total	2,542	69 (2.7)	2.2-3.4	53 (77.0)	15 (21.7)	1 (1.4)
9	ZAMBOANGA DEL NORTE*	546	1 (0.2)	0.0-1.3	0 (0.0)	1 (100.0)	0 (0.0)
	ZAMBOANGA DEL SUR*	597	2 (0.3)	0.1-1.3	1 (50.0)	1 (50.0)	0 (0.0)
	ZAMBOANGA SIBUGAY*	481	6 (1.3)	0.6-2.8	5 (83.3)	1 (16.7)	0 (0.0)
	Total	1,624	9 (0.6)	0.3-1.1	6 (66.7)	3 (33.3)	0 (0.0)
10	BUKIDNON*	522	20 (3.8)	2.5-5.9	18 (90.0)	2 (10.0)	0 (0.0)
	CAMIGUIN	231	0 (0.0)	--	--	--	--
	LANAO DEL NORTE*	426	5 (1.2)	0.5-2.8	5 (100.0)	0 (0.0)	0 (0.0)
	MISAMIS OCCIDENTAL*	365	2 (0.6)	0.1-2.2	2 (100.0)	0 (0.0)	0 (0.0)
	MISAMIS ORIENTAL	265	0 (0.0)	--	--	--	--

Region	Province	No. of students examined	*S. japonicum* prevalence		Intensity of infection (%)		
			No. (%)	95% CI	Light	Moderate	Heavy
	Total	1,809	27 (1.5)	1.0-2.2	25 (93.0)	2 (7.0)	0 (0.0)
11	COMPOSTELA VALLEY*	550	0 (0.0)	--	--	--	--
	DAVAO DEL NORTE*	527	3 (0.6)	0.2-1.8	1 (33.3)	1 (33.3)	1 (33.3)
	DAVAO DEL SUR*	461	14 (3.0)	1.8-5.1	12 (85.7)	1 (7.1)	1 (7.1)
	DAVAO ORIENTAL*	541	2 (0.4)	0.1-1.5	2 (100.0)	0 (0.0)	0 (0.0)
	Total	2,079	19 (1.0)	0.6-1.4	15 (78.9)	2 (10.5)	2 (10.5)
12	NORTH COTABATO*	551	19 (3.5)	2.2-5.4	1 (5.3)	4 (21.1)	14 (73.7)
	SARANGANI	265	0 (0.0)	--	--	--	--
	SOUTH COTABATO*	558	2 (0.4)	0.1-1.4	2 (100.0)	0 (0.0)	0 (0.0)
	SULTAN KUDARAT*	508	5 (1.0)	0.4-2.4	4 (80.0)	1 (20.0)	0 (0.0)
	Total	1,882	26 (1.4)	1.0-2.0	7 (26.9)	5 (19.2)	14 (53.8)
CARAGA	AGUSAN DEL NORTE*	369	16 (4.3)	2.7-7.0	13 (81.3)	2 (12.5)	1 (6.3)
	AGUSAN DEL SUR*	216	7 (3.2)	1.5-6.7	5 (83.3)	0 (0.0)	1 (16.7)
	DINAGAT ISLANDS	224	1 (0.5)	0.1-3.1	1 (100.0)	0 (0.0)	0 (0.0)
	SURIGAO DEL NORTE*	337	5 (1.5)	0.6-3.5	3 (60.0)	2 (40.0)	0 (0.0)
	SURIGAO DEL SUR*	279	1 (0.4)	0.1-2.5	1 (100.0)	0 (0.0)	0 (0.0)
	Total	1,425	30 (2.1)	1.5-3.0	23 (79.3)	4 (13.8)	2 (6.9)
ARMM	BASILAN	240	1 (0.4)	0.1-2.9	0 (0.0)	1 (100.0)	0 (0.0)
	LANAO DEL SUR*	601	18 (3.0)	1.9-4.7	15 (83.3)	3 (16.7)	0 (0.0)
	TAWI-TAWI	197	1 (0.5)	0.1-3.6	0 (0.0)	1 (100.0)	0 (0.0)
	Total	1,038	20 (1.9)	1.3-3.0	15 (75.0)	5 (25.0)	0 (0.0)
Overall		**26,171**	**233 (0.9)**	**0.8-1.0**	**171 (73.7)**	**41 (17.7)**	**20 (8.6)**

*No *S. japonicum* parasite was detected among school children in the provinces of Regions 3, 4A, 7, NCR and CAR.

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ORIGINAL ARTICLE

THE ASSOCIATION OF ADHERENCE TO ANTIMICROBIAL PROPHYLACTIC RECOMMENDATIONS FOR CLEAN NEUROSURGERIES WITH POST-OPERATIVE SURGICAL SITE INFECTION

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ABSTRACT

Objectives: The use of antimicrobial prophylaxis to prevent surgical site infections (SSI) is well established. This study examined the association of adherence to antimicrobial prophylaxis for clean neurosurgeries with post-operative surgical site infection (SSI) rates.

