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EDITORIAL

Of Hurdles, Battles, and The Art of War

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This issue marks our first for 2019. A bit way past our target date but worth the wait.

There were many hurdles to contend with as with previous issues. There were limited manuscript submissions, limited time, limited budget, limited manpower. Only the hurdle list is limitless and goes on and on.

We are not disheartened. We have engaged and collaborated with other Medical Journal Editors through scientific meetings, ventured into Journal Editing and Peer Review Workshops, and revisited basic Evidence-based Medicine Courses. All these in the first two quarters of 2019, as we pave a smoother road to Scopus.

These hurdles are nothing compared to real battles presented in this issue:

The fight with HIV in the Philippines exists. A study on "The Epidemiology and Outcome of Children Living with HIV in a Tertiary Hospital" is presented. Related to this, "The Effectiveness of digital media Technology-based Interventions on HIV & STI Risk Reduction Among Young People" is shared.

The struggle with Antimicrobial Resistant organisms is felt through "The Clinico-Epidemiologic Profile and Outcome of Pediatric Patients with Multi drug Resistant Gram-Negative Healthcare Associated Infections."

The scuffle with Sepsis is something to take on. Studies on "The Duration of Preterm Premature Rupture of Membranes as Predictor of Histologic Chorioamnionitis and Early Onset Neonatal Sepsis" and "Effectiveness of Daily Chlorhexidine Bathing in Reducing Healthcare-Associated Infections in the Pediatric Intensive Care Unit" are unveiled.

The brawl with Pneumonia is not to be left out through the study on "Comparison of Various Methods of Detection of Hypoxemia and Correlation of Hypoxemia with Clinical Features among Pediatric Patients with Community Acquired Pneumonia."

Lastly, as the dengue saga continues, we put forth a Dengue Disease Awareness Bulletin and Campaign for Pediatricians from the Philippine Pediatric Society and the Pediatric Infectious Disease Society of the Philippines. In time, we hope to win the real war against dengue.

Too many hurdles to overcome, too many battles to win, but as Sun Tzu in The Art of War said, "If you know the enemy and you know yourself, you need not fear the result of a hundred battles."

ORIGINAL ARTICLE

EFFECTIVENESS OF DIGITAL MEDIA TECHNOLOGY-BASED INTERVENTIONS ON HIV & STI RISK REDUCTION AMONG YOUNG PEOPLE: A META-ANALYSIS

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

3RD PRIZE 2019 PIDSP RESEARCH CONTEST

ABSTRACT

Background: Prevention strategies delivered through digital media technology (DMT) have been developed to reduce HIV incidence among young people. However, no best-practice DMT intervention strategies exist in handling HIV prevention programs among young people.

Objectives: To determine the effectiveness of DMT-based interventions in reducing risk-taking behaviours among young people that may predispose them to acquiring HIV and other sexually transmitted infections.

Subjects and Selection Criteria: Randomized controlled trials and quasi-experimental studies with rigorous controls comparing DMT-based interventions and controls on reducing risk-taking behaviors among young people aged 10-24 years were included.

Data Collection: Search methods were done on the following: MEDLINE, CENTRAL, Trials Register, Google Scholar, ScienceDirect, TRIP database, HERDIN, reference lists, & local databases until December 2017.

Analysis: Statistical analysis was done using Review Manager Version 5.3, heterogeneity examined, and analyses done under random effects model. Condom use, sexual behavior, number of sexual partners, STI testing, and sexual health knowledge in standardized effect sizes were calculated with 95% confidence intervals. Data were analyzed in subgroups: *Didactics*, *Modules*, *Virtual decision-making*.

Main Results: Identified sixteen studies with 7925 subjects comparing DMT interventions and controls. DMT interventions significantly increased condom use (d=0.29, 95% CI 0.18-0.41; p<0.00001), particularly in *Didactics* subgroup; and decreased frequency of sexual behavior (d=0.16, 95% CI 0.06-0.26; p=0.002), particularly in *Virtual decision-making* subgroup. Data significant but heterogeneous for improved sexual health knowledge. There was no statistical difference for decreased number of sexual partners and STI testing.

Conclusions: DMT-based interventions on condom use and frequency of sexual behavior were noted to be effective in reducing risk-taking behaviors among young people. These findings can be appropriately adapted for use in HIV/STI prevention campaigns.

KEYWORDS: *Digital media, HIV, STI, Adolescents*

INTRODUCTION

The Philippines is one of the seven countries that showed a dramatic increase in the number of new HIV cases. According to the HIV/AIDS & ART Registry of the Philippines (HARP), over 62,029 cases of HIV were reported since the year 1984 to December 2018. There is an average of 32 newly diagnosed cases of HIV per day, which are largely concentrated among key populations with risky behaviors, including unprotected sexual contact (mainly male-to-male). The youth age group (15-24 years old) comprises 29% of the reported cases and is the second highest new-case age range in the Philippines.[1]

Several activities have been implemented to campaign for HIV risk reduction including the development of National HIV Strategy Framework for Children and Young People, behavior change interventions, and school-based campaigns.[2] Various organizations in the Philippines, including Save the Children, Love Yourself PH, and the AIDS Society of the Philippines, have been tirelessly advocating for the prevention and treatment of HIV through raising awareness, highlighting the power and influence of social media, community involvement and advocacy through special events, and direct hands-on volunteer assistance.[3,4,5] To reduce the incidence of HIV among adolescents, interventions have been developed which range from broad factual discussions on HIV, instructional demonstrations on condom use, or motivational group sessions through various platforms including digital media. These digital media interventions would include programs delivered through webpages, texts, instant messaging programs, computer media technology, and mobile applications.[6,7,8,9] In a study by Daher *et al.* 2017, these digital media interventions work via various methods that includes simulations and role playing games that mimic certain key conditions and decision points prior to engaging in sexual encounters, social media interactions, avatar-guided computer programs, mobile apps, streamed soap opera videos, and combined innovations.[10] It may also include videos of vignettes of HIV+ individuals on how HIV affected their lives, interactive quizzes, online exercises and games, audio presentations, and modules on sexual and reproductive health.[11] These interventions work via presentation of key sexual risk reduction strategies through modules, didactic approaches, or real-life simulations. However, there are no best-practice intervention strategies yet that are unified in handling HIV awareness among adolescents and the youth.

Digital media technology-based interventions might work in HIV prevention programs for at-risk populations due to their low cost of delivery, customization of content and flexible dissemination with anonymity and privacy. Digital media has been found to be cost-effective and that they meet the complex needs of the underserved populations living with (or at a high risk of having) HIV/AIDS.[12] Among a variety of at-risk populations, computer-based interventions were found to hold promise in increasing the use of condoms and reducing sexual activity, number of sexual partners, and incident sexually transmitted infections, and were similar to commonly used human-delivered interventions in HIV prevention.[8] Digital media also work via creating a safe space for individuals to view materials, educate themselves, and address their concerns while maintaining anonymity and privacy.[13]

Heightened responsiveness in combination with behavioral control immaturity in adolescence contribute to making risky decisions.[14] The fact that there is a disproportionate HIV burden falling on this critical stage calls for the need of successful interventions critical to decrease risk of HIV and other sexually-transmitted infections (STI). Due to vastly expanding list of studies on various interventions in the reduction of HIV acquisition worldwide, especially in the dawn of new digital media technology-based interventions, it is useful to determine which intervention is effective and can

be adapted for use in HIV risk reduction campaigns for adolescents and youth. Recent randomized controlled trials have small samples and have low power to assess behavioral change, and this meta-analysis can possess more power to detect effects than individual studies.[15] This could also provide basis in establishing policies to utilize digital media in the implementation of HIV awareness, prevention, and risk reduction programs for adolescents and youth.

OBJECTIVES

The general objective of this meta-analysis is to determine the effectiveness of digital media technology (DMT)-based interventions in reducing risk-taking behaviors among young people that may predispose them to acquiring HIV and other STIs.

The specific objectives include determination of the effectiveness of DMT-based interventions in (1) improving intentions and actual condom use; (2) decreasing the frequency of sexual behavior or increase in delay in sexual activity (abstinence); (3) decreasing number of reported sexual partners (4) increasing STI testing measured through tests taken or indirectly through positive STI tests; and (5) improving sexual health knowledge, especially on HIV/AIDS awareness among young people.

METHODS

Criteria for considering studies for this meta-analysis

Types of studies - eligible studies are randomized controlled trials (RCTs) or quasi-experimental studies with rigorous controls.

Types of participants - young people (adolescents and youth), at least 10 to 24 years of age (comprising most of the population) or those who are at pre-tertiary level of education, regardless of sex and race with unknown HIV serostatus or HIV-negative individuals.

Types of interventions - interventions of interest involve digital media technology in the development or delivery of interventions that advocate HIV and STI risk reduction through educational, psychosocial, or behavioral approaches. Digital media technology-based interventions included prevention strategies delivered though computer-based or internet-based interventions, text/SMS-based strategies, desktop or laptop computers, mobile applications, interactive videos, telecommunication, videogames, or other digital media technology (DMT)-based approaches. Included studies tested the effectiveness of these DMT-based interventions on modifying sexual risk behaviors.

Types of outcome measures - studies with these outcomes should also provide the necessary information needed to calculate effect sizes.

Primary outcome - increase in measured actual condom use or intention to use condoms among study participants after exposure to intervention.

Secondary outcomes - (1) sexual behavior in terms of decrease in frequency or in terms of increased delay or abstinence; (2) decrease in number of partners involved in sexual activity; (3) increase in number of tests taken for detection of sexually transmitted infections other than HIV; and (4) improved sexual health knowledge.

Search methods for identification of studies

This meta-analysis employed search for relevant studies through several strategies. Studies that matched selection criteria and that were available as of December 2017 were included.

Electronic searches - search employed electronic reference databases, including: (1) PubMed/MEDLINE (2) ScienceDirect (3) Google Scholar (4) Turning Research into Practice (TRIP) database (5) Cochrane Review - CENTRAL (6) Trials Register and (7) Health Research and Development Information Network - HERDIN.

Requests were sent to researchers asking for copies of their papers applicable to this meta-analysis. Articles included in the reference sections

of existing list of articles were likewise searched. Local mobile applications and possible studies related to such apps were also searched.

Data Collection and Analysis

Selection of studies - search results were then merged using a reference management software (Mendeley Desktop v1.18) and it was ensured that no study was inadvertently included more than once in the meta-analysis. Titles and abstracts were examined to remove obviously irrelevant reports. Full texts of the potentially relevant reports were then retrieved and compiled. Each of the studies in the existing compilation were examined for compliance with the eligibility criteria by at least two authors to reduce the possibility of discarding relevant reports.[16] Disagreements were resolved through correspondence and discussion.

Data extraction and management - data from each of the selected studies were abstracted and coded into an electronic data spreadsheet (Microsoft Excel) and saved to file (and cloud for backup). Features included in the record included source details, eligibility and reasons for exclusion, sample demographics, type of DMT intervention used and details, methodological characteristics including research study design and type of comparison group, and outcomes assessed. Most of the data were derived from reports. The coders (authors) met to discuss each article after coding for any discrepancies. Intercoder reliability (Cohen's kappa statistic) was calculated to assess agreement between the authors. A value of κ = 0.69 was achieved, denoting substantial strength of intercoder agreement.[17]

Assessment of risk of bias in included studies - methodological quality to detect risks of bias was assessed independently by the review authors. Criteria outlined in the Cochrane Handbook for Systematic Reviews of Intervention[18] were followed. The following were assessed accordingly and stratified to low risk, high risk, or unclear: (1) sequence generation; (2) allocation concealment; (3) blinding; (4) incomplete outcome data; (5) selective reporting bias; and (6) other sources of bias. Disagreement was resolved through discussion of reviewers. If no agreement was reached, a third party was consulted.

Measures of treatment effect - effect sizes (standardized mean difference) indicated by using Cohen's *d*, were used to measure treatment effect. Cohen's *d* was used to standardize the results of studies to a uniform scale before combining,[18] hence delivering the same information regardless of the system used to obtain the observations.[19] These were calculated from data reported in each study using appropriate formulas and through the Review Manager v5.3 calculator. Effect sizes were reflected with 95% confidence intervals.

Unit of analysis issues - in cases in which more than one comparison condition exists within one study, the most minimal intervention was used to estimate "absolute" effect of the DMT-based intervention. All effect sizes were also computed using the longest-term follow-up assessment in studies with multiple follow-ups. Studies that showed DMT-based interventions outperforming controls will be given positive (+) effect sizes, otherwise they will be given negative (-) effect sizes.

Assessment of heterogeneity - in view of the clinical diversity within the set of chosen studies, a statistical test within the Review Manager v5.3 program was utilized to evaluate for heterogeneity (i.e., I^2 statistic, Chi^2 statistic). Heterogeneity was considered high when I^2 statistic exceeded 75% and Chi^2 *p* value was less than 0.1. Accurate extraction and recording of data were ensured to address clinical heterogeneity. Subgroup analysis was done to identify cause of heterogeneity.

Assessment of reporting biases - funnel plots were constructed from the intervention effect size estimates from the individual studies against its standard error. Failsafe tests were conducted and interpreted to assess reporting biases. In cases of outcomes in which there are less than ten studies available, funnel plot asymmetry tests were not

performed because their power is too low to distinguish chance from real asymmetry.[18]

Data synthesis - statistical analysis was done using Review Manager (RevMan) v5.3 software.[20] In light of the presence of clinical heterogeneity among studies in all outcomes, a random-effects model was used in this meta-analysis to avoid putting too much weight on large studies and to employ appropriate confidence intervals and p-values.

Subgroup analysis and investigation of heterogeneity - subgroup analyses were done considering the presence of clinical heterogeneity. Planned analyses in terms of sex, geographic location, and age subgroups were not feasible because specific data for each subgroup per study were not available for analysis. Subgroup analysis on main type of DMT-based intervention was used. These were categorized into:

1. *Didactics* - in which participants receive education and training through lectures delivered by videotaped actors or assisted by a counsellor through messaging systems
2. *Modules* - in which participants self-administer learning materials in pre-determined subsets of information in modular form
3. *Virtual decision-making* - in which participants encounter virtual simulations of real-life situations, decide on options and receive immediate feedback, education, and life skills.

Sensitivity analysis - sensitivity analysis was done to determine the effect of the quality of the trials without studies with high risk of bias (mostly the quasi-experimental studies).

RESULTS

Results of the Search

Extensive search through the several databases was accomplished using a pre-defined search strategy. Intervention search was intentionally designed to be broad in order to not miss relevant studies. The search yielded a total of 823 records. Additional 51 records were retrieved from searching other resources. Using a reference manager, duplicate records were eliminated to produce 860 records. Titles and abstracts were double-checked to remove obviously irrelevant reports. 674 records were excluded and if there is unclear eligibility based on the information provided, the study was retained for further evaluation.

Clinical trials were also searched revealing 87 records of ongoing and completed trials. Five studies were considered relevant in terms of intervention but only one of the five studies was retained for further evaluation. Local studies through HERDIN search yielded 178 records, in which seven studies were possibly relevant but did not meet inclusion criteria. Other local databases were searched for relevant studies but yielded no studies on effects of digital media-based technology on HIV risks.

One mobile application was found in searching local smartphone apps in the Philippines: "Battle in the Blood," a mobile game application designed to influence social norms, attitudes, and knowledge towards HIV/AIDS. An email was also sent to the mobile game developer to ask for potentially relevant studies involving this application. There were no published studies at the time of the search involving the use of this app in measuring HIV risk reductions among adolescents and youth.

A total of 186 records underwent further evaluation of abstracts and descriptions if they meet inclusion criteria. Full-text reports were retrieved for 35 articles and were examined for compliance with eligibility criteria, done by two independent reviewers. Sixteen studies were ultimately included in this meta-analysis, after eliminating studies for various reasons: k=8 studies were not randomized controlled trials, k=5 studies involved populations beyond youth age group, k=4 studies provided insufficient data needed to calculate effect sizes (e.g. no data table), and k=2 study had different outcomes measured.

Figure 1 shows the study flow diagram.

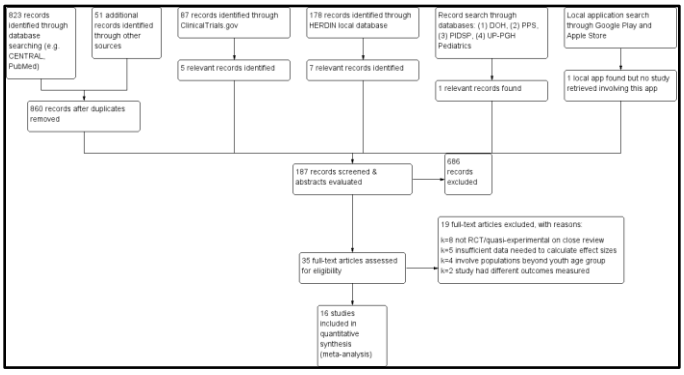

Figure 1. Study flow diagram

Included Studies

Population. The k=16 studies had a total N of 7925 and were published between 2004 to 2017. Two studies were split into two owing to them having two distinct populations each, making the total k=18. Most of the studies were conducted in the United States (k=14), and the others were conducted in Australia (k=1), China (k=1), and the Netherlands (k=1). One study did not specify its location of study. Twelve of the 18 studies involved both male and female participants while the rest (k=6) involved only females. Participants' age ranged from 11 to 25 years across all studies.

Study Design. Fourteen of the 18 studies were randomized controlled trials while the rest (k=4) where quasi-experimental studies with no mention of randomization but with rigorous controls. Follow-ups were scheduled in regular intervals up to six months (k=13; 3 studies having immediate follow-up), up to 24 months (k=4), and even as long as up to 36 months (k=1).

Program Characteristics. The most common intervention type were programs delivered via desktop computers on-site and/or internet-based (k=12). This was followed by virtual simulation and decision-making programs (k=2), text messaging and/or email messaging (k=2), videogame and/or interactive videos (k=2), telephone messaging (k=1), and television/radio-based programs (k=1). Most interventions utilize behavioral theories that have been commonly applied in HIV prevention. These studies were divided into subgroups as previously described; k=4 studies involved *Didactics*, k=7 studies utilized *Modules*, and k=7 studies employed *Virtual decision-making*.

Risk of Bias in Included Studies

Figure 2 presents the graphical summary of the risks of bias of the included studies.

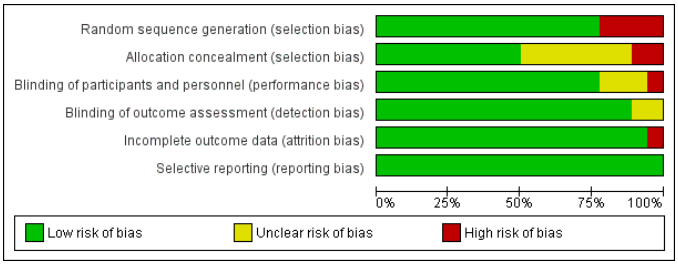

Figure 2. Risk of bias of included studies.