Methods: A retrospective descriptive study was conducted at the Philippine General Hospital (PGH) among pediatric patients who underwent clean neurosurgical procedures between January 1, 2018 – December 31, 2019. The outcome measured was the development of SSI. Univariate and multivariate analysis was performed to show the association of risk factors with SSI. Compliance to existing antibiotic prophylaxis recommendation was assessed.

Results: One hundred eighty-nine (189) medical charts were reviewed. Overall prevalence of SSI was 9.5% and fever was the most common initial symptom of SSI. *Staphylococcus species* was identified from cultures of surgical sites, consistent with existing literature, however gram-negative organisms including multidrug-resistant organisms (MDRO) were noted. All cases received prophylactic antibiotics, but adherence to all parameters (antimicrobial choice, dose, timing, route, re-dosing and duration of prophylaxis) was low at 7.9%. Appropriate antibiotics were prescribed in only 15.9% and antibiotics were discontinued beyond 24 hours post-surgery in 45.5% of cases. Patients who received a regimen fully compliant with antimicrobial prophylaxis recommendations did not develop SSI.

Conclusion: Adherence to existing antimicrobial prophylaxis protocol for neurosurgeries is low at 7.9%. Patients who received a regimen fully compliant with the recommendations did not develop SSI. Interventions to improve compliance to antimicrobial prophylaxis guidelines are needed.

KEYWORDS: *Surgical Site Infection, Adherence, Clean Neurosurgery, Prophylaxis*

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INTRODUCTION

Surgical site infections (SSI) are one of the most feared hospital-acquired infections in neurosurgery because of their potentially serious consequences and complications and increased morbidity & mortality.[1] SSI is associated with a 3% mortality rate, 75% of which are directly attributable to infection. It is also the most expensive type of hospital-acquired infection with an estimated annual expense of 3.3 billion US dollars.[2,3] Cost-effective strategies are continuously being developed to meet these challenges. Among infection control practices that have been implemented to decrease infection rates, surgical antimicrobial prophylaxis (SAP) has been shown to prevent SSI and has the potential to reduce complication rates and costs. Evidence-based recommendations on the use of SAP are still lacking, especially in clean neurosurgeries, where risk of infection is reported to be low (1-2%).[1,4] Current guidelines in the pediatric population were largely derived from adult neurosurgical studies.[1] One study by Korinek, et al. concluded that prophylaxis is effective in preventing SSI in low risk patients.[5] The presence of risk factors, which include age, nutritional status, immunosuppression, length of pre-operative stay and intra-operative factors, have also been cited as reasons for antimicrobial prophylaxis.[6]

A study conducted at the Philippine General Hospital (PGH) by Dy-Pasco, et al. in 2014 looked at surgical site infection among pediatric patients after clean neurosurgeries. Overall prevalence rate of SSI was 11.26%. Recommendations for antimicrobial prophylaxis for clean neurosurgeries were implemented at PGH last October 2013 by the sections of Neurosurgery and Infectious and Tropical Diseases in Pediatrics. Adherence to this guideline for pre-operative antibiotic use was low at 23.5%.[7] There is increasing concern about clinicians' compliance with current SAP recommendations. Adherence rates were unsatisfactory in industrialized countries like Japan, United Kingdom and the Netherlands.

Inappropriate timing, antibiotic selection and prolonged duration of antibiotic administration have been described. It was also noted that surgeons were accustomed to making decisions based on their own experiences and was counterintuitive for them to accept guidelines.[8]

Data obtained from this study may aid in identifying patients at risk for surgical site infection. Prevalence of surgical site infection in clean neurosurgical procedures and adherence to existing antimicrobial prophylaxis guidelines in the institution as part of continuing surveillance for hospital-acquired infection (HAI) was likewise evaluated.

METHODOLOGY

Study Design

This was a two year retrospective chart review of clean neurosurgeries done at the Departments of Pediatrics and Neurosurgery of the Philippine General Hospital from January 1, 2018 to December 31, 2019.

Study Population and Sample Size

Pediatric patients less than 19 years old who underwent elective clean neurosurgical procedures were included. Patients with a previous operation with an interval of more than 90 days from last operation were also included. Excluded were those admitted for an operation but with documented infection, those with multiple surgeries involving other organ systems, and those with a diagnosis of SSI from another hospital. Sample size was based on an 11.26% overall prevalence as reported by Dy-Pasco in 2014.[7] A minimum of 69 patients was required for the study.

Data Collection

A list of pediatric patients who underwent clean neurosurgical procedures (such as placement of ventriculo-peritoneal shunt, ommaya reservoir, craniotomy, craniectomy, tumor excision & spinal surgery) was obtained from the Department of Neurosurgery.

Clinical profile, risk factors and outcomes were collected for each patient. Demographic data obtained were age, gender, weight and nutritional status. Other risk factors were categorized as follows:

(1) Pre-operative Factors included location prior to surgery, number of pre-operative hospital stay before operation, diagnosis, previous neurosurgical operation, co-morbidities, ASA score, past infections, use of pre-operative steroids and previous chemotherapy or radiotherapy; and
(2) Intra-operative Factors included type of surgery, intra-operative antibiotic doses given, location of surgery and total duration of surgery from cutting time to finish time.