Selection Bias. Fourteen studies were randomized by software-generated random sequences. Four studies were marked high-risk [33,34,36]: these were the quasi-experimental studies, either randomization scheme was unclear, or investigators used institutional cycle design. In terms of allocation concealment, two studies were marked as high-risk since allocations were known to clinicians who sent emails to participants[30] or alternation was employed in allocation. Seven studies were marked unclear[25,26,33,34,36] since they did not specify how allocation was concealed. Most of the other studies were allocated using software algorithms independent of the investigators' knowledge.

Performance bias and detection bias. Only one study was marked as high risk for blinding of participants and personnel[28] since the study explicitly stated randomization of participants but in an unmasked fashion. Blinding was not specified in three studies[31,33,36] and were marked unclear. Most studies objectively collect data directly through participant answers, regardless of assigned group. In terms of blinding of outcome assessment, most studies employ self-reported outcomes. Two

studies were marked unclear[29,30] since it was not clear whether participants were blinded to the intervention they were taking.

Attrition Bias. Only one study was marked high risk[32] since their dropouts, although mentioned, were not included in study results. Other studies use intention-to-treat analyses, missing data balanced across groups, or reasons for missing data unrelated to outcome.

Reporting Bias. Expected outcomes were identified and reported as planned across all studies.

Efficacy of Interventions: Condom Use *(Figure 3)*

Thirteen studies were used to measure the primary outcome of condom use of young people. Analysis showed that the pooled standardized mean difference for this outcome was statistically significant at *d* = 0.29 (95% CI 0.18 to 0.41; Z = 4.97, *p*<0.00001; N = 5527). This meant that 61% of the intervention group was above the mean of the control group. There will be a 58% likelihood that any participant picked randomly from the DMT-based intervention group will be better at condom use than those from control.

To examine the possibility that publication bias inflated the condom use effect size (as evidenced by the funnel plot in Figure 4), fail-safe N values were calculated using the Rosenthal[21] and Orwin[22,23] methods. It would require 110 studies (by Rosenthal) or 287 studies (by Orwin) with non-significant findings to reduce the *d* = 0.31 to trivial effect.

Subgroup analysis was performed to address the presence of moderate heterogeneity (Tau² = 0.03; Chi² = 46.90, df = 13 (P < 0.0001); I² = 72%).

1. The *Didactics* subgroup (k=4) was homogeneous, and analysis showed statistically significant *d* = 0.55 (95% CI 0.41 to 0.68; Z = 7.89, p<0.00001, N = 866). This meant that 71% of the intervention group was above the mean of the control group. There will be a 65% chance that any participant picked randomly from the DMT-based *Didactics* subgroup will be better at condom use than those from control.
2. The *Modules* subgroup (k=5) was still moderately heterogeneous (I^2 = 61%), and analysis showed statistically significant *d* = 0.19 (95% CI 0.02 to 0.37; Z = 2.21, p=0.03; N = 1992). This meant that 58% of the intervention group was above the mean of the control group. There will be a 55% chance that any participant picked randomly from the DMT-based *Modules* subgroup will be better at condom use than those from control.
3. The *Virtual decision-making* subgroup (k=5) was still moderately heterogeneous (I^2 = 52%), and analysis showed statistically significant *d* = 0.25

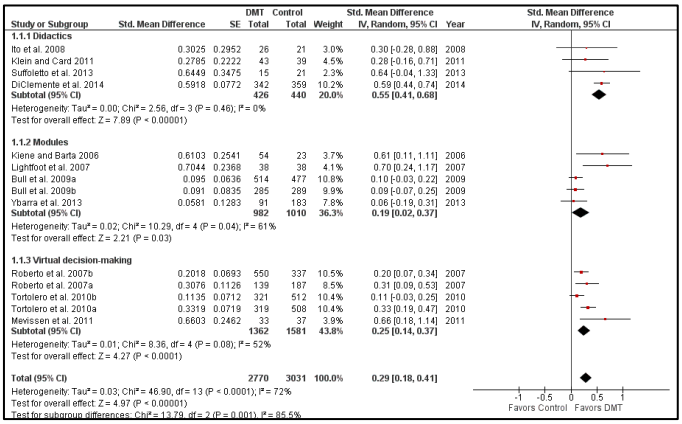

Figure 3. Forest plot comparing DMT-based interventions vs controls in increasing condom use among young people.

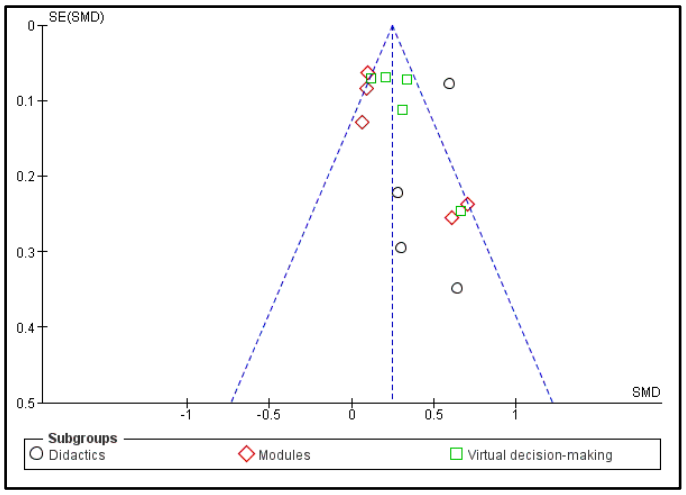

Figure 4. Funnel plot for condom use outcome.

(95% CI 0.14 to 0.37; Z = 4.27, p<0.0001; N = 2943). This meant that 60% of the intervention group was above the mean of the control group. There will be a 57% chance that any participant picked randomly from the DMT-based *Virtual decision-making* subgroup will be better at condom use than those from control.

In pursuing sensitivity analysis, it was noted that if quasi-experimental studies were excluded in the analysis of the *Modules* subgroup, the remaining k=4 studies would then have low heterogeneity (Tau^2 = 0; Chi^2 = 4.14, df = 3 (P = 0.25); I^2 = 28%). However, the pooled estimate for this outcome was not statistically significant at *d* = 0.11 (95% CI 0 to 0.23; Z = 1.91, p = 0.06; N = 1916).

Efficacy of Interventions: Frequency of Sexual Behavior *(Figure 5)*

Ten studies reported outcomes on frequency of sexual behavior, and the pooled standardized mean difference for this outcome was statistically significant at *d* = 0.16 (95% CI 0.06 to 0.26; Z = 3.12; p = 0.002; N = 4911). This meant that 56% of the intervention group was above the mean of the control group. There will be a 55% chance that any participant picked randomly from the DMT-based intervention group will have improved frequency of sexual behavior (abstinence) than those from control.

Figure 6 illustrates publication bias and Fail-safe N values were likewise computed for this outcome. It would require 27 studies (by Rosenthal) or 204 studies (by Orwin) with nonsignificant findings to reduce the *d* = 0.17 to trivial effect.

Subgroup analysis was performed to address the presence of moderate heterogeneity (Tau^2 = 0.02; Chi^2 = 25.83, df = 10 (P < 0.004); I^2 = 61%).

1. The *Didactics* subgroup (k=2) was homogeneous, but analysis showed results that are not statistically significant at *d* = 0.11 (95% CI -0.25 to 0.47; Z = 0.59, p = 0.55, N = 118).
2. The *Modules* subgroup (k=3) was highly heterogeneous (I^2 = 76%), and analysis showed

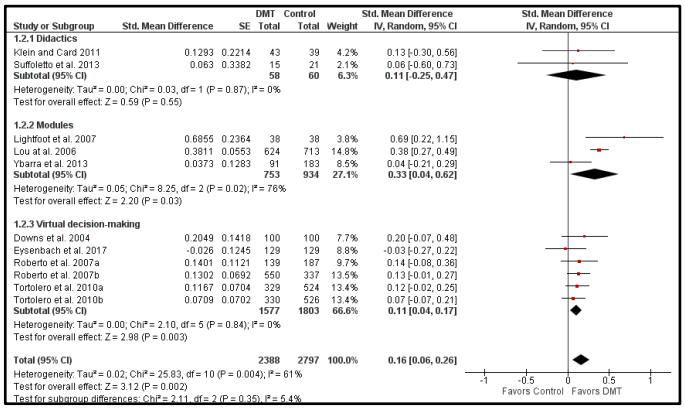

Figure 5. Forest plot comparing DMT-based interventions vs controls in decreasing sexual behavior among young people.

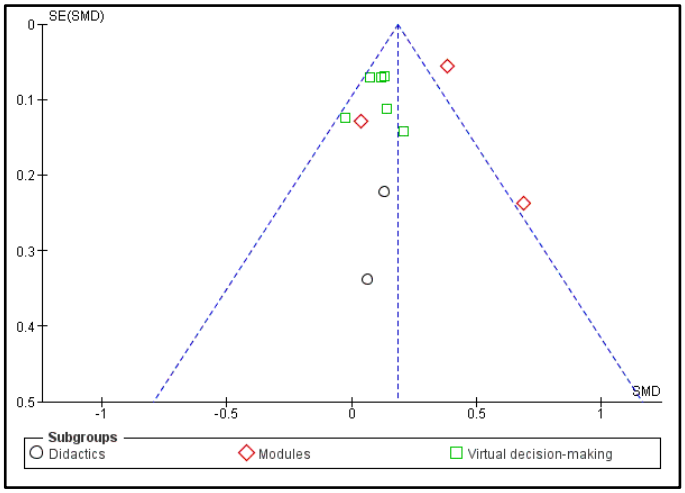

Figure 6. Funnel plot for frequency of sexual behavior as outcome.

statistically significant *d* = 0.33 (95% CI 0.04 to 0.62; Z = 2.20, p=0.03; N = 1687). This meant that 63% of the intervention group was above the mean of the control group. There will be a 59% chance that any participant picked randomly from the DMT-based *Modules* subgroup will have decreased frequency of sexual behavior than those from control.

3. The *Virtual decision-making* subgroup (k=6) was homogeneous, and analysis showed statistically significant *d* = 0.11 (95% CI 0.04 to 0.17; Z = 2.98, p = 0.003; N = 3380). This meant that 54% of the intervention group was above the mean of the control group. There will be a 53% chance that

any participant picked randomly from the DMT-based *Virtual decision-making* subgroup will have decreased frequency of sexual behavior than those from control.

In pursuing sensitivity analysis, it was noted that if quasi-experimental studies were excluded in the analysis of the whole group regardless of subgroup, the remaining k=7 studies would become homogeneous ($Tau^2 = 0$; $Chi^2 = 1.94$, df = 6 (P = 0.93); $I^2 = 0\%$). The pooled estimate for this outcome then was statistically significant at *d* = 0.09 (95% CI 0.01 to 0.16; Z = 2.04, p = 0.04; N = 2559).

Efficacy of Interventions: Number of Sexual Partners *(Figure 7)*

Two studies reported outcomes on number of sexual partners, and the pooled standardized mean difference for this outcome was not statistically significant at *d* = 0.42 (95% CI -0.13 to 0.98; Z = 1.50; p = 0.03; N = 402) and highly heterogeneous ($Tau^2 = 0.13$; $Chi^2 = 4.72$, df = 1 (P = 0.03); $I^2 = 79\%$). Subgroup analysis was not performed due to insufficient number of studies.

Efficacy of Interventions: STI Testing *(Figure 8)*

Three studies reported outcomes on STI testing, and the pooled standardized mean difference for this outcome was *d* = 0.26 (95% CI -0.06 to 0.58; Z = 1.59; p = 0.11; N = 629). However, data were highly heterogeneous ($Tau^2 = 0.06$; $Chi^2 = 6.75$, df = 2 (P = 0.03); $I^2 = 70\%$) and not statistically significant.

Efficacy of Interventions: Sexual Health Knowledge *(Figure 9)*

Six studies reported outcomes on sexual health knowledge, and the pooled standardized mean difference for this outcome was statistically significant at *d* = 0.42 (95% CI 0.26 to 0.57; Z = 5.31; p<0.0000 1; N = 4491). This meant that 66% of the intervention group was above the mean of the control group. There will be a 62% chance that any participant picked randomly from the DMT-based

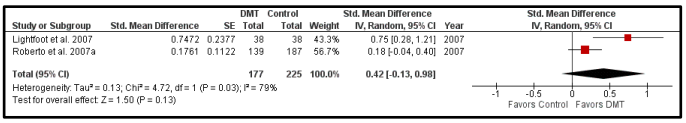

Figure 7. Forest plot comparing DMT-based interventions vs controls in decreasing number of sexual partners among young people.

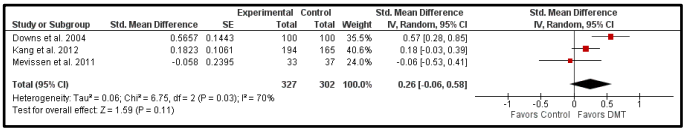

Figure 8. Forest plot comparing DMT-based interventions vs controls in improving STI testing among young people.

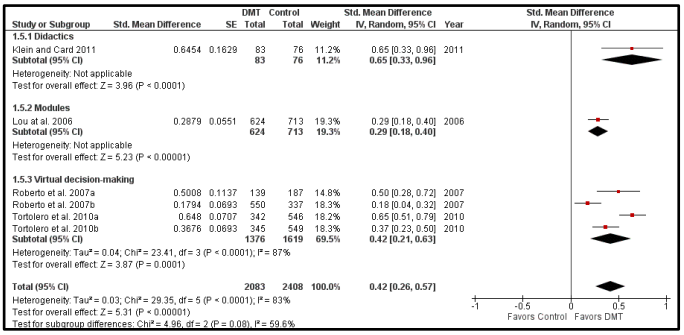

Figure 9. Forest plot comparing DMT-based interventions vs controls in improving sexual health knowledge.

intervention will have improved sexual health knowledge than those from control.

Subgroup analysis was performed to address the presence of high heterogeneity ($Tau^2 = 0.03$; $Chi^2 = 29.35$, df = 5 (P < 0.0001); $I^2 = 83\%$). However, the *Didactics* and *Modules* subgroups only had 1 study each and the rest (k=4) were under *Virtual decision-making* subgroup. Data remained heterogeneous ($Tau^2 = 0.04$; $Chi^2 = 23.41$, df = 3 (P <.0001); $I^2 = 83\%$) but statistically significant at *d* = 0.42 (95% CI 0.21 to 0.63; Z = 3.87; p = 0.0001; N = 2995).

DISCUSSION

Summary of Main Results

This meta-analysis highlights the effectiveness of digital media technology-based interventions in reducing risk-taking behaviors

among adolescents and youth that may predispose them to acquiring HIV and other STIs. In general, the pooled effect sizes of the selected studies show statistically significant adherence of participants to condom use. General heterogeneity was mainly attributed to the variety of digital media interventions used in each study. On closer look, the *Didactics* subgroup showed homogeneity and a statistically significant effect size in improving condom use. This could be due to role models (either videotaped narration or live interaction) serving as relevant avatars in guiding participants in the rationale, advantages, and correct use of condoms in sexual activity.

In terms of frequency of sexual activity, studies generally show significant effect sizes in decreasing frequency of sexual activity (or increasing waiting time or abstinence). Heterogeneity was mainly attributed as well to variety of interventions. On closer look, studies under *Virtual decision-making* subgroup show homogeneity and a statistically significant effect size. This could be due to the value of decision-making and immediate feedback on effects of such decisions (e.g. breaking abstinence) through simulated virtual dates, videogames, or cognitive rehearsals in selecting safe sex behaviors to practice.

Studies were also highly heterogeneous in terms of decreasing the number of sexual partners of young people owing to differences in interventions and possible differences in target population of the 2 studies (i.e. alternative education students). This outcome was also self-reported by participants, with one study having an unclear risk for performance bias. In any case, effect size was not statistically significant.

Digital media technology-based interventions did not show a statistically significant effect size on improving STI testing or detection. Studies were heterogeneous and type of intervention (computer-based recruitment or virtual STI clinic) seemed to have no significant effect on increasing STI testing. Studies also lack power (k=3) and there may be a need to conduct more randomized controlled trials in increasing testing among young people.

For sexual health knowledge, available data are heterogeneous owing to intrinsic differences in delivery of knowledge through didactic, modular, or virtual simulation approaches. Albeit the heterogeneity, the pooled effect size for the improvement of sexual health knowledge was considerable and statistically significant among studies and in all subgroups emphasizing the customization of rich content for immediate, low-cost delivery to target populations.

CONCLUSION & RECOMMENDATIONS

Implications for Practice

This meta-analysis was able to establish the effectiveness of digital media technology-based interventions in reducing risk-taking behaviors among young people as compared to controls. Programs in digital media form delivered via *Didactic* approaches are effective in increasing condom use while those with *Virtual decision-making* approaches are good for decreasing frequency of sexual behavior among adolescents and youth. Pending evaluations of cultural differences and digital media use in the country, these findings can be appropriately adapted for use in HIV/STI awareness, prevention, and risk reduction campaigns and policies considering the disproportionate HIV burden affecting the adolescent age group. Considering low cost of delivery, content customization, and flexible dissemination with anonymity and user privacy of digital media technology-based interventions, continued development and dissemination of such strategies can increase the public health impact of future HIV/STI programs.

This meta-analysis can open possibilities in the research of digital media technology-based interventions and their effects on not only changing individual-level behaviors but also addressing the

larger contextual landscape within which young people live. Studies focusing on effective types of digital media delivery on improving desired outcomes can be done. Local studies on effect of DMT-based interventions, such as mobile apps and games, on HIV/STI prevention are likewise recommended.

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DECLARATIONS OF CONFLICTS OF INTEREST

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Rivera A, Ong-Lim AL & Gonzales MLA. Effectiveness of Daily Chlorhexidine Bathing in Reducing Healthcare-Associated Infections in the Pediatric Intensive Care Unit of a Tertiary Government Hospital

ORIGINAL ARTICLE

EFFECTIVENESS OF DAILY CHLORHEXIDINE BATHING IN REDUCING HEALTHCARE-ASSOCIATED INFECTIONS IN THE PEDIATRIC INTENSIVE CARE UNIT OF A TERTIARY GOVERNMENT HOSPITAL

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

ABSTRACT

Introduction: Healthcare-associated infections (HCAIs) are a common complication of prolonged hospital stay, leading to increased morbidity and mortality. This study aims to determine the effectiveness of daily chlorhexidine bathing in reducing HCAIs in the pediatric intensive care unit (PICU).