Surgical site infection was identified based on symptom onset from date of surgery where date of procedure was counted as day 1. Symptoms evaluated were fever, shunt tract swelling, vomiting, mental status changes, purulent discharge from the surgical site and shunt erosion through the wound or skin. It was classified as superficial incisional, deep incisional and organ/space SSI according to the criteria set by the Centers for Disease Control and Prevention (CDC).[2,7]

Microorganisms isolated in CSF cultures of patients with SSI were identified. For those with absence of growth from CSF, SSI was considered if there was presence of purulent discharge, abscess or erosion from the wound and signs and symptoms as previously mentioned. Outcome of patients with SSI was determined as either 1) discharged improved or 2) expired.

Adherence to antimicrobial prophylaxis was evaluated and classified as compliant if the case satisfied all conditions as listed in the current institutional guidelines and non-compliant if the case did not satisfy all conditions. Specific components of the guidelines are the following:

(1) Oxacillin is recommended for patients admitted for <3 days with no infection before operation; for patients who stayed in the hospital for ≥3 days, or were previously treated for a hospital-acquired infection, either cefuroxime plus amikacin or cefazolin plus amikacin are recommended.
(2) Antibiotics should be administered within 60 minutes before skin incision, with re-dosing administered for procedures longer than 4 hours.
(3) The recommended prophylaxis is either a single dose or continuation of the antibiotic for less than 24 hours.[7,9]

Data Analysis

Data was gathered using standard data collection forms, entered into an Excel database and subjected to descriptive analysis. Frequency and proportion were used for categorical variables; median and inter quartile range were used for non-normally distributed continuous variables. Mann-Whitney U test and Fisher's exact/chi-square test were used to determine the difference of rank and frequency respectively, between patients with and without surgical site infection. Odds ratios and corresponding 95% confidence intervals from binary logistic regression were computed to determine significant factors for surgical site infection. All statistical tests were two tailed tests. The Shapiro-Wilk test was used to test the normality of continuous variables. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at 0.05 α-level of significance. STATA 13.1 was used for data analysis. The study was submitted and approved by the University of the Philippines Manila Research Ethics Board (UPMREB).

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RESULTS

Demographics of the Target Population

A total of 189 pediatric patients were admitted at the PGH between January 1, 2018 to December 31, 2019 who fulfilled the inclusion criteria. Demographic data are presented in Table 1. Majority of patients in this series were infants between 1 month to 1 year of age, with a median age of 5 years old.

Most patients who developed SSI were children 2-9 years old and most had normal nutritional status. Malnutrition did not seem to pose an additional risk for the development of infection as 50 of 57 patients (88%) who were underweight/wasted or overweight/obese did not develop SSI.

Table 1. Demographic and Clinical Profile of Pediatric Patients who underwent Clean Neurosurgical Procedures

Parameter	With SSI (n=18)	Without SSI (n=171)	Total (n= 189)
Median age in years, IQR	6.5, IQR = 4 to 13	5, IQR = 0.58 to 12	5, IQR = 0.58 to 12
Neonates (0-30 days)	0	12 (7.0)	12 (6.4)
Infants (1mo-1 year old)	3 (16.7)	60 (35.1)	63 (33.3)
Children (2-9 years old)	9 (50.0)	45 (26.3)	54 (28.6)
Adolescent (10-18 years old)	6 (33.3)	54 (31.6)	60 (31.8)
Sex, in frequency (%)			
Male	10 (55.6)	88 (51.5)	98 (51.8)
Female	8 (44.4)	83 (48.5)	91 (48.2)
Median weight in kg, IQR	20.8, IQR = 13.5 to 29	14.8, IQR = 8.7 to 33	16.5, IQR = 8.8 to 32.6
Median height in cm, IQR	118, IQR = 102 to 148	108, IQR = 8 to 140	108.5, IQR = 70 to 140
Median BMI, IQR	15.6, IQR = 13.9 to 17.4	17.2, IQR = 14.3 to 20.4	16.8, IQR = 14.1 to 20.1
Nutritional status, in frequency (%)			
Normal	11 (61.1)	108 (63.2)	119 (63.0)
Underweight	0	3 (1.8)	3 (1.6)
Wasted	5 (27.8)	23 (13.4)	28 (14.8)
Overweight	1 (5.6)	14 (8.2)	15 (7.9)
Obese	1 (5.6)	10 (5.8)	11 (5.8)
Incomplete/inconclusive	0	13 (7.6)	13 (6.9)

Pre-operative Risk Factors

Pre-operative risk factors are shown in Table 2. The most common area where patients were admitted prior to surgery was at the Neurosurgery Ward (Ward 6).

This was also where most SSI cases developed. Of the 23 patients who were admitted at the ER prior to their procedure, four (17%) developed SSI, unlike in other areas where rates were all under 10%. There is no marked difference between the SSI and non-SSI groups with respect to this variable (p-value of 0.543).

Pre-operative hospital stay was greater than 7 days in majority (36.5%) of cases, while an almost similar proportion (34.4%) were admitted between 3 to 7 days prior to the procedure. Those who stayed between 3 to 7 days in the hospital pre-operatively seemed to develop infection twice more frequently (9/65 or 14%) compared to those who stayed less than 3 days (4/55 or 7%) or more than 7 days (5/69 or 7%). However, a p-value of 0.369 for this variable indicates that there is no significant difference between groups. Most patients were diagnosed with intracranial mass, which comprised 53.7% of all cases. Majority of those who developed surgical site infection also belonged to this group, comprising 88.9% of eighteen SSI cases. There is a higher percentage of SSI cases among patients with intracranial mass (15.8%) compared to those with congenital hydrocephalus (3.1%), but the p-value (p = 0.126) for this variable is not significant.

Twenty-seven patients had a history of prior neurosurgical procedure and majority (25 patients) did not develop SSI. Of the five patients with co-morbidities, only one patient (with Cushing syndrome) developed SSI. Most cases (54.5%) had an ASA score of 2 and nine of the 18 cases who developed SSI belonged to this category. However a higher ASA score did not seem to predispose to the development of SSI, as the single patient with SSI with ASA score of 3 represented only 7.7% of the 13 patients in the group; this ratio was fairly similar to the ASA 1 (4/37 or 10.8%) and ASA 2 (9/103 or 8.7%) groups. The p-value for this variable is not significant (0.933).

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Ho JO, Ong-Lim AL. The Association of Adherence to Antimicrobial Prophylactic Recommendations for Clean Neurosurgeries with Post-operative Surgical Site Infection
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Only 7 of 189 patients had infections prior to surgery and 2 of 18 patients who developed SSI also had a previous episode of pneumonia. Pre-operative steroids were given in 24.3% of the 189 cases included in this series. Of the 46 patients who received steroids, only five (10.9%) developed SSI.

However this group also represented 27.8% of the 18 cases who developed SSI. None of the four cases who previously received chemotherapy or radiotherapy developed SSI. For the rest of the mentioned variables, the p-values were not significant.

Table 2. Pre-operative risk factors of patients with and without SSI

Parameter	With SSI (n=18)	Without SSI (n=171)	Total (n= 189)	P-value
	Frequency (%)			
Location prior to surgery				0.543
Ward 6	11 (61.1)	103 (60.2)	114 (60.3)	
Emergency room	4 (22.2)	19 (11.1)	23 (12.2)	
Ward 11	3 (16.7)	30 (17.5)	33 (17.5)	
Ward 9	0	4 (2.3)	4 (2.2)	
NICU	0	15 (8.8)	15 (7.9)	
Pre-operative hospital stay				0.369
< 3 days	4 (22.2)	51 (29.8)	55 (29.1)	
3 to 7 days	9 (50)	56 (32.8)	65 (34.4)	
≥7 days	5 (27.8)	64 (37.4)	69 (36.5)	
Diagnosis				0.126
Intracranial mass	16 (88.9)	85 (49.1)	101 (53.7)	
Congenital hydrocephalus	2 (11.1)	63 (36.8)	65 (34.2)	
Open lip schizencephaly	0	2 (1.2)	2 (1.1)	
Nasoethmoidal meningocele	0	1 (0.6)	1 (0.5)	
Postmeningitic hydrocephalus	0	4 (2.3)	4 (2.1)	
Shunt malfunction	0	8 (4.7)	8 (4.2)	
Tethered cord	0	4 (2.3)	4 (2.1)	
Syringomyelia	0	1 (0.6)	1 (0.5)	
Ruptured aneurysm	0	1 (0.6)	1 (0.5)	
Neurocutaneous melanosis	0	1 (0.6)	1 (0.5)	
Craniosynostosis	0	1 (0.6)	1 (0.5)	
Previous neurosurgical operation	2 (11.1)	25 (14.6)	27 (14.3)	1.000
Co-morbidities				0.500
Epilepsy	0	3 (1.8)	3 (1.6)	
Bronchial Asthma	0	1 (0.6)	1 (0.5)	
Cushing Syndrome	1 (5.6)	1 (0.6)	2 (1.1)	
ASA score				0.933
1	4 (22.2)	33 (19.3)	37 (19.6)	
2	9 (50)	94 (55.0)	103 (54.5)	
3	1 (5.6)	12 (7.0)	13 (6.9)	
No entry	4 (22.2)	32 (18.7)	36 (19.0)	
Past infections				1.000
Pneumonia	2 (11.1)	3 (1.8)	5 (2.6)	
Urinary Tract Infection	0	1 (0.6)	1 (0.5)	
Shunt infection	0	1 (0.6)	1 (0.5)	
Use of pre-operative steroids	5 (27.8)	41 (24.0)	46 (24.3)	0.774
Previous Chemotherapy or radiotherapy	0	4 (2.4)	4 (2.1)	1.000

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Intra-operative Details and Risk Factors

Craniotomy/craniectomy/burrholing with placement of a medical device comprised 50.3% of the clean neurosurgical procedures, as seen in Table 3. Ventriculoperitoneal shunt insertion (VPS) was the most commonly inserted medical device, accounting for 46.6% of total cases and 16.7% of SSI cases. Craniotomy/craniectomy/burrholing procedures without a medical device were performed for 83 out of 189 cases (43.9%), of which majority (65 out of 83 cases, or 78.3%) were tumor excisions. Of the 18 patients who developed SSI in this series, fourteen underwent tumor excision, three underwent VPS insertion, and one had tube ventriculostomy placement. Among the types of surgeries, there is a significant difference between the SSI and non-SSI groups (p = 0.023) and the proportion of SSI for procedures without a medical device was significantly higher (16.9%) compared with those with a medical device (4.2%).