Methodology: This is a randomized controlled, observer-blinded study conducted over a 6-month period. Included were 2 months to 18-year-old patients admitted to the PICU, randomly assigned to daily bathing with 2% chlorhexidine or to the standard practice of bathing with plain soap and water. Primary outcome was the incidence of HCAI in each group.

Results: A total of 50 patients were enrolled in the study. Overall incidence of HCAI was lower in the chlorhexidine group compared to the control group (12% versus 36%, RR=0.33, 95% CI 0.10 – 1.09, p=0.047). Incidence density rate was lower in the chlorhexidine group (5.91 versus 21.03 infections per 1000 person-days, p=0.049). Ventilator-associated pneumonia and bloodstream infections were lower in the chlorhexidine group, but results were not statistically significant. There were no significant differences in mortality rates and length of hospital stay. One adverse event of transient rash occurred in the chlorhexidine group.

Conclusion: Daily chlorhexidine bathing may be more effective in reducing HCAIs in the PICU compared to standard care.

KEYWORDS: *Chlorhexidine, healthcare-associated infection, pediatric intensive care unit*

INTRODUCTION

Health care-associated infection (HCAI) is a common complication of prolonged hospital stay leading to increased morbidity and mortality.[1] According to the World Health Organization (WHO), the overall prevalence of HCAIs in developed countries ranged from 5.1% to 11.6%, while in developing countries, this varied between 5% to 19%.[2] In the Philippines, there has been no consolidated report of rates of healthcare-associated infections across all institutions. HCAIs also pose an economic burden leading to increased health-related costs and utilization of health care resources.[3] A local study showed that the total cost of HCAIs reached P7.1M, with P3.8M shouldered by the patients and P3.3M by the hospital. This results in a cost of P49,000.00 per patient or P2,000.00 per patient-day.[4] The study reported a 19% mortality rate attributed to HCAIs. The latest data of the Section of Infectious and Tropical Diseases of Pediatrics in the tertiary government hospital where this study was conducted showed that the over-all HCAI rate for its different pediatric units, including the pediatric intensive care unit (PICU) and the neonatal intensive care unit (NICU), was relatively unchanged from a 9% rate in 2014 to 9.64% in 2015. In the 2015 report, HCAIs in the PICU accounted for the highest rate, which was 16.11%; NICU had a rate of 10.8%, while the rate for the two pediatric wards was at 9.6%.

Several infection control measures have been developed as components of a comprehensive program to decrease HCAI rates in the same hospital. These include hand hygiene, ventilator-associated pneumonia (VAP) care bundle, cohorting, barrier and isolation precautions, and regular infection control workshops.[5,6,7] Despite the implementation of these measures, HCAI rates in the PICU remained high over the past 5 years.

Chlorhexidine, although widely used in developed countries as part of aseptic technique measures, is less widely used locally. Chlorhexidine is relatively inexpensive and may prove to be a cost-effective measure when compared with the estimated cost of a hospital-acquired bloodstream infection.[4] A meta-analysis reported that daily chlorhexidine bathing can decrease the risk of HCAIs in the adult population.[5] Although several studies have already demonstrated its effectiveness, especially among the adult population, other studies, however, have shown conflicting results.[6,7,8,9] The adult ICU study showed that daily bathing with chlorhexidine did not decrease the incidence of HCAIs including central line-associated bloodstream infection (CLABSI), catheter-associated urinary tract infection (CAUTI), ventilator-associated pneumonia (VAP), or *Clostridium difficile*. [10] There was also no change in the rates of other secondary outcomes such as hospital-acquired bloodstream infections, blood culture contamination, and clinical cultures positive for multi-drug resistant organisms. The authors acknowledged, however, that their intervention period of 10 weeks was shorter compared to other studies. Their baseline infection rate was also low, suggesting that there could be a lower limit of infection rate wherein chlorhexidine bathing no longer adds any benefit.[10]

There are limited studies involving the pediatric population on this topic. One multi-center study done on critically ill children in ten pediatric ICUs compared 2% chlorhexidine-impregnated wipes for daily baths versus soap and water using a cluster-randomized cross-over trial, with two 6-month study periods separated by a 2-week washout period. The study showed a 36% reduction in the rate of bacteremia in the treatment group, with a significant decrease in the incidence of bacteremia (4.93/1000 at-risk days vs 3.28/1000 at-risk days, aIRR 0.64, p=0.044) and a non-significant decrease in CLABSI (3.00/1000 at-risk days vs. 2.20/1000 at-risk days, aIRR 0.68, p=0.249).[11] Locally, there are no studies on chlorhexidine bathing as one component of the hospital infection control program in the pediatric population. This study, therefore, aims to investigate the effect of daily chlorhexidine bathing in reducing HCAIs among children admitted in the PICU, aged 2 months to 18 years.

METHODS

This study is a single-center randomized controlled, observer-blinded study conducted in the pediatric ICU of a tertiary government institution over a 6-month period. Approval from the Research Ethics Board of the University of the Philippines Manila (UPMREB) was obtained prior to study initiation. Based on the study conducted by Milstone and colleagues, with 1.50 Rate Ratio and a target reduction in nosocomial infections by 45% favoring the intervention, a total sample size of 47 was computed to give the study 80% power at an alpha of 0.05.[11]

Patients admitted to the PICU are a heterogeneous group admitted either directly from the emergency room, pediatric wards, and operating room (surgical, neurosurgical, cardiac), or are transferred from another institution. The PICU is a 12-bed capacity ICU, with a 1:3 nurse to patient ratio. Study subjects were patients aged 2 months to 18 years admitted to the PICU with none of the following: 1) burn injuries or large wounds covering >20% body surface area, 2) patients with a history of allergy to chlorhexidine, 3) patients less than 2 months old, 4) critically ill patients whom the primary physician deemed bathing as unsafe, and 5) patients admitted to the PICU for less than 48 hours. During the pre-trial period, all PICU nursing aides who were to perform the bathing procedure were educated on the proper bathing technique using an instructional video.[12]

Admissions to the PICU were checked daily. For those who fulfilled the inclusion criteria and agreed to participate in the study, informed consent was sought from the parent or primary caregiver. In addition, for those who were able to provide assent, verbal assent was obtained from those aged 7 to 11 years old and written assent from those aged 12 to less than 18 years old. The patients were then randomized to either the control group, using soap and water, or to the intervention group, using 2% chlorhexidine gluconate (CHG) (MIcroshield®, Johnson and Johnson) based on a computer-generated randomization program.

Blinding of the bathers, parents or caregivers, and patients was not possible due to difference in appearance and smell of the chlorhexidine solution. However, the outcome assessor was blinded to the patient assignment. Demographic data and admitting diagnosis were obtained from the patient's chart. Randomization was done by a third party and concealment of treatment allocation was done using consecutively numbered sealed opaque envelopes that were opened only upon enrolment of the patient.

Bathing Procedure. The bathing procedure was carried out once every 24 hours by the PICU nursing aide on duty daily until discharge, following their routine schedule for bathing patients in two batches, either in the evening or early morning. Although bathing at the same time would have been ideal, the regular schedule for bathing of the PICU nursing aide was followed in order to minimize disruption in their activities. In both groups, bathing attendants practiced proper handwashing before handling the patient.

In the chlorhexidine or intervention group, six clean reusable washcloths were provided for each patient, which were color coded per body part (neck & chest, arms, legs, perineum, back and buttocks). Washcloths were dipped in a basin labeled solely for each patient's use, containing 2% CHG. This was prepared as a 1:2 dilution (500 ml of 4% CHG diluted in 1 liter of distilled water), and stored in clean, disposable plastic bottles. A different washcloth for everybody area was used. The solution was allowed to dry, without rinsing. Bathers were instructed to avoid contact with the face, mucous membranes, and wounds, and not use additional water during baths.

In the soap and water or control group the same procedure was followed using a liquid non-antiseptic soap that was rinsed after application. Random compliance checks, three times each week was done by a research assistant who was knowledgeable on the proper bathing technique. If there was a breach in the procedure, the research assistant would inform the investigator without

revealing the subject, and verbal reminders were sent to all nursing aides.

Patients were monitored daily for development of HCAIs, these were suspected when the patient developed any signs of systemic inflammatory response syndrome (SIRS) 48 hours after the patient was admitted to the PICU. All patients suspected to have HCAI underwent work-up. Specific HCAIs determined were the following: sepsis [bacteremia or laboratory-confirmed blood stream infection (BSI), clinical sepsis, or CLABSI], health-care associated pneumonia (VAP and non-VAP), CA-UTI, and surgical site infection (SSI). Diagnosis of the specific HCAI was based on CDC operational definitions. [13]

The pediatric residents on duty in the PICU were tasked to extract specimens for the laboratory tests. The occurrence of a HCAI was recorded per incident, thus, the patient was monitored from the time of admission until either 48 hours after discharge from the PICU had elapsed, or death had occurred. The investigator was not involved in the management of the patients' clinical conditions.

Patients were also monitored for adverse events (such as development of skin rashes or anaphylaxis) and need for medical management or withdrawal from the study.

Outcome and Outcome Measurements. Each patient's demographic and clinical data, including age, sex, diagnosis, length of PICU stay, outcome of hospitalization, and presence and duration of indwelling device were obtained. Clinical culture results were obtained from the microbiology laboratory and patient's medical chart.

The primary outcome measure was the frequency of HCAIs defined as the incidence proportion of each group. HCAI proportion is computed as the total number of HCAI over the total number of patients at risk. Secondary outcome measures were individual rates of HCAIs, mortality rate, deaths attributable to sepsis or HCAI, and occurrence of adverse events.

Data Analysis. Statistical analysis was performed using STATA 12.0 statistical software. Descriptive statistics were used to summarize the clinical characteristics of the patients. Frequencies and proportions were used for nominal variables, and median and range were used for ordinal variables. Mann-Whitney U test and Chi-square or Fisher's Exact test was used to determine the difference of medians and frequencies between control and chlorhexidine groups, respectively. All valid data were included in the analysis. Results were reported as risk ratio with 95% confidence interval and as infection incidence density rates per 1000 ICU days of healthcare-associated infections. Null hypothesis was rejected at 0.05α-level of significance.

RESULTS

A total of 85 patients were admitted to the pediatric ICU during the 6-month study period. Twenty-eight (28) were excluded (21 neonates, 3 critically ill not deemed safe for bathing by primary physician, 4 admitted for less than 48 hours). Of the 57 eligible subjects, 7 refused to give consent, leaving a total of 50 enrolled patients (25 in the control group and 25 in the chlorhexidine group). All patients were analyzed and there were no drop outs during the study period.

Table 1 provides the clinical profile of the subjects. The 2 groups were comparable in terms of age, sex, number of patients who were intubated, had central lines or surgery, duration of intubation or central catheter lines, and post-surgical patients.

Table 1. Demographic profile of the study population

	Chlorhexidine (n=25)	Soap&Water (n=25)	P-Value
	Frequency (%); Median (Range)		
Age in months	48 (3 to 204)	24 (3 to 216)	0.954*
Sex			1.000ǂ
Male	17 (68)	17 (68)	
Female	8 (32)	8 (32)	
Number of intubated patients	16 (64)	15 (60)	0.771ǂ
Number of patients with central line	11 (44)	10 (40)	0.774ǂ
Number of post-surgical patients	13 (52)	13 (52)	1.000ǂ
Length of intubation (days)	18 (5 to 48)	12 (4 to 110)	0.513*
Length of central catheter line (days)	13 (5 to 26)	5.5 (4 to 22)	0.189*

*Statistical tests used: * - Mann-Whitney U test; ǂ - Chi Square Test; ɬ – Fisher's Exact test*

Table 2 compares the incidence of healthcare-associated infections between the chlorhexidine and the control groups. The overall incidence of HCAI is lower in the chlorhexidine group (12%) compared to the control group (36%). The risk ratio indicates a possible beneficial effect of bathing with chlorhexidine compared to soap and water although the upper limit of the 95% confidence interval crossed the level of no significant difference and the p value showed only borderline significance, probably due to the small number of patients who developed HCAI (RR = 0.33, 95% CI 0.10 – 1.09, p=0.047). There was a trend for reduced incidence of ventilator-associated pneumonia (RR 0.500, 95% CI 0.05-5.17) and sepsis (RR 0.200, 95% CI 0.03-1.59) in the treatment group as compared to the control group, however, these were not statistically significant. In addition, there were only 2 culture-positive infections in the treatment group: 1 VAP (*Stenotrophomonas maltophilia*) and 1 CA-UTI (*Klebsiella oxytoca*), while the control group had 6 culture-positive infections 1 *Pseudomonas aeruginosa* (VAP), 1 *Klebsiella pneumonia* (BSI), 1 *Burkholderia cepacia* (CLABSI), 1 Candida (CLABSI), 1 *Staphylococcus epidermidis* (BSI), 1 mixed infection with *Klebsiella pneumoniae*, *Serratia marcescens*, and *Pseudomonas aeruginosa* (VAP). There were no surgical site infections in the chlorhexidine group, on the other hand no urinary tract infection was noted for the control group.

Table 2. Comparison of incidence of HCAI between the treatment and control groups

	Chlorhexidine (n=25)	Soap&Water (n=25)	Relative Risk (95% CI)	P-value
	Frequency (%)			
Ventilator associated Pneumonia	1 (4)	2 (8)	0.500 (0.05 – 5.17)	0.552
Blood stream infection/clinical sepsis	1 (4)	5 (20)	0.200 (0.03 – 1.59)	0.082
Surgical site infection	0	2 (8)	-	-
UTI	1 (4)	0	-	-
Total	3 (12)	9 (36)	0.33 (0.10 – 1.09)	0.047

Statistical tests used: Fisher's Exact Test

Table 3 compares the incidence of healthcare-associated infections between the chlorhexidine and control groups among patients with an indwelling device (endotracheal tube and central venous catheter) and post-surgical patients. Among patients who were intubated, there was a lower incidence of bacteremia or pneumonia in the chlorhexidine group (18.75%) compared to the control group (53.3%) (RR 0.352, CI 0.083 - 1.167, p value 0.044). Although this indicates that bathing with chlorhexidine may be more beneficial than the control, the upper limit of the 95% CI crosses the level of no significant difference, probably because of the small number of the measured outcomes. Among patients with a central venous catheter, there was also a lower incidence of bacteremia in the chlorhexidine group compared to the control group (18.2% versus 30%), but the difference was not statistically significant (RR 0.788 (0.097 – 5.195), p value 0.769). Among post-surgical patients, the number of patients who developed HCAIs was also lower in the treatment group (7.7% versus 38.5%), but the difference was not significant as well (RR 0.20, CI 0.009 – 1.47).

Table 3. Comparison of incidence of HCAI between treatment and control groups–with an indwelling device and post-surgical patients

Patients with Risk Factor for HCAI	Chlorhexidine	Control	Relative Risk (95% CI)	P-value
	Frequency (%)			
Intubated patients	3/16 (18.75)	8/15 (53.3)	0.352 (0.083 - 1.167)	0.044
Patients w/ central lines	2/11 (18.2)	3/ 10 (30)	0.788 (0.097 – 5.195)	0.769
Post-surgical patients	1/13 (7.7)	5/13 (38.5)	0.200 (0.009 – 1.474)	0.063

Statistical test used: Fisher's Exact Test

Table 4 compares the incidence density rates of healthcare-associated infections between the chlorhexidine and control groups. Overall, the chlorhexidine group was less likely to incur healthcare-associated infections (5.91 versus 21.03 infections per 1000 person-days, p=0.049). However, the rate ratio 95% CI ranged from 0.05 to 1.13. We have insufficient evidence to demonstrate a difference in the incidence density rate of VAP (RR 0.42, 95% CI 0.007 – 8.09), sepsis (RR 0.17, 95% CI 0.004 – 1.51), and overall HCAIs (RR 0.28, 95% CI 0.05 – 1.13).

Table 4. Comparison of incidence density rate per 1000 ICU days of HCAI between treatment and control groups

	Chlorhexidine (508 ICU days)	Control (428 ICU days)	Rate ratio (95% CI)	P-Value
	Incidence density rate per 1000 person days			
Ventilator-associated pneumonia	1.97	4.67	0.42 (0.007 to 8.09)	0.532
Blood stream infection/clinical sepsis	1.97	11.68	0.17 (0.004 to 1.51)	0.083
SSI	0	4.67	-	-
UTI	1.97	0	-	-
Total	5.91	21.03	0.28 (0.05 to 1.13)	0.049

Statistical test used: Fisher's Exact Test

Table 5 provides the clinical outcomes of the pediatric ICU patients included in this study. In terms of length of hospital stay, there was a higher median number of hospital days in the chlorhexidine group versus the control group (17 days versus 12 days, p=0.097), however the difference was not statistically significant. For both groups, there were four patients in each group who expired, with a crude mortality rate of 16% (p=1.00).

There were no serious adverse reactions noted during the study. One patient in the treatment group was reported to have a localized rash on the trunk after the 3rd day of chlorhexidine bathing that spontaneously resolved. This patient was also undergoing chemotherapy during the time of the study.

Table 5. Clinical outcomes of treatment and control groups

	Chlorhexidine (n=25)	Control (n=25)	P-value
Length of hospital stay, median (range in days)	17 (5 to 48)	12 (4 to 110)	0.097*
In-hospital overall mortality incidence	4 (16%)	4 (16%)	1.000ǂ
Sepsis-related death	0	2 (50)	
Pneumonia-related death	1 (25)	1 (25)	
Adverse event			
Rash	1 (4)	0	1.000ǂ

*Statistical tests used: * - Mann-Whitney U test; ǂ Fisher's Exact test*

DISCUSSION

This study conducted in a tertiary government hospital PICU showed that daily bathing with 2% chlorhexidine was able to reduce the occurrence of HCAIs by 67%. The overall HCAI incidence density rate per 1000 PICU days was also four times higher in the control group (5.91 in treatment group versus 21.03 infections in control group per 1000 person-days). The results were not statistically significant, however, which may be attributed to the small number of patients who developed HCAI.

Previous large-population studies and two meta-analyses on chlorhexidine bathing in adult ICU

units have shown benefits in the reduction of HCAIs in this population. Furthermore, a recent meta-analysis concluded that daily chlorhexidine bathing appears to be of most clinical benefit in reducing CLABSI and methicillin-resistant *Staphylococcus aureus* (MRSA) infections when infection rates are high in that certain population.[18] The findings in our study support and are consistent with these studies in the adult population. The only large-scale study done among children by Milstone and colleagues showed a significant reduction in HCAIs by 36%. Our study is the first known local study conducted in critically ill children admitted in the intensive care unit, comparing bathing with chlorhexidine with the standard bathing with soap and water. This study differed from that of the former in that their study was a multi-center, cross-over trial using cluster randomization, while our study used a single center, randomized controlled design.

The recorded reduction in incidence rates of VAP and CLABSI in the chlorhexidine group was consistent with previous studies on daily chlorhexidine bathing in children and adults. Although this reduction was not statistically significant in our study, again owing to the small number of HCAIs, analyses showed consistently a lower incidence and incidence density rate in the chlorhexidine group. This study also demonstrated that for patients with an endotracheal tube or a central line, or who had undergone an operative procedure, the risk for acquisition of a HCAI related to the risk factor may be lower in those who use chlorhexidine. For intubated patients, the risk for HCAIs was reduced by 65% in those who received daily chlorhexidine bathing. This is especially applicable in our PICU since over 60% of the patients are intubated. For patients with a central access, there was a 21% reduction in HCAI in the treatment group. Although this was not statistically significant, this was consistent with the previous study on critically ill children that also reported a significantly lower incidence of bacteremia in pediatric patients with a central line who received daily chlorhexidine bathing.[11] For post-surgical patients, the study showed a lower incidence proportion of patients who developed HCAI among patients who received chlorhexidine, with an 80% risk reduction, however, this was also not statistically significant. A larger number of post-surgical patients are needed to verify this result. A previous study on adult surgical ICU patients also failed to find a significant reduction of HCAIs in patients given daily chlorhexidine baths.

Although this was not the objective of this study, it was also noted that the overall HCAI rate during the 6-month study period was lower compared to the same period of the previous year, dropping from 18% to 10%, equivalent to a 44% reduction. Although hand hygiene and daily bathing of patients were reinforced, there was no new infection control measure implemented during this time, aside from the daily chlorhexidine bathing.

No significant difference in mortality rates were found in both groups, as with the study by Noto.[10] There was also no significant difference in the length of hospital stay in both groups. It has been suggested that although chlorhexidine may be effective in reducing HCAIs, there is no evidence for improved survival, other than the prevention of a HCAI.

Chlorhexidine bathing with 2% solution has been shown to be safe to use for children 2 months and above, and this study supports this finding.[15,16,17] There was only one adverse event in the chlorhexidine group, consisting of a transient localized rash on the trunk. This is consistent with findings from other studies of the most common adverse effect of the solution, which is transient contact dermatitis. However, since this patient had received chemotherapy a week prior to enrolment, it is uncertain if the rash was due to chlorhexidine or was drug-induced. Chlorhexidine was continued in this patient, without recurrence of the rash.

One great concern of HCAIs is the burden of cost to the patient. Although the scope of this study did not include determining cost-effectiveness, the relatively low cost of chlorhexidine bathing (P67.00 per patient-day or P1,361.60 per patient) warrants

an assessment of the cost-effectiveness of this intervention in preventing HCAI and other adverse outcomes.

The strength of this study may be attributed to it being a randomized-controlled trial, with both groups receiving their treatment assignment in a parallel manner. A few limitations, however, should be considered. First was the inability to blind the bathers due to the appearance of the chlorhexidine solution. However, the outcome assessor was blinded to the treatment. Second, this trial was designed as an effectiveness trial, not an efficacy trial, wherein the interventions were performed as a component of routine patient care and there was no dedicated study bather. Lastly, this is a single government center study, hence, the findings may not be generalizable to other medical centers.

CONCLUSIONS AND RECOMMENDATIONS

The above findings suggest that daily chlorhexidine bathing in the PICU may be effective in reducing the incidence of HCAIs. A bigger sample population is further recommended to verify these results and strengthen the power of the study. It is recommended that this study be duplicated in other areas, such as in the pediatric wards, neonatal ICU or hematology-oncology ward, to assess its effectiveness in different settings and in different patient populations. It is a simple, easily implementable, and a relatively cheap infection control measure, and is safe to use in children.

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Pantig FM & Gatchalian S. Comparison of Various Methods of Detection of Hypoxemia and Correlation of Hypoxemia with Clinical Features Among Pediatric Patients 3 Months to 5 Years Old with Community-Acquired Pneumonia at a Tertiary Hospital Emergency Room

ORIGINAL ARTICLE

COMPARISON OF VARIOUS METHODS OF DETECTION OF HYPOXEMIA AND CORRELATION OF HYPOXEMIA WITH CLINICAL FEATURES AMONG PEDIATRIC PATIENTS 3 MONTHS TO 5 YEARS OLD WITH COMMUNITY-ACQUIRED PNEUMONIA AT A TERTIARY HOSPITAL EMERGENCY ROOM

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

4TH PRIZE 2019 PIDSP RESEARCH CONTEST

ABSTRACT

Introduction: Pulse oximetry is frequently utilized as a rapid, non-invasive, point-of-care alternative to arterial blood gas analysis in measuring oxygen saturation of children with pneumonia.

Objectives: To compare portable fingertip pulse oximetry saturation (SpO_2^{PF}), handheld pulse oximetry saturation (SpO_2^{H}) and arterial oxygen saturation (SaO_2) in detection of hypoxemia, and correlate hypoxemia with clinical features in children with pneumonia.

Methodology: This was a prospective, observational, cross-sectional study involving patients 3 months to 5 years old with pneumonia. Oxygen saturation was measured using a portable fingertip pulse oximeter, a handheld pulse oximeter, and arterial blood gas analysis.

Results: Eighty-six children were included. SpO_2^{PF} underestimated oxygen levels by 0.126% (95% CI -0.240 to 0.491), while SpO_2^{H} underestimated it by 0.323% (95% CI -0.075 to 0.721). Between portable and handheld readings, the mean difference was 0.198% (95% CI -0.089 to 0.484). Across the three methods, limits of agreement ranged from -3.388 to +4.035%. There was no statistically significant difference in variance among the three measurements. Children with tachypnea (cOR 2.623, 95% CI 1.06 – 6.48, p = 0.037), difficulty breathing (cOR 6.316, 95% CI 1.96 – 20.34, p = 0.002), and subcostal retractions (cOR 2.842, 95% CI 1.05 to 7.69, p = 0.040) were more likely to have hypoxemia.

Conclusion: Pulse oximetry closely correlates with arterial blood gas analysis within acceptable limits of agreement and with no significant differences in variance among measurements. Difficulty breathing, tachypnea and subcostal retractions were significantly more likely to be observed in hypoxemic children.

KEYWORDS: *community-acquired pneumonia; pulse oximetry; hypoxemia*

INTRODUCTION

Pneumonia is defined by the World Health Organization (WHO) as an acute disease episode with cough or difficult breathing combined with age-adjusted tachypnea.[1,2] In 2015, the WHO reported 920,000 deaths due to pneumonia globally in the under-five age group. This translates to 16% of all deaths under five years for the said year. While this is a substantial decline from the reported 1.7 million deaths in the year 2000, pneumonia mortality rates have decreased at a significantly slower rate compared with declines in other childhood illnesses such as diarrhea, malaria, and AIDS.[3] In the Philippines, 12,224 deaths were reported due to pneumonia in the under-five age group in the year 2015, accounting for 19% of all childhood deaths, which is slightly higher than the worldwide mortality rate.[4]

Hypoxemia in pneumonia has been shown to be a predictor of mortality, with a reported two- to five-fold increase in death due to pneumonia in patients with hypoxemia.[5,6] The gold standard for detection of hypoxemia is arterial blood gas (ABG) analysis.[7] The procedure is invasive as it requires taking an arterial blood sample from the patient, which also poses a potential risk for needlestick injury in health care workers. Blood gas analyzers are expensive, chemical reagents add to the cost, and a laboratory facility with trained personnel is necessary, which may be unaffordable and prohibitive for hospitals and patients with limited resources. Furthermore, high-level skill is needed in clinical interpretation of blood gas analysis results. Thus, arterial blood gas analysis may not be suitable or feasible for most hospitals with limited resources, and is mostly unavailable in primary care and local health care facilities.

Pulse oximetry has been identified as a simple and effective intervention for identifying children in urgent need of oxygen, thus preventing child deaths from lack of oxygen supplementation.[3] It is a cost-effective tool that can identify 20-30% more cases of hypoxemic children than using clinical signs alone. In addition to averting mortalities, oximetry helps to identify children requiring referral, increases the incidence of correct identification of severe pneumonia cases, decreases unnecessary oxygen supplementation, and reduces the incidence of incorrect diagnosis and inappropriate treatment with antibiotics.[8] Indeed, the introduction of pulse oximetry in clinical practice has led to an advancement in patient assessment and monitoring, because it allows for a simple, non-invasive, and reasonably accurate estimation of arterial oxygen saturation for the detection of hypoxemia. Pulse oximetry has proved to be a simpler, inexpensive, non-invasive, point-of-care alternative method to arterial blood gas analysis in measuring the oxygen saturation in arterial blood. It is non-invasive, causes less pain and distress to patients, allows for continuous monitoring or regular spot-checks, and does not require highly technical and clinical skill in its use and interpretation. The technology is affordable, sustainable and highly cost-effective for developing countries.[9] Knowledge of the oxygen saturation, correlated with the patient's presenting signs and symptoms, has been shown to alter a physician's decision on treatment, need for and level of admission, diagnostic investigation, and therapeutic interventions. With the widespread use of pulse oximetry at the frontline of patient assessment at the emergency room, this study aimed to compare portable fingertip pulse oximetry oxygen saturation (SpO_2^{PF}), handheld pulse oximetry oxygen saturation (SpO_2^{H}) and arterial oxygen saturation (SaO_2), and correlate these SpO_2^{PF}, SpO_2^{H} and SaO_2 with clinical features in children 3 months to 5 years old diagnosed with community-acquired pneumonia.

METHODOLOGY

Study Subjects

This study was a prospective, observational, cross-sectional study involving patients 3 months to 5 years of age admitted at the Pediatric Emergency

Room (PER) of the Philippine General Hospital from April to July 2018 with an admitting impression of pediatric community-acquired pneumonia of any severity. Non-probability, quota sampling was applied. Recruitment of eligible patients proceeded until the required number of participants was achieved. The inclusion criteria included: 1) patients 3 months to 5 years old admitted at the PER for 48 hours or less at the time of study enrolment; and 2) patients who satisfied the 2016 Philippine Academy of Pediatric Pulmonologists (PAPP) definition and criteria for diagnosis of pneumonia[10], and were decided by the attending pediatrician to be treated as such. The exclusion criteria were: 1) patients with any of the following conditions: pulmonary anatomic abnormality, existing cardiac condition, chronic lung conditions (bronchial asthma, bronchopulmonary dysplasia, congenital pulmonary adenomatoid malformation, pulmonary tuberculosis, chronic lung disease, lung malignancy, and others as diagnosed by the attending pediatrician); 2) patients discharged from another institution within 48 hours of admission in the PER to exclude patients with possible healthcare-associated pneumonia.

Patients were assessed by the triage officer upon arrival at the PER, and those warranting admission were admitted to the PER following standard protocol. Patients who satisfied the inclusion criteria were approached by the primary investigator who provided the parents/legal guardians with the information sheet regarding the study, and answered any questions raised by the parents/legal guardians pertaining to the study. A written informed consent was obtained from parents/legal guardian. Patients who did not consent to participate in the study continued to receive routine patient care.

Sample Size

A minimum of 76 pediatric patients were required for this study based on 80% power (101 patients for 90% power), a level of significance of 5%, assumed clinically significant difference of SpO_2 and SaO_2 equal to 1, and their standard deviation equal to ± 2.19. The values used were from a reference article by Ross and Helms.[11]

Intervention

Patient demographic data were obtained upon admission and were recorded on the data collection form. Pertinent details in the clinical history, physical examination, and degree of severity of signs and symptoms upon admission were noted and recorded on the data collection form.

After primary assessment by the attending physician, stabilization of the patient, and institution of initial therapy and other interventions, the primary investigator measured the SpO_2^{PF} level on the thumb (right or left) of the subject using the portable fingertip pulse oximeter (ChoiceMMed® Health Care MD300C21C LED Fingertip Pulse Oximeter, manufactured by Beijing Choice Electronic Tech Co., Ltd., China). This was followed by measurement of the SpO_2^{H} level on the same digit using the handheld pulse oximeter (Contec® CMS60D handheld pulse oximeter, manufactured by Contec Medical Systems Co. Ltd., Qinhuangdao, China). For both readings, the sensor was attached to the child's digit and the reading was taken after 30 seconds to allow ample time for stabilization of reading. The portable fingertip pulse oximeter did not require routine calibration or maintenance, while the handheld pulse oximeter was calibrated before leaving the factory and needed to be calibrated once a year.[12,13] The fingertip pulse oximeter and handheld pulse oximeter probe was cleaned according to manufacturer's recommendations before and after use on each patient. Pulse oximeters used were purchased specifically for the study; these were not provided/sponsored by the company. Choice of pulse oximeter brands was based on availability at the time of purchase.

The SaO_2 was measured via arterial blood sample drawn by the primary investigator from the radial artery of the same extremity. A heparinized

1cc syringe was used, prepared as follows: heparin was taken in the syringe to lubricate the inner wall of the syringe, and then was expelled from the syringe completely.[14] One (1) ml of arterial blood sample was collected, and was transported in ice to the ABG laboratory. The blood sample was processed using the institution's arterial blood gas analyzer (Nova PHOX Blood Gas Analyzer, manufactured by Nova Biomedical, Waltham Massachusetts, USA). The blood sample used was then disposed following the institution's standard protocol for disposal of biological material. The ABG tests were included in the patient's allocated funds for diagnostic tests.

In the event that venous blood was drawn instead of an arterial blood, a repeat blood extraction was performed by the primary investigator following the procedure previously described. A venous blood gas sample was determined based on, but not limited to, the following characteristics: dark red color, slow flow of blood into the syringe, non-pulsatile blood flow, and other characteristics as determined by the primary investigator.

The portable fingertip and handheld pulse oximetry results and the arterial blood gas results were relayed to the attending physician of the patient for appropriate intervention and management of the patient. Standard medical care was given to all patients upon the discretion of the attending physician. The primary investigator collected and recorded data on the treatment given that included, but was not limited to, oxygen supplementation either via nasal cannula, or face mask, endotracheal intubation, among others.

The study did not in any way cause any undue delay in the provision of standard of care to patients. Hence, if the attending physician deemed it necessary to perform an arterial blood gas determination, the attending physician proceeded with the procedure and other necessary interventions. A patient who already underwent ABG was still included in the study if his/her attending physician deemed it necessary to perform another arterial blood gas determination and had made a reorder for the test.

Only one-time determination of SpO_2^{PF}, SpO_2^{H} and SaO_2 was performed by the primary investigator. The fraction of inspired oxygen (FiO_2, in percent) upon measurement of SpO_2^{PF}, SpO_2^{H} and SaO_2 was documented. All pulse oximeter readings preceded arterial blood sampling to reduce patient irritability, resistance, and motion artifacts in measuring saturation that may alter results. The subject's participation in the study lasted from completion of the informed consent form up to the release of arterial blood gas results.

This study was approved by the hospital Research Ethics Board. The investigators reported no conflicts of interest.

Definition of terms

Hypoxemia was determined by using the partial pressure of oxygen in arterial blood (PaO_2) determined by blood gas analysis, and is defined as a PaO_2 less than 80 mm Hg in patients breathing room air (FiO_2 0.21). In patients on oxygen supplementation, the minimally predicted PaO_2 for that level of inspired oxygen computed by Shapiro et al. was used. A measured value that was less than the predicted value presumes that the patient will be hypoxemic breathing room air. [15]

Non-hypoxemic is defined as a PaO_2 of 80 mm Hg or higher in patients breathing room air (FiO_2 0.21), or a PaO_2 that is equal to or greater than the computed predicted value for patients on oxygen supplementation.

Statistical Analysis

Descriptive statistics were used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables.

Independent sample t-test, Mann-Whitney U test and Fisher's Exact/Chi-square test were used

to determine the difference of mean, median and frequency between groups, respectively.

A Bland Altman analysis was performed to see limits of agreement and the mean difference between the portable fingertip and handheld pulse oximetry saturation (SpO_2) and arterial blood oxygen saturation (SaO_2).

Odds ratio and the corresponding 95% confidence interval from binary logistic regression were computed to determine the significant predictor of hypoxemia.

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

RESULTS

During the course of the study, 86 children were included, 55 (63.9%) of whom were classified as hypoxemic while the rest were non-hypoxemic. Table 1 shows that the socio-demographic and clinical data of both groups were comparable except for the following findings: more children in the hypoxemic group presented with tachypnea, difficulty of breathing and subcostal retractions; most of them also stayed in the ER for 24 hours or less (58.7% admitted to general wards, 41.3% discharged from the PER).

Table 1. Socio-demographic and clinical data of children with PCAP ages 3 months to 5 years (n = 86)

	Hypoxemic children (n = 55)	**Non-hypoxemic children (n = 31)**	**P-value**
	Frequency (%); Median (Range)		
Age	1 (0.25 – 4)	1 (0.25 – 3.83)	0.907*
Age distribution			0.897†
<1 year	24 (43.64)	13 (41.94)	
1 – 3 years	26 (47.27)	14 (45.16)	
>3 years	5 (9.09)	4 (12.90)	
Sex			0.423‡
Male	35 (63.64)	17 (54.84)	
Female	20 (36.36)	14 (45.16)	
Temperature on admission			0.341‡
< 37.8°C	11 (20)	9 (29.03)	
≥ 37.8°C	44 (80)	22 (70.97)	
Cough			1.000†
None	7 (12.73)	3 (9.68)	
Present	48 (87.27)	28 (90.32)	
Tachypnea			**0.034‡**
None	19 (34.55)	18 (58.06)	
Present	36 (65.45)	13 (41.94)	
Alar flaring	32 (58.18)	15 (48.39)	0.381‡
Head bobbing	12 (21.82)	6 (19.35)	0.787‡
Stridor	1 (1.82)	3 (9.68)	0.131†
Grunting	3 (5.45)	2 (6.45)	1.000†

	Hypoxemic children (n = 55)	Non-hypoxemic children (n = 31)	P-value
	Frequency (%); Median (Range)		
Cyanosis	13 (23.64)	4 (12.90)	0.230‡
Apnea	1 (1.82)	1 (3.23)	1.000†
Difficulty in breathing	50 (90.9)	19 (61.29)	**0.001**‡
Difficulty in swallowing	4 (7.27)	2 (6.45)	1.000†
Ear complaints	4 (7.27)	4 (12.90)	0.451†
Eye complaints	7 (12.73)	3 (9.68)	1.000†
Vomiting	20 (36.36)	14 (45.16)	0.423‡
Diarrhea	8 (14.55)	8 (25.81)	0.198‡
Seizure	5 (9.09)	6 (19.35)	0.193†
Retractions			
Subcostal	45 (81.82)	19 (61.29)	**0.036**‡
Intercostal	3 (5.45)	1 (3.23)	1.000†
Suprasternal	3 (5.45)	2 (6.45)	1.000†
Supraclavicular	3 (5.45)	1 (3.23)	1.000†
Breath sounds			0.533‡
Normal	11 (20)	8 (25.81)	
Abnormal	44 (80)	23 (74.19)	
WBC count			0.499‡
$\leq 12 \times 10^9$ / L	14 (25.45)	10 (32.26)	
$> 12 \times 10^9$ / L	41 (74.55)	21 (67.74)	
Outcome			0.683†
Discharged from PER	25 (45.45)	17 (54.84)	
Admitted to ward	29 (52.73)	14 (45.16)	
Admitted to ICU	1 (1.82)	0	
Length of ER stay			**0.012**‡
$\leq$ 24 hours	35 (63.64)	11 (35.48)	
> 24 hours	20 (36.36)	20 (64.52)	

Table 2 shows oxygen supplementation of children included in the study: 1) no oxygen supplementation, 2) low flow oxygen delivery, via either nasal cannula or oxygen face mask, and 3) endotracheal intubation.