Majority of procedures (50.8%) were performed in the Neurological and Spinal Surgery 2 (NSS 2) operating room and of the 18 cases with SSI, ten also had procedures performed in this area. There is a higher proportion of SSI in neurosurgeries done in other areas (1 in 4 cases). There is no significant difference between the two groups with respect to location or area of surgery (p-value = 0.643).

Most of the surgical procedures (79.9%) done in this series were completed within 4 hours or less. Among the 38 surgeries that took at least 4 hours to perform, seven (18.4%) developed SSI, a larger proportion compared to the 7.3% who developed SSI in the other group. Nevertheless, there is no significant difference between the two groups (p-value = 0.058).

Table 3. Intra-operative Details and Risk Factors

Parameter	With SSI (n=18)	Without SSI (n=171)	Total (n= 189)	P-value
	Frequency (%)			
Type of surgery				0.023
Craniotomy/Craniectomy/ Burrholing without medical device*	14 (77.8)	69 (40.4)	83 (43.9)	
Tumor excision	14	51	65	
Endoscopic third ventriculostomy and other biopsy procedures	0	18	18	
Craniotomy/Craniectomy/ Burrholing with a medical device	4 (22.2)	91 (53.2)	95 (50.3)	
VPS	3	85	88	
Ommaya/Becker	0	4	4	
Tube ventriculostomy	1	2	3	
Cranioplasty	0	1 (0.6)	1 (0.5)	
Spine surgery	0	10 (5.9)	10 (5.3)	
Location of Surgery				0.643
Neurological&SpinalSurgery(NSS 2)	10 (55.6)	86 (50.3)	96 (50.8)	
Pediatric Neurosurgical Craniomaxillofacial Operating Unit (PNCOU)	6 (33.3)	65 (38.0)	71 (37.6)	
Left Central Block (LCB)	1 (5.6)	7 (4.1)	8 (4.2)	
Others	1 (5.6)	4 (2.3)	5 (2.7)	
No entry	0	9 (5.3)	9 (4.8)	
Surgical time				0.058
≤ 4hrs	11 (61.1)	140 (81.9)	151 (79.9)	
> 4 hrs	7 (38.9)	31(18.1)	38 (20.1)	

Results of Univariate Analysis

The independent variables were assessed by univariate analysis as seen in Table 4. The association between these identified factors and surgical site infection was expressed as odds ratios (OR) as well as 95% confidence intervals. For risk factors with more than two categories, odds ratios were computed relative to the reference category (for example, in pre-operative hospital stay, <3 days was used as reference to the other 2 groups: 3 to 7 days and >7days).

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Other odds ratios were computed based on presence or absence of specific variables, such as diagnosis, presence of medical device and pre-operative antibiotics. Univariate test of any variable resulting in a p-value of <0.05 was used as a candidate for multivariate analysis. It was determined that intracranial mass, type of surgery and duration of surgery were significant factors in the univariate analysis.

Based on the odds ratios and statistically significant p-values obtained, patients diagnosed with intracranial mass were 9 times more likely to have surgical site infection (OR 9.3, 95% CI 1.85 to 37.14, p = 0.006) as compared to those who were not diagnosed to have intracranial mass. Moreover, patients with >4 hours of surgery time were 2.9 times more likely to have surgical site infection (OR 2.9, 95% CI 1.03 to 8.00, p = 0.043) as compared to those who had a surgical time of ≤4 hours.

Presence of VPS may be a protective factor for SSI (OR 0.20, 95% CI 0.06 to 0.72, p = 0.014) as shown in the univariate analysis. This is consistent with the results in those who underwent craniotomy/craniectomy/burrholing with medical devices (OR 0.22, 95% CI 0.07 to 0.69, p = 0.009). Results from multivariate analysis was not significant due to lack of significant covariates left within the model. Other factors such as age, pre-operative hospital stay, previous neurosurgical operation, ASA score, use of pre-operative steroids, pre-operative antibiotics and location of surgery did not reach any significance.

Patients with Surgical Site Infection

Eighteen of 189 patients had post-operative surgical site infection and fever was the most common presenting symptom in 13 (72.2%) patients, occurring at a median time of 6 days post-surgery. Two cases presented with cerebrospinal fluid leakage, one case initially presented with vomiting, while the other case presented with erythema and purulent discharge on the surgical site.

Table 4. Risk Factors with Univariate Analysis

Parameter	Crude Odds ratio	95% CI	P- value
Age (years)			
Neonates (0-30 days)	(reference)		
Infants (1mo-1year old)	0.45	0.11 to 1.89	0.275
Children (2-9)	1.8	0.60 to 5.44	0.298
Adolescent (10-18)	-	-	-
Pre-operative hospital stay			
< 3 days	(reference)		
3 to 7 days	2.05	0.59 to 7.06	0.256
> 7 days	1.00	0.25 to 3.90	0.996
Diagnosis			
Congenital hydrocephalus	0.21	0.05 to 0.96	**0.044**
Intracranial mass	9.29	1.85 to 37.14	**0.006**
Previous neurosurgical operation	0.73	0.16 to 3.37	0.687
ASA score			
1	(reference)		
2	0.79	0.23 to 2.74	0.710
3	0.69	0.07 to 6.78	0.748
No entry	1.03	0.24 to 4.48	0.967
Use of preoperative steroids	1.22	0.41 to 3.63	0.721
Pre-operative antibiotics			
Cefuroxime	1.35	0.48 to 3.78	0.564
Cefuroxime + Amikacin	0.61	0.17 to 2.23	0.458
Ceftriaxone	1.70	0.45 to 6.44	0.435
Type of surgery			
Craniotomy/Craniectomy/ Burrholing without a medical device	(reference)	-	-
Craniotomy/Craniectomy/ Burrholing with a medical device	0.22	0.07 to 0.69	**0.009**
Presence of VPS	0.20	0.06 to 0.72	**0.014**
Location of surgery			
NSS2	1.24	0.46 to 3.28	0.671
PNCOU	0.82	0.29 to 2.28	0.697
LCB	1.38	0.16 to 11.88	0.770
Others	2.46	0.26 to 23.24	0.433
Surgical time			
≤ 4hrs	(reference)	-	-
> 4 hrs	2.87	1.03 to 8.00	**0.043**

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Outcomes of SSI

Majority of patients had organ/space SSI such as meningitis (7 cases) and ventriculitis (9 cases). There was one case of superficial incisional SSI and another case of deep incisional SSI where MRSA was identified from an abscess at the surgical site. Nine cases were readmitted due to SSI. Eight cases had nosocomial infections post-operatively (pneumonia, sepsis and urinary tract infections).

Outcomes of SSI are presented in Table 5. One case of SSI expired due to brain herniation secondary to acute parenchymal hemorrhage, *Acinetobacter baumanii* multidrug-resistant organism *(*MDRO) ventriculitis and sepsis. The rest improved with antibiotics and were all discharged.

Table 5. Outcomes of Surgical Site Infection

Outcome	Frequency (%) (n = 18)
Discharged, improved	17 (94.4%)
Expired	1 (5.6%)

The characteristics of infecting microorganisms are presented in Table 6 together with their corresponding culture sites. In three cases, *Staphylococcus* species was seen on cultures obtained on initial operation, while gram-negative microorganisms and MDROs were seen on succeeding operations. Three patients had 2 microorganisms isolated (*Staphylococcus hemolyticus and Acinetobacter baumanii* (MDRO), *Staphylococcus epidermidis* and *Stenotrophomonas maltophilia,* and *Staphylococcus epidermidis* and *Klebsiella pneumoniae* (MDRO)) in their cultures. Fifty percent of cases were culture-negative.

Prevalence of SSI and Adherence to Antibiotic Prophylaxis

The overall prevalence of SSI in this study is 9.5% (Table 7). Cases were considered fully compliant if parameters such as choice of antibiotic, dose, route, timing, re-dosing and duration of prophylaxis were followed based on the current recommendations.[7] All patients who received an antibiotic regimen fully compliant with the recommendations did not develop SSI.

Table 6. Characteristics of Infecting Organisms

Organism	Site	No. of organisms*
Initial operation during time of admission		
Staphylococcus aureus (methicillin-sensitive) -- 1 (methicillin-resistant) -- 1	Subgaleal fluid Abscess	2
Staphylococcus hemolyticus (methicillin-resistant)	Subgaleal fluid	1
Succeeding operations during time of admission		
Staphylococcus epidermidis (methicillin-resistant)	Cerebrospinal fluid	2
Klebsiella pneumoniae (MDRO)	Cerebrospinal fluid	3
Acinetobacter baumanii (MDRO)	Cerebrospinal fluid	1
Stenotrophomonas maltophilia	Cerebrospinal fluid	1
Pseudomonas aeruginosa	Cerebrospinal fluid	1
Burkholderia cepacia	Cerebrospinal fluid	1
Culture – negative		9

*Three patients had 2 microorganisms isolated in their cultures.

Table 7. Surgical Site Infections According to Adherence to Recommended Regimen

Compliance	Number of surgeries	SSI cases	Infection rate (%)
Compliant	15	0	0%
Non-compliant	174	18	10.3%
Total	**189**	**18**	**9.5%**

Several parameters were assessed between those with and without SSI with respect to adherence to antibiotic prophylaxis (Table 8). All patients were given antibiotic prophylaxis intravenously.

Only 15.9% of cases were given appropriate pre-operative antibiotics based on existing institutional recommendations. Cefuroxime and ceftriaxone were the two most commonly used antibiotics among non-compliant cases. The rest were given antibiotics such as cefotaxime, meropenem or a combination of ceftazidime and oxacillin, ceftriaxone and metronidazole, or cefuroxime and oxacillin.

With regards to dosage, majority were given the correct dose; however, there were some cases where antibiotics were underdosed or overdosed.