In this study, 91% of hypoxemic children received oxygen therapy delivered via various methods (nasal cannula, face mask or intubation), while 9% of hypoxemic children were not given oxygen supplementation. In contrast, 48.4% of non-hypoxemic children were managed with oxygen therapy, while the remaining did not receive oxygen.

In the hypoxemic group that received oxygen therapy, 67.27% received low flow oxygen delivery either via nasal cannula or facemask, and 23.63% had assisted ventilation via endotracheal intubation. In the non-hypoxemic group, 51.61%

received no oxygen supplementation, the 48.4% that received oxygen therapy, 41.93% received low flow oxygen delivery, while 6.45% were intubated.

The hypoxemic group required oxygen supplementation, greater FiO_2 concentrations, and needed endotracheal intubation and mechanical ventilation, compared to their non-hypoxemic counterpart.

Table 2. Oxygen supplementation of children with PCAP ages 3 months to 5 years (n = 86)

	Hypoxemic children (n = 55)	**Non-hypoxemic children (n = 31)**	**P-value**
	Frequency (%); Median (Range)		
No oxygen supplementation (n = 21)	5 (9.09)	16 (51.61)	**<0.001**‡
Oxygen supplementation (n = 65)	50 (90.9)	15 (48.39)	
Low flow oxygen delivery (n = 50)	n = 37 (67.27)	n = 13 (41.93)	**0.033**‡
Route			
Nasal cannula	13 (35.14)	9 (6.23)	
Face mask	24 (64.86)	4 (30.77)	
FiO_2 (liters per minute)	6.27 ± 3.56	3.24 ± 1.96	**0.006**§
FiO_2 (%)	44.65 ± 14.31	31.69 ± 5.99	**0.003**§
Endotracheal intubation (n = 15)	n = 13 (23.63)	n = 2 (6.45)	
Route			
Mechanical ventilation	11 (20)	0	**0.006**†
Bag-valve ventilation	2 (3.64)	2 (6.45)	0.617†
FiO_2 (liters per minute) (bag-valve ventilation)	10	10	-
FiO_2 (%) (bag-valve ventilation)	80	80	-
FiO_2 (%) (mechanical ventilation)	83.64 ± 22.92	-	-

The agreement between the three different methods of measuring oxygen saturation was assessed (Table 3, Figures 1-3). On the average, SpO_2^{PF} underestimated oxygen levels by 0.126% (95% CI -0.240 to 0.491), while SpO_2^{H} underestimated it by 0.323% (95% CI -0.075 to 0.721). Between portable and handheld readings, the mean difference was at 0.198% (95% CI -0.089 to 0.484). The limits of agreement indicate how closely the estimation agrees with the actual oxygen saturation. Across the three methods, limits of agreement ranged from -3.388 to +4.035%. However, these limits of agreement are applicable only for approximate oxygen saturations of 93% to 99%. The variances of the estimates from the three methods were analyzed. In all three cases, p-values were >0.05 which means there was no statistically significant difference in variance among measurements.

Table 3. Comparison of Bland-Altman statistic portable fingertip and handheld pulse oximetry saturation (SpO_2) and arterial blood oxygen saturation (SaO2) of children with PCAP ages 3 months to 5 years (n = 86)

	Mean difference	Limits of Agreement	Range	Pitman's Test of difference in variance (r)	P-Value
SaO_2 and Portable fingertip (SpO_2^{PF})	0.126 (-0.240 to 0.491)	-3.282 to 3.533	93.20 to 99.85	0.150	0.168
SaO_2 and Handheld (SpO_2^{H})	0.323 (-0.075 to 0.721)	-3.388 to 4.035	93.20 to 99.65	0.008	0.943
Portable fingertip ($SpO2^{PF}$) and Handheld ($SpO2^{H}$)	0.198 (-0.089 to 0.484)	-2.474 to 2.869	93.00 to 99.50	-0.166	0.126

Figure 1. Bland-Altman plot depicting agreement between portable fingertip (SpO_2^{PF}) and SaO_2

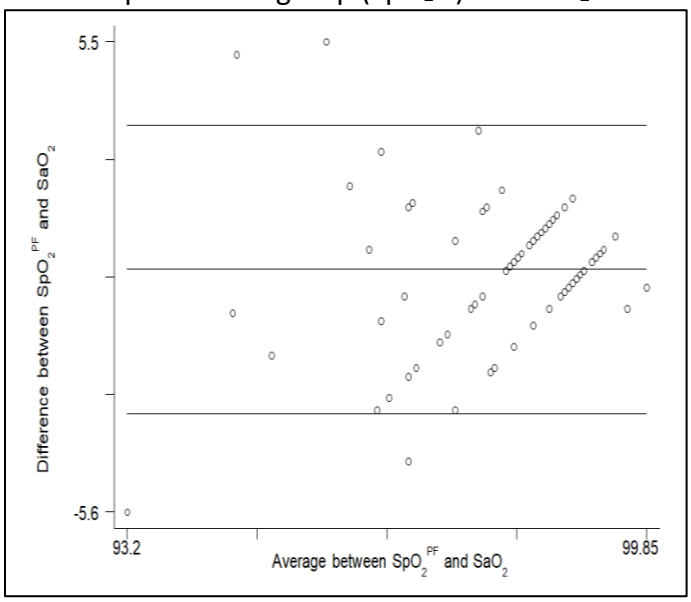

Figure 2. Bland-Altman plot depicting agreement between handheld pulse oximetry oxygen saturation (SpO_2^{H}) and SaO_2

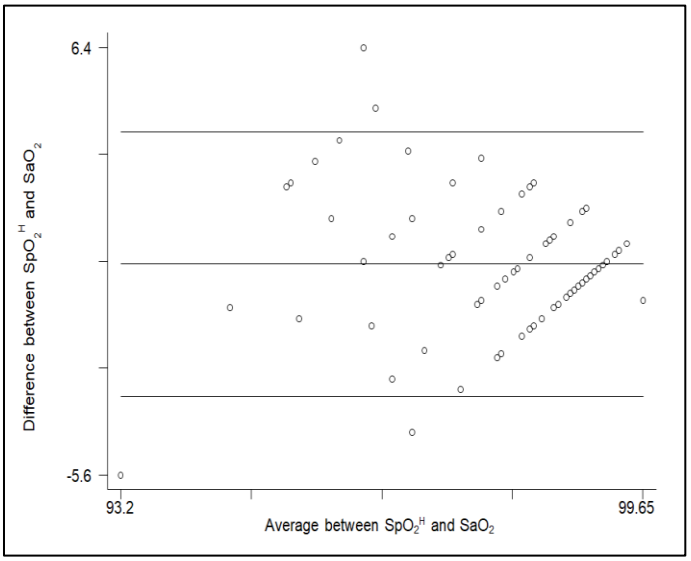

Figure 3. Bland-Altman plot depicting agreement between portable fingertip (SpO_2^{PF}) and handheld pulse oximetry oxygen saturation (SpO_2^{H})

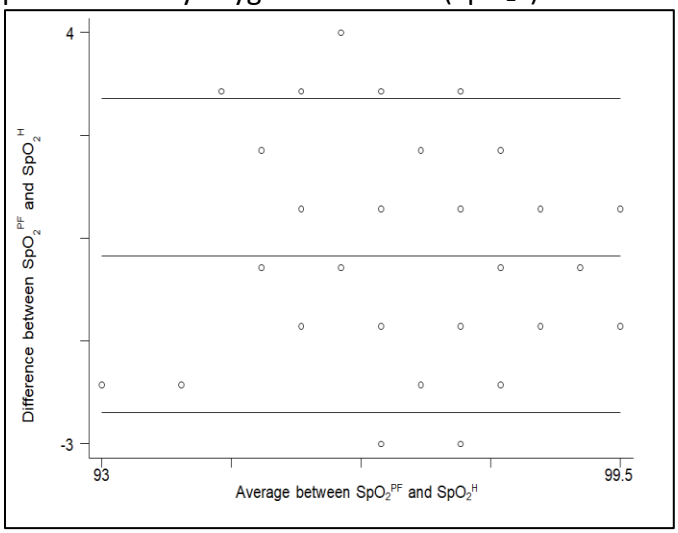

Table 4 shows the factors associated with hypoxemia. Children with tachypnea were 2.6 times more likely to have hypoxemia compared to those with normal respiratory rates (cOR 2.623, 95% CI 1.06 – 6.48, p = 0.037). Children perceived to have difficulty in breathing were 6.3 times more likely to have hypoxemia compared to those without difficulty breathing (cOR 6.316, 95% CI 1.96 – 20.34, p = 0.002). Children who present with subcostal retractions were 2.8 times more likely to have hypoxemia compared to those without (cOR 2.842, 95% CI 1.05 to 7.69, p = 0.040).

Table 4. Factors associated with hypoxemia among children with PCAP ages 3 months to 5 years (n = 86)

	Hypoxemic children (n = 55)	Non-hypoxemic children (n = 31)	Odds Ratio (95% CI)	P-value
	Frequency (%); Mean ± SD; Median (Range)			
Age (years)	1 (0.25 – 4)	1 (0.25 – 3.83)	1.091 (0.70 – 1.70)	0.700
Sex				
Male	35 (63.64)	17 (54.84)	(reference)	-
Female	20 (36.36)	14 (45.16)	0.694 (0.28 – 1.70)	0.424
Fever				
Absent	11 (20)	9 (29.03)	(reference)	-
Present	66 (76.74)	22 (70.97)	1.636 (0.59 – 4.53)	0.343
Cough				
None	7 (12.73)	3 (9.68)	(reference)	-
Present	48 (87.27)	28 (90.32)	0.735 (0.18 – 3.07)	0.673
Tachypnea				
None	19 (34.55)	18 (58.06)	(reference)	-
Present	36 (65.45)	13 (41.94)	**2.623 (1.06 – 6.48)**	**0.037**
Alar flaring	32 (58.18)	15 (48.39)	1.484 (0.61 – 3.60)	0.382
Head bobbing	12 (21.82)	6 (19.35)	1.163 (0.39 – 3.48)	0.788
Stridor	1 (1.82)	3 (9.68)	0.172 (0.02 – 1.74)	0.136
Grunting	3 (5.45)	2 (6.45)	0.837 (0.13 – 5.30)	0.850
Cyanosis	13 (23.64)	4 (12.90)	2.089 (0.62 – 7.08)	0.237
Apnea	1 (1.82)	1 (3.23)	0.556 (0.03 – 9.20)	0.682

Difficulty in breathing	50 (61.29)	19 (61.29)	**6.316 (1.96 – 20.34)**	**0.002**
Difficulty in swallowing	4 (7.27)	2 (6.45)	1.137 (0.20 – 6.59)	0.886
Ear complaints	4 (7.27)	4 (12.90)	0.529 (0.12 – 2.28)	0.394
Eye complaints	7 (12.73)	3 (9.68)	1.361 (0.33 – 5.69)	0.673
Vomiting	20 (36.36)	14 (45.16)	0.694 (0.28 – 1.70)	0.424
Diarrhea	8 (14.55)	8 (25.81)	0.489 (0.16 – 1.47)	0.203
Seizure	5 (9.09)	6 (19.35)	0.417 (0.12 – 1.50)	0.180
Retractions				
Subcostal	45 (81.82)	19 (61.29)	**2.842 (1.05 – 7.69)**	**0.040**
Intercostal	3 (5.45)	1 (3.23)	1.731 (0.17 – 17.39)	0.641
Suprasternal	3 (5.45)	2 (6.45)	0.837 (0.13 – 5.30)	0.850
Supraclavicular	3 (5.45)	1 (3.23)	1.731 (0.17 – 17.39)	0.641
Breath sounds				
Normal	11 (20)	8 (25.81)	(reference)	-
Abnormal	44 (80)	23 (74.19)	1.391 (0.49 – 3.94)	0.534
WBC count				
$\leq 12 \times 10^9$ / L	14 (25.45)	10 (32.26)	(reference)	-
$> 12 \times 10^9$ / L	41 (74.55)	21 (67.74)	1.395 (0.53 – 3.67)	0.500

Final analysis (Table 4.1) shows difficulty of breathing as a final predictor, where children presenting with difficulty of breathing are 6.3 times more likely to be hypoxemic (95% CI 1.96 – 20.34, p value 0.002). This model explains 9.45% in the variation of hypoxemia, and was statistically significant at $p < 0.0001$.

Table 4.1 Final prediction model of hypoxemia among of children with PCAP ages 3 months to 5 years (n = 86)

	Adjusted Odds Ratio	**95% Confidence Interval**	**p – value**
Difficulty in breathing	6.316	1.96 – 20.34	0.002

R2 = 9.45%, p-value = <0.0001

DISCUSSION

This study in children ages 3 months to 5 years old with community-acquired pneumonia of different severity demonstrated that 63.9% of children presented with hypoxemia, who required oxygen supplementation, greater FiO_2 concentrations, and needed assisted ventilation, compared to non-hypoxemic children. Difficulty breathing, tachypnea and subcostal retractions were significantly more likely to be observed in hypoxemic children. Comparing oxygen saturation values measured using pulse oximetry and arterial blood gas analysis showed no significant differences among measurements.

The prevalence of hypoxemia obtained in this study was higher compared to that reported in the systematic review by Subhi et al. in 2009 of a range of 9.4 to 13.3% measured by pulse oximetry.[16] A more recent cross-sectional study by Alwadhi et al. in 2017 reported a prevalence of 50.9% by pulse oximetry in children 2 months to 5 years old with severe pneumonia/very severe disease by WHO definition.[17] Wide variations in reported prevalence

of hypoxemia in children with pneumonia may be due to differences in characteristics of study populations, severity of pneumonia, cut-off values and definitions of hypoxemia, methods of measurement of hypoxemia, presence of comorbid conditions, and geographic region and altitude of study setting. [16,18]

Numerous studies have recognized the need to identify predictors of hypoxemia in resource-limited settings, each with varying results. This present study identified difficulty breathing, tachypnea, and subcostal retractions as significantly more likely to be observed in those with hypoxemia. These findings are consistent with previous studies conducted on predictors of hypoxemia.[18,19,20,21,22] Final prediction model in this study showed difficulty in breathing as a final predictor of hypoxemia.

Lower chest wall indrawing or subcostal retraction was found to be correlated to mortality in a multi-hospital, retrospective cohort study by Agweyu et al. involving over 16,000 children 2 months to 5 years old with pneumonia.[23] This clinical sign has been studied with great interest recently since the WHO revised the classification of pneumonia in 2013, downgrading lower chest wall indrawing from a vital physical sign previously used to identify severe pneumonia warranting referral to a facility and injectable antibiotics, to a sign of non-severe pneumonia which warrants oral antibiotic therapy and home care.[24,25,26] Moore et al. implemented the revised WHO recommendations at a developing country capital's general hospital and assessed the feasibility of outpatient management of 120 children 1 month to 12 years old with pneumonia with chest indrawing.[27] Their study concluded that there was a 95% treatment success rate with outpatient management, with no adverse events and no mortalities. However, the study emphasized that several safeguards were in place to identify high-risk children – those with severe malnutrition, HIV infection, danger signs, or hypoxemia by pulse oximetry. In this study and similar to other studies, chest indrawing was identified as a predictor of hypoxemia, and may remain to be a strong indicator for hospital admission, despite the wide variability in its sensitivity and specificity to detect hypoxemia. [28]

Oxygen therapy is essential for the management of hypoxemia in children with pneumonia, yet different guidelines have varying recommendations and cut-off values for providing oxygen supplementation.[1,10,29] The WHO listed several conditions that must be satisfied for hypoxemic children to receive oxygen supplementation: 1) the child must be recognized as hypoxemic by a trained health care provider on the basis of clinical signs or with a pulse oximeter; and 2) the hypoxemic child must receive adequate, uninterrupted oxygen therapy for an adequate duration.[9] In this study, half of non-hypoxemic children were given oxygen therapy, implying a need for reevaluation of practices of emergency room pediatricians on judicious use of oxygen in children with pneumonia, and the benefit of pulse oximetry at the frontline of patient assessment. Unnecessary oxygen entails additional cost and may cause oxygen toxicity leading to acute lung injury due to hyperoxia, which presents with signs and symptoms similar to pneumonia causing undue confusion in the recognition of these features as either pneumonia progression or manifestations of oxygen toxicity.[30] Previous studies reported two infants given supplementary oxygen to have pneumocephalus as severe adverse event to oxygen therapy. [28] A model was proposed by Wu et al. on titration of oxygen flow rates in children receiving oxygen therapy for pneumonia as a method to prevent oxygen toxicity and for oxygen conservation in resource-limited settings.[31] This model involves fixed schedules of titration which translated to oxygen savings of 8% to 12%; however, oxygen titration in children with pneumonia cannot be restricted to a standardized protocol but must be guided by improvement or deterioration of clinical signs and symptoms supported by objective

measurement of oxygenation status. Further, the significant potential risk of non-hypoxemic children to develop hypoxemia during the course of hospital admission must be recognized, and continued observation and monitoring cannot be overemphasized. The computation for hypoxemia in this study was not done real-time; instead, it was evaluated during data analysis. The attending pediatrician was not aware of the fact that a non-hypoxemic patient was on oxygen therapy or vice-versa, as this study did not involve standard medical care administered to the patients. The ABG results were at the disposal of the attending pediatricians to guide them on their medical management.

This study compared oxygen saturation values measured using pulse oximetry and arterial blood gas analysis. Both portable fingertip and handheld pulse oximeters underestimated arterial blood gas oxygenation, although only by 0.136% - 0.323%. No significant statistical differences were noted among measurements indicating that any method of measuring oxygen saturation is acceptable, and either portable fingertip or handheld pulse oximetry closely correlates with the gold standard.