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Pre-operative antibiotics were also given at the appropriate time (within 60 minutes prior to surgical incision) in 88.4% of cases. Administration of appropriate intra-operative doses was also noted in most cases. Post-operatively, antibiotics were discontinued within 24 hours of surgery in 45.5% of cases. The most common duration of antibiotics was 2 days, followed by 3 and 7 days, respectively. Except for overall compliance rate, there were no significant differences seen in all parameters between those with SSI and those without. Adherence to pre-operative antibiotic recommendations for clean neurosurgery was low at 7.9%.

Table 8. Parameters of Compliance in Antibiotic Prophylaxis between Patients with or without SSI

Parameters	SSI (N= 18)	Without SSI (N= 171)	Total (N = 189)
	Frequency, (%)		
Prophylaxis given	18 (100%)	171 (100%)	**189 (100%)**
Antibiotic type			
Correct choice	3 (16.7)	27 (15.8)	**30 (15.9)**
Dosing			
Correct dose	1	21	22
Under dose	1	2	3
Over dose	1	4	5
Route - Intravenous	18 (100%)	171 (100%)	**189 (100%)**
Timing			
within 60 minutes	17 (94.4)	150 (87.7)	**167 (88.4)**
> 60 minutes	1 (5.6)	14 (8.2)	**15 (7.9)**
At surgical incision time	0	1 (0.6)	**1 (0.5)**
After incision time	0	6 (3.5)	**6 (3.2)**
Intra-operative			
Not needed and not given	10 (55.6)	134 (78.4)	**144 (76.2)**
Needed and given	3 (16.7)	11 (6.4)	**14 (7.4)**
Needed but not given	4 (22.2)	16 (9.4)	**20 (10.6)**
Not needed, but still given	1 (5.6)	10 (5.9)	**11 (5.8)**
Post-operative			
Discontinued antibiotics within 24 hours after end of surgery	7 (38.9)	79 (46.2)	**86 (45.5)**
Full Compliance	0%	7.9%	**7.9%**

DISCUSSION

There are published studies on compliance to guidelines on antibiotic prophylaxis from many countries. However, not all considered compliance to all aspects of the guidelines. It remains to be a challenge worldwide to implement proper surgical antimicrobial prophylaxis as it requires knowledge of international recommendations and repeated evaluation of guidelines.[10]

In our study, the presence of fever was the most common symptom seen among SSI patients, consistent with findings from previous studies where fever in the absence of another clear source of infection was suggestive of CSF shunt infection.[11] Fever was the most common symptom for patients who developed post-operative infections.[7,11-12]

Several published studies reported that risk factors for SSI are still unclear and conclusions vary.[12,13] Although this study showed that intracranial mass, duration of operation (in hours) and type of surgery were independent risk factors for the development of SSI in the univariate analysis, these were not statistically significant in the multivariate logistic regression model. Majority of patients with SSI were diagnosed with intracranial mass who also underwent craniotomy, craniectomy or burrholing procedures without a medical device, which were mostly tumor excision cases. Intracranial mass as a risk factor for SSI is also consistent with other studies which show that meningioma, brain metastasis surgery and intracranial malignant lesions are risk factors for SSI.[5,14]

The larger proportion of SSI cases in surgeries done for >4 hours support that duration of surgery is a significant risk factor. In a study by Korinek, et al. which looked at risk factors for neurosurgical site infections after craniotomy, duration of surgery was confirmed to be an independent risk factor which may indicate difficulties in surgery, surgeon expertise and occurrence of intra-operative complications.[5]

Patients with a medical device generally have higher SSI rates as described by Simon, et al. (11%), Kulkarni, et al. (10.4%) and Claus, et al. (1.5% to 38%).[12,15-16] However in this study, presence of VPS appears not to be a risk factor for SSI. It is important to note that congenital hydrocephalus cases accounted for the most number of VPS insertion cases and majority of them also had surgeries in ≤4 hours.

With regards to causative microorganisms, intra-operative cerebrospinal fluid (CSF) sample collection was not done routinely during initial operation in SSI patients, especially in those who underwent tumor excision. The need to obtain samples was driven by clinical judgement, especially when patients showed signs and symptoms of surgical site infection. It was suggested in a study by Chidambaram to perform fixed intervals for CSF analysis post-operatively to more closely follow trends.[17] In some cases, since cultures were only obtained in succeeding operations, it was hard to assess whether the microorganism was already present during the initial operation.