Limits of agreement estimate the interval within which a proportion of the differences between measurements lie. Acceptable limits must be defined or postulated based on clinical necessity, biological considerations, or according to the objective of the study.[32] The limits of agreement of all three methods of measurement were computed to range from -3.388 to 4.035%, with the widest range observed between SaO_2 and SpO_2^H, and the narrowest range seen between SpO_2^{PF} and SpO_2^H. In all three cases, there was no statistically significant difference in variance among measurements. However, since the subjects recruited in this study demonstrated oxygen saturations of 93% and above, these results are applicable only for approximate oxygen saturations of 93-99% as reported in this study, and generalizability is limited to this range of oxygen saturations. This may further be supported by relating these findings to the oxygen-hemoglobin dissociation curve, which demonstrates a steep drop in PaO_2 as the oximeter reading falls below 90%.[33] Furthermore, this generalization is only limited to the particular models of pulse oximeters used in this study; varying results may be generated using different models.

Arterial blood gas still remains to be the gold standard in determination of oxygen saturation, and it has the added advantage of determining acidosis and hypercapnia which are clinically significant parameters in the management of children with pneumonia. However, for the purpose of detecting oxygen saturation, pulse oximetry is an acceptable alternative especially in low-resource settings.

CONCLUSIONS AND RECOMMENDATIONS

Pulse oximetry, either using portable fingertip pulse oximeter or handheld pulse oximeter, closely correlates with arterial blood gas analysis within acceptable limits of agreement and with no significant differences in variance among measurements. Difficulty breathing, tachypnea and subcostal retractions were significantly more likely to be observed in hypoxemic children.

Further studies can be done using a larger sample population to increase the power of the study or a wider age range involving the neonatal and the older pediatric population. Because clinical features may be observer-dependent, standardized evaluation may be used to ensure uniformity in assessment of clinical findings. Further studies can also be done to evaluate the effect of pulse oximetry measurement on the management and outcomes of children with pneumonia. Likewise, investigating the use of pulse oximetry in patients stratified according to pneumonia severity may be done to further evaluate the utility of pulse oximetry across the spectrum of symptom severity.

The applicability of this study is limited to the pulse oximeter models used, and other pulse

oximeter models available in different settings may be evaluated by adapting a similar protocol.

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ORIGINAL ARTICLE

DURATION OF PRETERM PREMATURE RUPTURE OF MEMBRANES AS PREDICTOR OF HISTOLOGIC CHORIOAMNIONITIS AND EARLY ONSET NEONATAL SEPSIS: A COHORT STUDY

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

ABSTRACT

Background: Preterm premature rupture of membranes (PPROM) has been associated with chorioamnionitis but studies are inconsistent on the relationship between PPROM latency and the risk of chorioamnionitis and early onset sepsis.

Objective: To define the association of PPROM latency and the risk of histologic chorioamnionitis (HCA) and early onset neonatal sepsis (EONS).

Methodology: A prospective cohort study was done at a public tertiary hospital on 569 mothers with spontaneous rupture of membranes and with fetuses <37 weeks age of gestation. The profiles of the mothers and neonates were described and the association of PPROM with HCA and EONS was defined using test of association and Receiver Operating Characteristics (ROC) curve analysis. The association of HCA with maternal and neonatal characteristics as well as adverse neonatal outcomes were also determined.

Results: A total of 569 mothers with PPROM were included. Incidence of HCA and EONS were 13% and 24% respectively. PPROM latency was significantly associated with HCA and is a fair predictor of HCA (AUC = 0.7013; 76% accuracy at 31.5-hour cut-off) but failed as a predictor of EONS (AUC = 0.4799). PPROM, platelet count, CRP, and neutrophil count were independent predictors of HCA. HCA was associated with EONS and mortality. Mortality was higher in the presence of both HCA and EONS.

Conclusion: Longer PPROM is associated with HCA and is a fair predictor of HCA at a cut-off of 31.5 hours. PPROM fails as a predictor of EONS.

KEYWORDS: *preterm premature rupture of membranes, histologic chorioamnionitis, early onset neonatal sepsis, latency period*

INTRODUCTION

The Philippines has had the 8th highest number of preterm births and 12th highest preterm rate (14.9%) worldwide in 2010[1].

Preterm premature rupture of membranes (PPROM) is defined as rupture of membranes at less than 37 weeks age of gestation. At the Philippine General Hospital, it is estimated to occur in about 30% of all preterm births that are complicated with early onset neonatal sepsis (EONS)[2]. PPROM and chorioamnionitis along with funisitis, maternal fever and low birth weight are risk factors that have been associated with EONS[3-6]. In PPROM, the rate of microbial invasion of the amniotic cavity is heightened, increasing the likelihood of EONS. Presently, EONS remains to be one of the most common causes of neonatal morbidity and mortality in the pre-term population[7].

Current researches are inconsistent on the relationship of duration of PPROM (PPROM latency) and the risk of HCA and EONS. PPROM latency of 18 hours has been associated with EONS[7] and current recommendation of the American Academy of Pediatrics (AAP) cites 18 hours as the cut-off value to merit investigation and management of potential sepsis in infants <37 weeks age of gestation. However, cut-off values of >48 hours and <4 weeks have also been associated with EONS[4,8]. A study found an association between PPROM latency period of >48 hours with HCA[9] but there were conflicting results with the study of Xie, et.al.[10]. In another observational study, a PPROM latency period >72 hours was associated with clinical chorioamnionitis[11].

This study was done to define the association between the duration of PPROM with the incidence of HCA and EONS. We hypothesized that a longer duration of PPROM is associated with an increased risk for HCA and EONS. Specifically, we aimed to (a) describe the profile of mothers with PPROM and their neonates, (b) determine the predictive ability of PPROM for HCA and EONS, (c) determine maternal and neonatal factors associated with chorioamnionitis, and (d) describe the neonatal outcomes associated with pathologic chorioamnionitis.

METHODOLOGY

A. Study Design:

This is a prospective cohort study.

B. Setting:

The study was conducted in a public tertiary hospital from October 1, 2015 to May 15, 2017.

C. Study Population:

Mothers with fetus at <37 weeks age of gestation and with spontaneous rupture of membranes in varying durations were included. Age of gestation was determined by last menstrual period or early ultrasound. There were no exclusion criteria.

D. Conduct of the study

Recruitment and informed consent

The conduct of the study started when the patient was admitted at the delivery room due to ruptured membranes. The resident or fellow informed the primary investigator of the admission. The primary investigator explained the objective and procedure of the study, and obtained verbal and written informed consent. Patients were enrolled after written consent was obtained.

Data Collection

After enrollment, the profile of the mother was obtained and recorded using a Maternal Data Record Form. Variables collected were maternal age, gravidity and parity, co-morbidities, infections, ultrasound results, and medications (specifically antibiotics and antenatal steroids). Parameters such as mode of delivery, white blood cell (WBC) counts, body temperature and PPROM latency periods were also recorded in the Maternal Data Record Form. After delivery, neonatal data were also recorded on the Newborn Data Record Form as follows: gestational age, birth weight, Apgar score, anthropometric measurements, physical examination, and vital signs. Laboratory

examinations such as complete blood count, blood culture and/or cerebrospinal fluid (CSF) culture and C-Reactive Protein (CRP) for the first 24 hours of life were obtained. All placentas were saved and sent to and examined by the pathologist on the same day (the day of delivery). The pathologist, a co-investigator in the study, examined the placenta and determined the presence or absence of chorioamnionitis. Histologic grading was also assigned once the placenta was confirmed to be positive for chorioamnionitis. The pathologist was a senior resident in his 3rd to 4th year of training during study implementation and was blinded to the maternal and neonatal data and PPROM latency.

The outcomes measured were HCA and EONS. The neonates were monitored closely over three days for clinical and laboratory features that fulfill the criteria for EONS. The clinical practice in the institution was to start on empiric antibiotics if PPROM duration is more than 24 hours. Those who met the above criteria were started on Ampicillin and Gentamycin per order of the Resident-in-charge under the supervision of a Fellow. The antibiotics were continued or stopped based on the blood culture results. The Residents and Fellows who were not part of the study team were oriented on the conduct of the study.

The Flow Diagram of the study is presented in Figure 1.

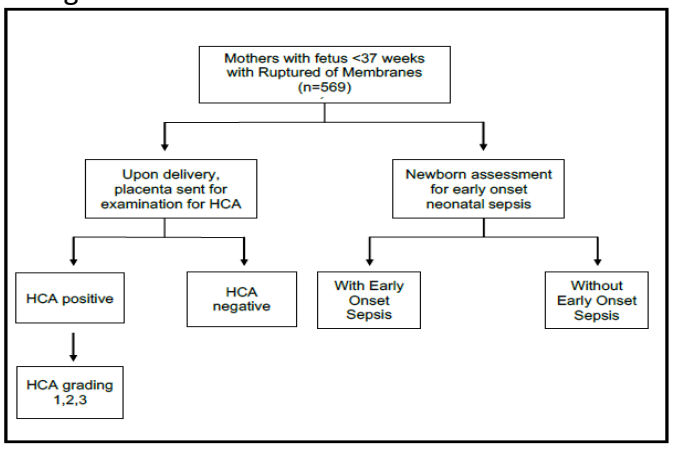

Figure 1. Study flow diagram

E. Sample Size:

To compute for the sample size, we calculated for the minimum sample required for both HCA and for EONS and the higher sample size was followed in this study. The values used for this sample size computation was based on a study by Daunoravičienė et al. in 2014[12]. The calculations are presented below.

Calculation 1 based on PPROM and chorioamnionitis:

For HCA, a minimum sample size of 111 subjects are required for this study. This value gives 80% power to detect an effect size of 45.11 at 0.05 α-level of significance.

Legend:

n = minimum sample

q1= proportion of mothers who developed chorioamnionitis = assumed as 0.5 to obtain a sample size adequate for any proportion of chorioamnionitis, since the said proportion is unknown for this population.

q2= proportion of mothers who did not develop chorioamnionitis = 0.5 (1 – q1)

Zα = 1.96

Zβ = 0.842

E= effect size = 45.11 based on Daunoravičienė et al. 2014[12].

S=standard deviation of the membrane rupture duration (hours) of women with chorioamnionitis = 84.72 based on Daunoravičienė et al. 2014[12].

Sample size formula:

$$d = \frac{E}{S} = \frac{45.11}{84.72} = 0.532$$

$$N = \frac{\left(\frac{1}{q_1} + \frac{1}{q_2}\right) \times \left(z_\alpha + z_\beta\right)^2}{d^2}$$

$$N = \frac{\left(\frac{1}{0.5} + \frac{1}{0.5}\right) \times \left(1.96 + 0.842\right)^2}{0.532^2}$$

$$N = 111$$

Calculation 2 Based on PPROM and Sepsis:

A minimum sample size of 539 subjects are required for this study. This value gives 80% power to detect an effect size of 15.7 at 0.05 α-level of significance. The values used for this sample size computation were based on a study by Daunoravičienė et al. 2014[12].

Legend:

n = minimum sample

q1= proportion of neonates who had sepsis = assumed as 0.5 to obtain a sample size adequate for any proportion of sepsis, since the said proportion is unknown for this population.

q2= proportion of neonates who did not develop sepsis = 0.5 (1 – q1)

Zα = 1.96

Zβ = 0.842

E= effect size = 15.7 based on Daunoravičienė et al. 2014[12].

S= standard deviation of the membrane rupture duration (hours) of women who gave birth to neonates with infection = 65.04 based on Daunoravičienė et al. 2014[12].

Sample size formula:

$$d = \frac{E}{S} = \frac{15.7}{65.04} = 0.241$$

$$N = \frac{\left(\frac{1}{q_1} + \frac{1}{q_2}\right) \times \left(z_\alpha + z_\beta\right)^2}{d^2}$$

$$N = \frac{\left(\frac{1}{0.5} + \frac{1}{0.5}\right) \times (1.96 + 0.842)^2}{0.241^2}$$

$$N = 539$$

In this study, the sample size followed was the higher value obtained which is a minimum of 539 mothers/preterm infants.

F. Statistical Analysis:

Descriptive statistics was used to summarize the clinical characteristics of the mothers and infants. Frequency and percentages were used for nominal variables while median and range for ordinal variables. For interval or ratio variables, mean and standard deviation (SD) were computed or, if not normally distributed, the median and range were computed instead.

Independent t-test was used to compare the means of the 2 groups. Chi- square was used to compare the frequencies between groups. If ≥25% of cells have expected value <5, then Fisher Exact test was used instead.

A receiver operating curve was used to compute area under the curve of the different PPROM latencies and presence of HCA as well as different PPROM latencies and presence of EONS. AUC more than 0.90 is considered an excellent predictor of subsequent histologic chorioamnionitis. AUC of 0.80 - <.90 is considered a good predictor but an AUC of 0.70-<0.80 is considered a fair predictor. AUC of <0.70 is a poor predictor of outcome.

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

G. Definition of Terms:

Preterm premature rupture of membranes (PPROM) is defined as spontaneous pre-labor rupture of membranes before 37 weeks gestation diagnosed by the obstetrician using sterile speculum examination to confirm amniotic fluid pooling in the vagina[5].

Latency period or PPROM latency is defined as the time from rupture of membranes to the time of delivery.

Early onset neonatal sepsis (EONS) is defined by the World Health Organization as blood or cerebrospinal fluid culture-proven infection occurring in the newborn at ≤3 days of life.

Histologic chorioamnionitis (HCA) is defined as inflammation of the placental chorionic disk and extraplacental membranes. Grading of histologic chorioamnionitis is as follows: Stage 1 (Mild); Acute subchorionitis/acute chorionitis, neutrophils in

subchorionic fibrin or interface between deciduas and chorion. Stage 2 (Moderate); Acute chorioamnionitis, neutrophils in connective tissue plane between chorion and amnion. Stage 3 (Severe); necrotizing chorioamnionitis, necrosis, amnion sloughing, thickening of amnion basement membrane and neutrophilic karyorrhexis, multifocal abscess may be present.

H. Ethical considerations:

The study was conducted according to the principles of the International Conference on Harmonization - Good Clinical Practice. It was approved for implementation by the Institution and Hospital Research Ethics Board Review Panel. Informed consent was obtained prior to enrollment of each subject. The study records were locked in the Office of the Section of Newborn Medicine. Data confidentiality was maintained throughout the study and access was allowed only to parties permitted by the principles of ICH-GCP and by laws/regulations including the Data Privacy Act of 2012. Archived study files will be destroyed by paper shredder ten years after completion of the study.

RESULTS

Profile of mothers with PPROM and their neonates

We analyzed 569 mothers with PPROM. Five hundred and eighty-two eligible, consecutive mothers who achieved the inclusion criteria were asked to participate. Thirteen declined leaving 569 mothers (98%) who all gave informed consent for the study. The clinical characteristics of women are presented in Table 1.1. They had a mean (± standard deviation [SD]) maternal age of 19.7 ± 6.8 years, BMI of 23.3 ± 3.8 kg/m2, gravidity of 2 to 3, and parity of 1 to 2. Those with comorbidities of diabetes mellitus (DM), thyroid disease, preeclampsia or eclampsia, anemia, and/or TB represented 30% of the study participants (details not shown in table). Medications taken during the prenatal period included antibiotics and steroids in 46% and 24%, respectively. Twenty-four (4%) were alcohol drinkers, while 19 (3%) were smokers. Deliveries were spontaneous in 65% and via Caesarean section in the rest. The mean (±SD) of women's Amniotic Fluid Index (AFI) was 1.9 ± 0.3 cm (not shown in table). Mean PPROM latency among patients was around 16 hours (range 0.1 to 398 hours) and 44% had PPROM latency of >18 hours. Chorioamnionitis developed in 13% (n = 75) of mothers. Of these, 36% and 59% had HCA grades 1 and 2 respectively.

Table 1.1 Clinical characteristics of 569 mothers who delivered with a history of PPROM

	Frequency (%); Mean ± SD
Age (years)	29.67 ± 6.84
BMI	23.33 ± 3.82
Gravidity	
1	163 (28.65)
2 – 3	259 (45.52)
4 and up	147 (25.83)
Parity	
0	165 (20.9)
1 – 2	243 (42.71)
3 and up	161 (28.3)
With co-morbidities	169 (29.7)
Lifestyle	
Alcohol drinker	24 (4.22)
Smoker	19 (3.33)
Prenatal medications*	
Antibiotics	264 (46.40)
Steroids	134 (23.55)
Mode of delivery	
SVD	373 (65.38)
CS	195 (34.62)
PPROM latency count (hours)	15.88 (0.08 to 397.7)
< 18 hours	318 (55.9)
≥ 18 hours	251 (44.1)
Chorioamnionitis	
Positive	75 (13.18)
Grade 1	27 (36.0)
Grade 2	44 (58.7)
Grade 3	4 (5.3)
Negative	494 (86.82)

** - Multiple Responses*

The mean neonatal age at delivery was 33.2 ± 2.6 weeks, and the median birthweight was 1780 grams (range 500 to 4800). The mean (±SD) of Ballard scores was 32.6 ± 3.3. Those with APGAR scores ≥7 at the 1st and 5th minutes comprised 73% and 99% of infants respectively (Table 1.2).

Table 1.2 Clinical characteristics of 569 neonates who were delivered due to PPROM

	Frequency (%); Mean ± SD; Median (Range)
Birth weight (grams)	1780 (500 to 4800)
Age of gestation (weeks)	33.20 ± 2.63
Total Ballard score	32.55 ± 3.30
Abdominal circumference (cm)	26.67 ± 2.91
Chest circumference (cm)	27.79 ± 2.99
Head circumference (cm)	30.40 ± 2.31
Neonate sex	
Male	203 (35.68)
Female	366 (64.32)
APGAR score	
At 1st minute	
≥ 7	413 (72.6)
< 7	156 (27.4)
At 5th minute	
≥ 7	565 (99.3)
< 7	4 (0.7)

The median length of hospital stay of infants was 34 days, with a median of 5 antibiotic days (Table 1.3). Early onset sepsis occurred in 24% of the neonates, respiratory distress syndrome (RDS) in 30%, retinopathy of prematurity (ROP) in 18%, and bronchopulmonary dysplasia (BPD) in 5%. There were 33 (6%) neonates who died. Blood cultures were positive in 23% of the neonates, and CSF cultures were positive in five (<1%) neonates. Ninety-four percent of infants had CRP levels below 6 mg/L and 79% had WBC between 10 – 20 x 10^9/L. Three fourths had a neutrophil percentage of the total WBC of >0.7 (not shown in table). In 18%, the platelet counts were below 100 x10^9/L.

Table 1.3 Clinical outcomes of 569 neonates who were delivered due to PPROM

	Frequency (%); Median (Range)
Length of hospital stay (days)	34 (12 to 44)
Number of days given antibiotic	5 (3 to 21)
Adverse outcomes*	
Early onset sepsis	138 (24.25)
RDS	171 (30.05)
ROP	101 (17.75)
BPD	31 (5.45)
Mortality	33 (5.8)
Blood CS	
With growth	128 (22.5)
No growth	441 (77.5)
CSF CS	
Positive	5 (0.88)
Negative	564 (99.12)
CRP	
> 6	35 (6.15)
< 6	534 (93.85)
WBC	
0 – 10	122 (21.44)
10 – 20	447 (78.56)
20 and above	0
Platelet count (x10^9/L)	
> 250	439 (77.15)
250 – 100	25 (4.39)
100 and below	105 (18.45)

Predictive ability of PPROM latency for HCA

To determine the optimal cut-off for latency of PPROM to predict HCA, we constructed a receiver operating characteristic (ROC) curve (Figure 2). The ROC curve has an area under the curve (AUC) of 0.7013 which means that the said test has fair accuracy in terms of predicting HCA. Nevertheless, not a single cut-off point had a sensitivity and specificity that were both ≥ 80%. Looking at the different cut-off values, the optimal cut-off of 31.5 hours has the highest accuracy when the sensitivity and specificity are combined (sensitivity of 53%, specificity of 80%, accuracy of 76%) as well as the highest Youden's Index (0.3329) among all other cut-off values. The standard cut-off of 18 hours has a lower accuracy (61%) and Youden's Index (0.2905).

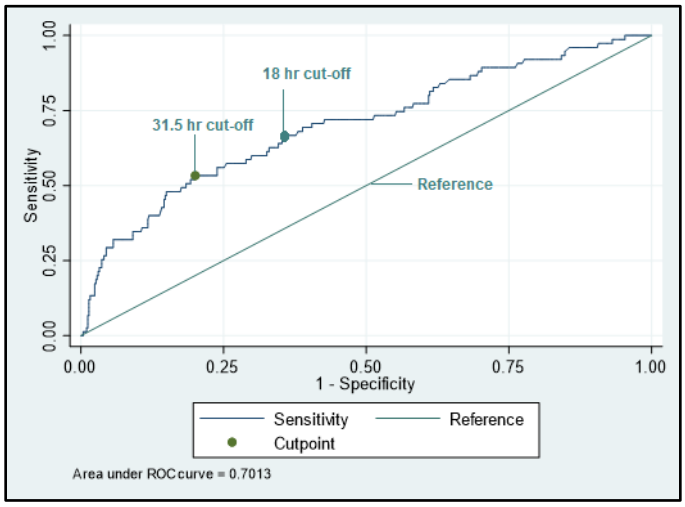

Figure 2. Receiver operating characteristic curve of PPROM latency as predictor of histologic chorioamnionitis

To determine the optimal cut-off for latency of PPROM to predict EONS, we constructed a receiver operating characteristic (ROC) curve (Figure 3). The ROC has an AUC of 0.4799 which means that the said test fails in terms of predicting EONS. An AUC which is close to 0.5, as it is in this case, indicates that the diagnostic test is similar to "chance alone" in predicting the condition (in this case EONS). It is not recommended to use PPROM

as a diagnostic test for EONS and as such, identifying an optimal cut-off value will not be useful.

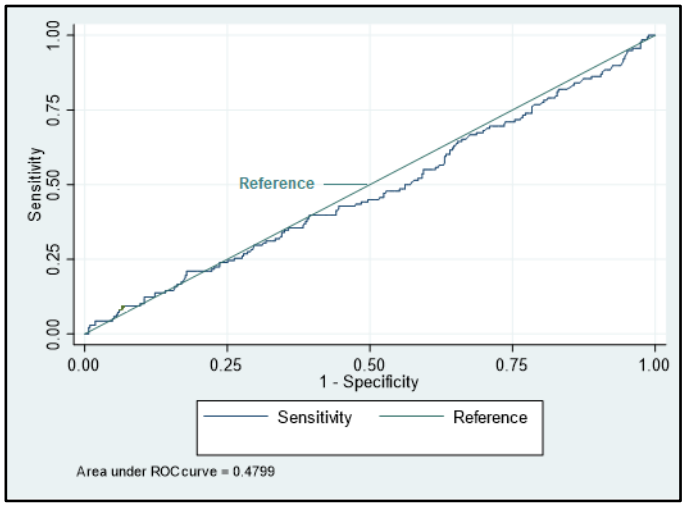

Figure3. Receiver operating characteristic curve of PPROM latency as a predictor of early onset neonatal sepsis

The association of PPROM at different cut-off values with HCA and EONS are presented in Tables 2 and 3. The cut-off used were the standard cut-off of 18.0 hours and the cut-off identified in the ROC in Figure 1, which is 31.5 hours. Table 2 shows that at both cut-off values, there is a significant association of HCA for both 18 and 31.5 hours (both p-values <0.001). However, the odds ratio for the 31.5-hour cut-off was higher than the 18.0-hour cut-off (4.56 vs. 2.86), indicating that the higher cut-off is a better predictor of HCA, as also shown by the ROC analysis in the previous section.

Table 2. Association of PPROM duration with histologic chorioamnionitis

Cut-offs for PPROM	Positive for HCA	%	OR	95% CI	p-value*
Less than 18	23	7.20	2.86	1.80-4.54	<0.001
18 or more	52	20.70			
Less than 31.5	35	8.10	4.56	2.75-7.55	<0.001
31. 5 or more	40	28.80			

**Statistical test: Chi square*

On the other hand, Table 3 shows that at both cut-off values (18 hours and 31.5 hours), there is no evidence of a significant association between PPROM latency and EONS (p-values = 0.925 and 0.934 for 18 - and 31.5-hour cut-offs, respectively and the odds ratios are not different [both 0.98]). This indicates that neither cut-off is predictive of EONS as also revealed by the ROC analysis in the previous section.

Table 3. Association of PPROM duration with early onset neonatal sepsis

Cut-offs for PPROM	Positive for EONS	%	OR	95% CI	p-value*
Less than 18	86	27.00	0.98	0.75-1.29	0.925
18 or more	67	26.70			
Less than 31.5	116	27.00	0.98	0.63-1.51	0.934
31. 5 or more	37	26.60			

**Statistical test: Chi square*

Maternal and Neonatal Factors Associated with HCA

Neonatal factors crudely associated with developing HCA were having PPROM latency period ≥ 18 hours (OR 3.352, 95% CI 1.99 - 5.65), PPROM latency period ≥ 31.5 hours (OR 4.56, 95% CI 2.75 - 7.55), WBC counts of 10-20 x10^9/L (OR 0.455, 95% CI 0.27 - 0.77), and platelet levels greater than 250 x10^9/L (OR 0.277, 95% CI 0.16 - 0.47). No significant associations with maternal characteristics were found. (Table 4.1)

Table 4. 1 Binary logistic regression for predictors of chorioamnionitis

	HCA Positive (n=75)	HCA Negative (n=494)	Crude Odds ratio (95% CI)	*p*-value
	Frequency (%)			
Maternal characteristics				
Age	30.59 ± 6.83	29.53 ± 6.83	1.024 (0.99 - 1.06)	0.213
Parity				
0	25 (33.3)	140 (28.3)	(reference)	-
1 – 2	31 (41.3)	212 (42.9)	0.819 (0.48 - 1.45)	0.491
3 and up	19 (25.3)	142 (28.7)	0.749 (0.39 - 1.42)	0.377
Mode of delivery				
SVD	48 (64.0)	324 (65.6)	(reference)	-
CS	27 (36.0)	170 (34.4)	1.072 (0.65 - 1.78)	0.788
Lifestyle				
Alcoholic drinker	5 (6.67)	19 (3.85)	1.786 (0.65 - 4.94)	0.264
Smoker	4 (5.33)	15 (3.04)	1.799 (0.58 - 5.57)	0.309
Pre-natal meds				
Antibiotics	33 (44)	231 (46.76)	0.895 (0.55 - 1.46)	0.655
Steroids	15 (20)	119 (24.09)	0.788 (0.43 - 1.44)	0.438
Co-morbs				
With at least one co-morbidity	24 (32.0)	145 (29.4)	1.133 (0.67 - 1.91)	0.64
Diabetes mellitus	8 (10.67)	37 (7.49)	1.475 (0.66 - 3.3)	0.345
Hypertension	7 (9.33)	34 (6.88)	1.393 (0.59 - 3.27)	0.446
Thyroid	4 (5.33)	23 (4.66)	1.154 (0.39 - 3.43)	0.797
Preeclampsia	0 (0)	18 (3.64)	1	-
Eclampsia	1 (1.33)	11 (2.23)	0.593 (0.08 - 4.66)	0.62
Anemia	0 (0)	13 (2.63)	1	-
Tuberculosis	0 (0)	12 (2.43)	1	-
Others	8 (10.67)	64 (12.96)	0.802 (0.37 - 1.75)	0.579
Neonatal characteristics				
Age of gestation				
< 34 weeks	35 (46.67)	230 (46.56)	1.004 (0.62 – 1.63)	.986
≥ 34 weeks	40 (53.33)	264 (53.44)	0.996 (0.61 - 1.62)	0.986
Birth weight (grams)				
< 2000 grams	44 (58.67)	323 (65.38)	(reference)	-
≥ 2000 grams	31 (41.33)	171 (34.62)	1.331 (0.81 - 2.18)	0.258
PPROM duration				
< 18 hours	23 (30.67)	295 (59.72)	(reference)	-
> 18 hours	52 (69.33)	199 (40.28)	3.352 (1.99 - 5.65)	<0.001
PPROM 31.5				
< 31.5 hours	35 (46.67)	395 (79.96)	(reference)	-
> 31.5 hours	40 (53.33)	99 (20.04)	4.56 (2.75 - 7.55)	<0.001
CRP				
< 6	73 (97.33)	461 (93.32)	(reference)	-
> 6	2 (2.67)	33 (6.68)	0.383 (0.09 - 1.63)	0.194
WBC				
0 – 10	26 (34.67)	96 (19.43)	(reference)	-
10 – 20	49 (65.33)	398 (80.57)	0.455 (0.27 - 0.77)	0.003
Platelet count				
≤ 100	29 (38.67)	78 (15.38)	(reference)	-
100 – 250	4 (5.33)	21 (4.25)	0.499 (0.16 - 1.56)	0.237
> 250	42 (56)	397 (80.36)	0.277 (0.16 - 0.47)	<0.001
Neutrophil				
< 0.7	19 (25.33)	125 (25.3)	(reference)	-
0.7	43 (57.33)	317 (64.17)	0.892 (0.5 - 1.59)	0.7
> 0.7	13 (17.33)	52 (10.53)	1.645 (0.76 - 3.57)	0.209
IT ratio				
< 20	72 (96)	478 (96.76)	(reference)	-
> 20	3 (4)	16 (3.24)	1.245 (0.36 - 4.36)	0.733

Controlling for the effect of other variables, significant predictors of HCA are having platelet count >250 x10^9/L (adjusted OR [aOR] 0.215, 95% CI 0.12–0.38), PPROM duration ≥ 31.5 hours (aOR 5.058, 95% CI 2.95 - 8.68), CRP level above 6 (aOR 0.186, 95% CI 0.04 - 0.85), and having a neutrophil percentage of the total WBC greater than 0.7 (aOR 2.95, 95% CI 1.4 – 6.2). While controlling for other variables PPROM duration ≥31.5 is around 5 times more likely among those with HCA and neutrophil >0.7 is around 3 times more likely among those with HCA. On the other hand, those with platelet count >250 and CRP>6 are less likely (20% and 19% likelihood respectively) among those with HCA. A platelet count <250 and CRP<6 are associated with higher HCA. (Table 4.2)

Table 4.2 Significant predictors of chorioamnionitis

	Adjusted Odds ratio [aOR] (95% CI)	*p*-value
Platelet count > 250	0.215 (0.12 - 0.38)	**<0.001**
PPROM duration ≥ 31.5 hours	5.058 (2.95 - 8.68)	**<0.001**
CRP >6	0.186 (0.04 - 0.85)	**0.031**
Neutrophil >0.7	2.946 (1.4 - 6.2)	**0.004**

R2=15.79%, p-value <0.001

Neonatal Outcomes Associated with Pathologic Chorioamnionitis

Histologic chorioamnionitis was associated with 2.55 times the odds of having early onset neonatal sepsis and 4.97 times the odds of mortality. We had insufficient evidence to demonstrate a significant association between HCA with RDS, BPD, and ROP (Table 5). Histologic chorioamnionitis carried 2.6 odds for early-onset neonatal sepsis, and 5.0 odds for a fatal outcome.

Table 5 Association between histologic chorioamnionitis and selected neonatal outcomes

	HCA Positive (n=75)	HCA Negative (n=494)	Crude Odds Ratio (95% CI)	p-value
	Frequency (%)			
Early onset neonatal sepsis (EONS)	31 (41.33)	107 (21.66)	2.548 (1.53 - 4.23)	**<0.001**
Respiratory Distress Syndrome (RDS)	20 (26.67)	151 (30.57)	0.826 (0.48 - 1.43)	0.493
Broncho Pulmonary Dysplasia (BPD)	3 (4)	28 (5.67)	0.693 (0.21 - 2.34)	0.555
Retinopathy of Prematurity (ROP)	16 (21.33)	85 (17.21)	1.305 (0.72 - 2.38)	0.385
Mortality	13 (17.33)	20 (4.05)	4.969 (2.36 - 10.49)	**<0.001**

Having either or both HCA and EONS increased the probability of mortality compared to having none of these (P<.0001). Deaths occurred in 23% of neonates with both HCA and EONS, higher

than in cases with positive HCA but no EONS (14%), with positive EONS but no HCA (9%), and neither EONS nor HCA (3%) (Table 6). There was no association between HCA and RDS, BPD, or ROP.

Table 6. Neonates with early onset sepsis and with positive chorioamnionitis

	With EONS; With HCA (n = 31)	No EONS; With HCA (n = 44)	With EONS; No HCA (n = 107)	No EONS; No HCA (n = 387)	*P* value
	Median (Range); Frequency (%)				
Length of hospital stay (days)	34 (15 – 41)	33 (15 – 42)	34 (12 – 43)	34 (12 – 44)	0.839*
Duration of antibiotics (days)	10 (7 – 14)	4 (3 – 14)	7 (3 – 21)	5 (3 – 14)	0.143*
Adverse outcomes					
With RDS	10 (32.26)	10 (22.73)	33 (30.84)	118 (30.49)	0.738‡
With BPD	2 (6.45)	1 (2.27)	6 (5.61)	22 (5.68)	0.852§
With ROP	5 (16.13)	11 (25.0)	20 (18.69)	65 (16.8)	0.564‡
Mortality	7 (22.58)	6 (13.64)	10 (9.35)	10 (2.58)	**<0.0001**‡

EOS – Early Onset Sepsis; HCA – Histologic Chorioamnionitis
*Statistical tests used: * - Kruskal Wallis test; § - Fisher's exact test; ‡ - Chi square test*

DISCUSSION

We analyzed women with different durations of PPROM by sending the placenta for histologic examination after delivery and assessing maternal and neonatal outcomes including HCA and EONS. The incidence of HCA and EONS were 13% and 24%, respectively. PPROM latency was significantly associated with HCA and is a fair predictor of HCA (AUC =0.7013; 76% accuracy at 31.5-hour cut-off) but failed as a predictor of EONS (AUC of 0.4799). PPROM, platelet count, CRP, and neutrophil count were independent predictors of HCA. HCA was associated with EONS and mortality with mortality being higher in the presence of both HCA and EONS.

The incidence of HCA was 13% among these patients with PPROM. Curiously, this is lower than those found in other studies among PPROM patients where incidences as high as 68% and 70% have been reported[9,10]. Conversely, the incidence of EONS in this study (24%) was higher than the other studies mentioned (both 6.5%)[9,10].

We determined if the duration of membrane rupture could be a predictor of HCA and EONS. ROC curve analysis was done to determine whether there is another cut-off point that can give a better sensitivity and specificity, compared with the cut-off of 18 hours that is used in standard practice. An area under the curve of 0.7013 showed that the test (PPROM latency) could fairly predict HCA. Comparing the different levels of PPROM latency, the cut-off at 31.5 hours versus the standard 18 hours showed a higher accuracy. However, for EONS, PPROM duration had an area under the curve of 0.4799, indicating that PPROM duration cannot be used to predict EONS.

The association of longer PPROM latency with HCA has also been noted in other studies. Xie, et.al., found that a PPROM >48 hours was associated with HCA[9]. Daunoraviciene et.al., studied in retrospect 135 pairs of neonates and their mothers who had PPROM at 32 to less than 34 weeks of gestation. Women with inflammation and neonates with congenital infection had longer latency periods and higher CRP values compared to those women with no inflammation and neonates with no infection, concluding that a longer latency period and higher maternal CRP can be used as prognostic indicators of intrauterine infection and congenital infection[12].

In the crude analysis, the 31.5-hour cut-off had a stronger association with HCA than the standard cut-off of 18 hours. Furthermore, even after controlling for the effect of other variables, it is notable that PPROM at ≥31.5-hour cut-off was most strongly associated with HCA among the significant predictors identified. Consistent with the results of the ROC curve and the test of association of the 2 cut-off values with HCA, this study shows that PPROM at the cut-off of 31.5 hours is an independent predictor of HCA. Based on the results of this study, the PPROM cut-off of 18 hours may lead to over-treatment with antibiotics in preterm infants whose mothers did not have chorioamnionitis and a cut-off 31.5 hours may decrease overtreatment. However, since PPROM latency per se is only a fair predictor of HCA, it would be prudent for the physician to look into other associated factors or predictors when making their

assessment, rather than relying on PPROM latency alone.

When managing patients with PPROM, it is important, as much as possible, to avoid early termination of pregnancy while preventing possible complications of prolonged PPROM. Comparing the different levels of PPROM duration, the cut-off of 31.5 hours versus the recommended 18 hours, the longer latency showed the optimal specificity and accuracy of predicting histologic chorioamnionitis. This suggests that the 31.5-hour cut-off may be considered for serial testing in identifying mothers with PPROM who will need to be observed and treated, especially taking into consideration those with lower age of gestation to prevent earlier termination of pregnancy. Despite previous research findings that EONS is significantly associated with PPROM latency, in this research, there is no significant evidence of PPROM latency predicting EONS, hence not supporting its use in diagnosing EONS.