The organisms obtained on initial operation were consistent with pathogens commonly identified as a complication of clean neurosurgical procedures (gram positive organisms such as *Staphylococcus aureus* or other coagulase-negative *Staphylococci*).[5,18] The presence of hospital-acquired gram negative organisms and MDRO can be explained by the occurrence of other nosocomial infections in SSI patients. Prolonged and inappropriate prophylactic antibiotics have been associated with the occurrence of nosocomial infections and the development of multidrug-resistant organisms.[1,19-20]

For outcomes of SSI patients in this study, one expired due to post-operative complications, accounting for a 5.6% SSI-related mortality. The relatively higher rate, compared to 3% as described in other large sample studies, can be attributed to the smaller sample size used in the study.[3] Patients who develop SSI have a 2 to 11 times higher risk of death compared to patients without an SSI.[3]

There is increased morbidity, mortality, length of hospital stay and cost due to SSI, particularly from post-operative infections in neurosurgery.[21]

Prevalence of SSI

The prevalence of SSI in clean neurosurgical procedures in this study was 9.5%, compared to the 1-2% prevalence rate reported in literature. Other studies report lower prevalence from 1-8% after cranial surgery. No other related large pediatric studies were done correlating efficacy of antibiotics to prevent SSI in low-risk craniotomies. The value we obtained may be higher compared to published literature due to our small sample size, as compared to other studies which involved larger samples who were mostly adults.[1,5] Most SSI patients were also diagnosed with an intracranial mass who had tumor excisions which lasted >4 hours which may explain the calculated rate. The current rate we obtained, however, is slightly lower than the prevalence rate reported by Dy-Pasco, et al. in 2014 at 11.3%.[7]

Adherence

Many factors may affect the low adherence to the recommended antibiotic prophylaxis regimen. In a previous study by Dy-Pasco, et al. in 2014, low adherence to recommended pre-operative antibiotics was also noted at 23.5%, however, the study did not look at other parameters such as dose, route, timing, re-dosing and duration of prophylaxis.[7] A medical records-based, cross-sectional study done in 2015 at Philippine General Hospital by Nabor, et al. looked at compliance with international guidelines on antibiotic prophylaxis and showed that only 13% conformed to all parameters, but this involved other types of elective surgeries.[22] There is a wide variation in overall compliance to guidelines ranging from 0% to 71.9%.[23] According to literature, compliance seems to be lower in neurosurgery than in other procedures.[24-27] Among the various parameters in surgical prophylaxis, inappropriate choice of antibiotic and prolonged duration of administration are the two most common areas for non-compliance seen among the cases analyzed in the study, also consistent with previous studies.[23]

Administration of a single agent cefuroxime accounted for majority of cases demonstrating non-compliance and inappropriate antibiotic use when compared with recommendations, but the use of broad spectrum pre-operative antibiotics, such as ceftriaxone and ceftazidime, were also described.

One study showed that third-generation cephalosporins failed to show superiority over conventional regimens on both incisional and organ related SSI in neurosurgery and mentioned that its use has been associated with resistance to gram negative pathogens.[21] Most studies report an adherence rate of less than 70% with respect to antibiotic selection and the main discord was use of broader spectrum agents than what is recommended.[23]

Post-operatively, most antibiotics were not discontinued within 24 hours after surgery. It was noted that physicians continued antibiotics while awaiting final intra-operative cultures. In majority of cases, reasons for extending antibiotics were not documented. Early post-operative fever is also a concern. This is said to be non-infectious but it is one of the reasons why majority of non-compliant cases continued antibiotics up to 48-72 hours post-surgery.[28] Most studies show less than 50% compliance to duration of antimicrobial prophylaxis but higher compliance to dose and indication.[23,25-26,29] This is consistent with our study which showed a 45.5% compliance rate on this parameter. This poses a huge problem as prolonging antibiotics contributes to antibiotic resistance and predisposes to *Clostridium difficile* infections.[24]

Greater compliance was observed in terms of antimicrobial indication, dose, number of intra-operative doses and timing of prophylaxis, which is also consistent with other studies.[24] Compliance to existing antibiotic prophylaxis recommendation is still encouraged as those who adhered to all parameters did not develop SSI.

This study had several limitations as this involved data collection through chart review. Several sources of bias may be present owing to inaccurate documentation resulting in poor quality of data. A number of patients were also excluded from the data analysis since charts were incomplete or missing. The height of some patients were not documented which affected accurate calculation of BMI.

Patients who had post-operative surgical site infection but were seen at another hospital and those who did not follow up were also not accounted for, which may cause an underestimation of infected cases. Patients who were seen at the outpatient clinic who had SSI were also excluded, as there was no accurate documentation of cases.

CONCLUSION

Adherence to existing pre-operative antimicrobial prophylaxis for neurosurgery is problematic and low in our setting. Except for compliance rates, there were no significant differences in adherence to parameters of antibiotic prophylaxis between patients who had SSI and those who did not. Patients who received an antibiotic regimen fully compliant with the recommendations did not develop SSI. Increased compliance to existing antibiotic prophylaxis recommendation is still desired.

RECOMMENDATIONS

It remains challenging to ensure that surgeons fully adhere with existing guidelines on antibiotic prophylaxis. Interventions to improve compliance are necessary, such as close collaboration with the pediatric infectious disease specialists, hospital infection control unit, neurologists, neurosurgeons and the healthcare staff involved in the neurosurgical operation.

Continuing education on surgical prophylaxis emphasizing rationale use of antibiotics to increase awareness on existing guidelines and updates on local resistance rates, including antimicrobial stewardship, should be regularly done. Studies exploring factors influencing adherence to guidelines may be conducted. Timely follow-up of intra-operative cultures is also necessary to immediately identify SSI and prevent inappropriate use of antibiotics leading to resistant organisms.

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