This study revealed that PPROM, platelet count, CRP, and neutrophil count were independent predictors of HCA. HCA was associated with EONS and mortality with mortality being higher in the presence of both HCA and EONS. Various factors have been cited in the literature on PPROM as being associated with chorioamnionitis and early onset sepsis. Alam MM et.al., retrospectively investigated 428 neonates born to mothers with premature rupture of membranes for more than 18 hours. The results showed that the risk factors associated with the development of culture-proven EONS include maternal fever, PPROM>48 hours, neonatal prematurity, and low birth weight, along with neonatal thrombocytopenia and raised CRP[13]. In a study of 838 preterm infants born at less than 30 weeks gestational age by Strunk, *et.al.* increased risk of EONS was associated with HCA[14]. Nayot et.al., studied 1535 singleton pregnancies with PPROM and associated a PPROM latency of >72 hours with clinical chorioamnionitis[11]. But somewhat counterintuitively, it also associated PPROM latency of ≤72 hours combined with <32 weeks gestational age with a two-fold higher incidence of severe neonatal morbidity[11].

In the association between HCA and mortality, mortality was significantly higher in the presence of both HCA and EONS. This is not surprising considering that infection in HCA could predispose to EONS, which in turn is associated with higher risk of mortality. Management-wise this stresses the importance of early detection of HCA with a higher index of suspicion at PPROM latency of ≥ 31.5 hours especially in the presence of other associated factors, with the physician anticipating the need for more aggressive management to prevent poor neonatal outcomes. The combination of HCA and EONS is a special concern in this case as it is associated with a significantly higher mortality than the presence of only one of either condition. However, the results of this study do not suggest any drastic change in what is considered as the optimal treatment of infants with EONS, which is broad spectrum antimicrobials (ampicillin and an aminoglycoside) and adjustment of coverage once a pathogen has been identified[7]. Aside from neonates with histologic chorioamnionitis and early onset neonatal sepsis having a high mortality rate (22.6%), there is also high mortality among neonates with HCA but no signs of EONS (13.6%) compared with neonates with neither HCA nor EONS (2.58%). This may indicate that even initially asymptomatic preterm infants who have HCA, need antibiotic therapy. The AAP recommendation is to start antibiotic therapy among preterm infants with maternal chorioamnionitis[7]. This result supports what is believed to be the current optimal management of clinical chorioamnionitis, which includes antibiotic therapy and delivery[15].

CONCLUSION

The mothers with PPROM had a mean age of 19.7 years, with 1 to 2 children, and a 13% incidence of HCA. Their neonates averaged 1,780 grams

birthweight, 33 weeks AOG, 34 days in the hospital, and had a 24% incidence of EONS.

PPROM latency at 31.5-hour cut-off value was a fair predictor of HCA (76% accuracy; AUC of 0.7013) and was a better predictor of HCA than the 18-hour cut-off (61% accuracy). However, PPROM latency failed as a predictor of EONS (AUC of 0.4799).

After controlling for other variables PPROM ≥ 31.5 hours, platelet count <250, CRP <6, and neutrophil count >0.7 were shown to be independent predictors of HCA. HCA was also associated with adverse neonatal outcomes, particularly EONS and mortality, with mortality being higher in the presence of both EONS and HCA.

RECOMMENDATION

In the context of PPROM, it is recommended to include placental examination in clinical practice. Without it, there may be underdiagnosis or late diagnosis of chorioamnionitis and possible complications and neonatal outcomes such as early onset sepsis.

Future research is also recommended to validate the cut-off of 31.5 hours and for further evaluation of the effects of histologic chorioamnionitis on neonatal outcomes.

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ORIGINAL ARTICLE

CLINICO-EPIDEMIOLOGIC PROFILE AND OUTCOME OF PEDIATRIC PATIENTS WITH MULTI DRUG RESISTANT GRAM-NEGATIVE HEALTHCARE ASSOCIATED INFECTIONS AT THE PHILIPPINE GENERAL HOSPITAL

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

ABSTRACT

Introduction: Multi Drug Resistant Organisms (MDRO) are microorganisms that are resistant to one or more classes of antimicrobial agents, and these have become significant pathogens to contend with in the treatment of Healthcare Associated Infections.

Objectives: This study aimed to determine the clinico-epidemiologic profile and outcome of pediatric patients with healthcare-associated multi-drug resistant gram-negative infections, and its antimicrobial susceptibility patterns.

Methodology: This was a retrospective study done on pediatric patients with gram negative healthcare associated MDRO sepsis compared to non-MDRO sepsis admitted at the ICU and pediatric wards of a tertiary government hospital from July 2015 to June 2016. Descriptive statistics was used to summarize the clinical characteristics of patients. Odds ratio and the corresponding 95% confidence interval from binary logistic regression was computed to determine significant predictors for the development of multi drug resistance. Outcome of patients with MDRO gram-negative infection was noted, as well as its antimicrobial susceptibility patterns.

Results: A total of 199 patients developed HAI, and 41% were identified to be gram negative MDR cases. Pediatric patients with healthcare associated infections-due to MDR gram negative organisms had shorter hospital stay and a higher mortality rate of 78% compared to 41% among non MDR patients. The most commonly isolated gram negative organisms were Burkholderia cepacia, 38%; Klebsiella pneumoniae, 31%; and Acinetobacter baumanii, 18%; while the most common MDR gram negative isolates were Klebsiella pneumoniae, 65%; Acinetobacter baumanii, 22%; and Pseudomonas aeruginosa, 7%.

Significant predictors for MDRO were age (0-28 days old), ICU admission, intravascular catheterization and use of total parenteral nutrition.

Conclusion: Profile of pediatric patients with healthcare-associated multi-drug resistant gram-negative infections were neonates admitted in the ICU with a shorter hospital stay and a high mortality rate. The identified risk factors for developing Multi Drug Resistant Gram Negative sepsis were age of 0-28 days, admission to ICU, intravascular catheterization and parenteral nutrition. Patients with gram-negative MDR infections have a high mortality rate and isolates are susceptible mostly to Colistin.

KEYWORDS: *multiple drug resistance, healthcare associated infections, gram negative bacterial infections*

INTRODUCTION

Healthcare-Associated Infections (HAIs) are infections appearing in hospitalized patients not present nor incubating at the time of admission, the onset of which is beyond 48 hours from admission to the hospital, within 3 days of discharge or 30 days after an operation[1]. The rates of multi-drug resistance among pathogens causing healthcare-associated infections are increasing, mainly among gram-negative organisms[2].

Multi Drug Resistant Organisms (MDROs) are microorganisms, predominantly bacteria, that are resistant to one or more classes of antimicrobial agents. Prevalence of MDROs varies temporally, geographically, and by healthcare settings. MDRO infections result in significant morbidity and mortality and have now impacted in the care of infants and children[3]. There is paucity of data addressing treatment options for multi drug resistant Gram-negative (MDRGN) infections in children, so data must be extrapolated from adult literature[1].

The increase in multi-drug resistance in the healthcare setting demonstrates a need for studies on the epidemiology and outcomes of MDRO healthcare-associated infections, thus, this study aimed to determine the clinical and epidemiologic profile of pediatric patients with healthcare-associated gram-negative infections, as well as risk factors for development of infections with MDRO. . Outcome of patients with MDRO gram-negative infections was noted, as well as its antimicrobial susceptibility patterns.

MATERIALS AND METHODS

The study was conducted after approval from the University of the Philippines Manila Research Ethics Board (UPMREB) Panel was obtained.

This is a retrospective study on healthcare associated gram negative MDRO compared to non MDRO cases admitted in the pediatric wards, Pediatric Hematology-Oncology Unit, Pediatric Intensive Care Unit and Neonatal Intensive Care Unit of a tertiary government hospital from July 2015 to June 2016.

Multidrug-resistant gram negative and non-multidrug-resistant gram negative infections with isolates which grew on culture of blood obtained via aseptic technique 48 hours after admission, or within 3 days after discharge, or within 30 days post-surgery were identified. Risk factors such as presence of intravascular catheter, initiation of targeted antimicrobial therapy, surgery, and the presence of clinical manifestations of infection, i.e. at least one clinical finding of temperature >38^{o}C or <36^{o}C, chills, hypotension for age, tachycardia or bradycardia for age were noted.

Reports of gram-negative blood isolates in pediatric patients were obtained from the central laboratory. Cases of healthcare associated bacteremia were selected among these gram-negative blood isolates, and correlated with the clinical course of the patient.

These cases of gram-negative blood isolates which were correlated with clinical data were double checked with the Nosocomial Infection Report Form of the Section of Infectious and Tropical Diseases in Pediatrics. The investigator subsequently retrieved the medical charts of these patients with healthcare associated gram-negative bacteremia.

The following information were obtained from the Nosocomial Infection Report Form (NIR): age, gender, location, type of healthcare-associated infection and the blood isolate and its antimicrobial susceptibility. Patient risk factors noted were presence or absence of malnutrition, malignancy/blood dyscrasia, steroid intake, catheterization, prematurity, central line, parenteral nutrition, nasogastric tube, surgery, mechanical ventilation, and antibiotic use for more than two weeks.

All data were entered into a case report form containing pertinent demographic data from the NIR form as well as identified risk factors.

MDROs cases were determined from the antibiotic susceptibility pattern of the blood isolates.

Descriptive statistics was used to summarize the clinical characteristics of the patients. Frequency and proportion were used for nominal variables, median and Inter-Quartile Range for ordinal variables, and mean and Standard Deviation for interval/ratio variables. Mann-Whitney U and Fisher's Exact/Chi-square test was used to determine the difference of mean, median and frequencies between groups, respectively. Odds ratio and the corresponding 95% confidence interval from binary logistic regression was computed to determine significant predictors for the development of multi drug resistance. All valid data were included in the analysis. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05α-level of significance. STATA 12.0 was used for data analysis.

RESULTS

A total of 199 patients were identified to be HAI sepsis cases, and 41% were identified to be MDR cases (Table 1). Profile of MDR and non-MDR patients were compared and the variables noted to significantly differ for the two groups were age (p=0.000), distribution in the pediatric age group (p=0.000), weight (p=0.000), height (p=0.000), area of admission (p=0.000), underlying conditions and comorbidities, and duration of nosocomial infection (p=0.001) as seen in table 1.

A look into the clinical outcomes of patients showed that there were significant differences in the duration of hospital stay between MDR and Non-MDR patients (p=0.012) and in mortality rates (p=0.000) as seen in Table 2.

The most commonly isolated microorganisms in HAIs were Burkholderia cepacia (38%) Klebsiella pneumoniae (31%), and Acinetobacter baumanii (18%).

The top MDROs isolated among patients with HAIs were K. pneumoniae (65%), A. baumanii (22%), and P. aeruginosa (7%) as seen in Table 4.

The top non-MDR Gram negative organisms isolated among patients were B. cepacia (64%), A. baumanii (14%), and K. pneumoniae (7%) as seen in Table 5.

We analyzed select patient characteristics to determine whether these were associated with the development of MDR. Significant factors identified were admission to the ICU (p=0.006) and intravascular catheterization (p=0.040).

For the final model for predicting multidrug resistance (Table 6), significant factors were age of 0-28 days old (p=0.042), admission to ICU (p=0.002), intravascular catheterization (p=0.009) and use of PPN/TTN (p=0.044). This model however accounted for only 22.42% of the variability of developing into an MDR among patients (p-value = 0.000; R^2= 22.42%).

DISCUSSION

Infections with Multi-Drug Resistant Organisms have become a significant global health problem. Our study conducted in a national university hospital showed that we have not been spared from this occurrence.

One-hundred ninety-nine patients with Gram Negative Bacteremia were included in the study, and 41% of these were MDRO. Among these patients with MDRGNB, 80% were neonates, while in those with non-MDRGNB, 40% were neonates. A review by Zaidi et al. showed that hospital-born babies in developing countries are at increased risk of neonatal infections because of poor intrapartum and postnatal infection-control practices. Reported rates of neonatal infections were 3–20 times higher than those reported for hospital-born babies in industrialized countries.[4]

Majority of cases of MDRGNB were admitted at the ICUs (83%), compared to non-MDRGNB which were at the regular wards (59%). The type and level of care also influence the prevalence of MDRO

infections. Admission to ICUs, especially those in tertiary care facilities, may contribute to a higher prevalence of MDROs than those admitted in non-ICU settings[5].

Majority of patients with MDRGNB are neonates, thus prematurity, use of gastric tubes, Hypoxemic Ischemic Encephalopathy (HIE), Hyaline Membrane Disease (HMD), Necrotizing Enterocolitis (NEC), and other Gastrointestinal (GI) abnormalities were seen more in MDRGNB patients. These findings were found to be statistically significant.

The top 4 Gram Negative Isolates were B. cepacia, K. pneumoniae, A. baumanii and P. aeruginosa. The susceptibility pattern of these isolates to various antibiotics were determined. B. cepacia was susceptible to Ceftazidime and Cotrimoxazole. K. pneumoniae was susceptible to Colistin. A. baumanii was susceptible to Colistin and Ciprofloxacin. P. aeruginosa was susceptible to Colistin. These susceptibility patterns reflect the presence of MDR K. pneumoniae, A. baumanii, and P. aeruginosa since the organisms showed resistance to one or more drugs in three or more classes of antimicrobial agents for which they are known to be susceptible (such as carbapenems, fluoroquinolones, and third generation cephalosporins).

Isolates known to have MDR resistance in Southeast Asia in the study of Zaidi, AK et al, were, Klebsiella, E. coli, and S. aureus.[4]

Outcomes of pediatric patients with healthcare associated gram-negative infections showed that patients with MDRGNB have shorter hospital stay due to high mortality rates of 78% compared to 41% among patients with non-MDRGNB. Previous studies on MDRO showed increased length of stay, increased cost, and high mortality rate with associated outbreaks[5].

We identified possible risk factors for developing MDRO among patients with Healthcare-associated GNB. Neonates, admission to intensive care units, intravascular catheterization, and use of parenteral nutrition were found to be significant risk factors.

Pediatric patients in the ICU are particularly susceptible to nosocomial infections due to use of invasive devices and multiple procedures. Although any serious infection will warrant admission to the ICU, infection may also be a complication after ICU admission. Multiple studies documented the increase in the incidence of nosocomial infections due to antibiotic-resistant organisms, particularly in Pediatric Intensive Care Units .[6]

A research done in Greece in 2014, reported risk factors for MDR K. pneumoniae in a NICU as follows: neonates who received parenteral nutrition, delivery by Cesarean Section, low gestational age, and low birth weight. Transmission of MDROs in high risk units can occur at the time of delivery, or by person-to-person transfer through the hands of the nursing staff, contaminated equipment, food, or the environment.[7]

On the contrary, another study done by Tsai et al in Taiwan on risk factors and outcomes for MDRGNB in the NICU revealed that extremely low birthweight, prematurity and underlying chronic conditions are not associated with MDRGNB.[8]

A study done in the Philippines by Litzow et al, revealed that prematurity and low birthweight infants requiring mechanical ventilation were significant risk factors for invasive MDRGNB in the NICU. [9]

Preventing the occurrence of healthcare-associated infections depends on appropriate clinical practices that should be incorporated in routine patient care. These include optimal management of vascular and urinary catheters, prevention of lower respiratory tract infections in intubated patients, accurate diagnosis of infectious conditions, and judicious antimicrobial selection and utilization.[5] If these processes are consistently observed it can have a significant impact on HAIs and on MDRGB infections as well.

Table 1. Demographic and clinical profile of pediatric patients with healthcare-associated Gram-negative infections, Philippine General Hospital (n=199)

	MDR GNB (n=81)	Non MDR GNB (n=118)	P- value
	Frequency (%); Mean ± SD; Median (Range)		
Age (Months)	0 (0 to 216)	2 (0 to 216)	0.000‡
Age Group			0.000§
0-28 days	65 (80.25)	47 (39.83)	
29 days to 3 months	13 (16.05)	16 (13.56)	
4 months to <2 years	2 (2.47)	17 (14.41)	
2 to 5 years	0	11 (9.32)	
> 5 years	1 (1.23)	27 (22.88)	
Sex			0.641
Male	48 (59.26)	66 (55.93)	
Female	33 (40.74)	52 (44.07)	
Weight (kg)	2 (0.65 to 25)	3.85 (0.70 to 67)	0.000‡
Height (cm)	42 (23 to 144)	57.5 (28 to 176)	0.000‡
Admission Ward			0.000§
Ward 9 or 11	14 (17.28)	70 (59.32)	
PICU/NICU	67 (82.72)	43 (36.44)	
Hema onco ward	0 (0)	5 (4.24)	
Underlying conditions*			
With Malnutrition	6 (7.41)	26 (22.03)	0.006
With Catheterization	37 (45.68)	31 (26.27)	0.005
With PPN/TTN	38 (46.91)	22 (18.64)	0.000
With Malignancy/blood dyscracia	0 (0)	16 (13.56)	0.001
With Prematurity	46 (56.79)	31 (26.27)	0.000
With Mechanical ventilation	71 (87.65)	76 (64.41)	0.000
With Steroid intake	0 (0)	3 (2.54)	0.272§
Central line	8 (9.88)	9 (7.63)	0.577
On antibiotics > 2 weeks	24 (29.63)	31 (26.27)	0.603
With NGT	81 (100)	92 (77.97)	0.000
With Surgery	18 (22.22)	24 (20.34)	0.749
Comorbities*			
Pneumonia	9 (11.11)	32 (27.12)	0.006
Congenital Heart Disease	14 (17.28)	20 (16.95)	0.951
Malignancy	2 (2.47)	19 (16.10)	0.002
Hyaline Membrane Disease	22 (27.16)	13 (11.02)	0.003
GI abnormalities	2 (2.47)	13 (11.02)	0.025
Necrotizing Enterocolitis	20 (24.69)	9 (7.63)	0.001

	MDR GNB (n=81)	Non MDR GNB (n=118)	P- value
	Frequency (%); Mean ± SD; Median (Range)		
CNSI	2 (2.47)	9 (7.63)	0.205§
Down Syndrome	4 (4.94)	8 (6.78)	0.515§
Intracranial Bleed	1 (1.23)	1 (0.85)	1.000§
Chiari II malformation	3 (3.70)	2 (1.69)	0.399§
Bronchopulmonary Dysplasia	3 (3.70)	4 (3.39)	1.000§
ARDS	0	3 (2.54)	0.272§
Persistent Pulmonary Hypertension	7 (8.64)	4 (3.39)	0.126
Pneumothorax	4 (4.94)	2 (1.69)	0.227§
Rheumatic Heart Disease	0	1 (0.85)	1.000§
Tuberculosis	0	3 (2.54)	0.272§
Gastroschisis	8 (9.88)	3 (2.54)	0.053§
Gut Obstruction	2 (2.47)	5 (4.24)	0.703§
Omphalocoele	1 (1.23)	2 (1.69)	1.000§
Peripheral Nervous system abnormalities	0	3 (2.54)	0.272§
Cerebral Palsy	0	2 (1.69)	0.515§
Genetic Abnormalities	1 (1.23)	1 (0.85)	0.765§
Kidney Diseases	2 (2.47)	3 (2.54)	1.000§
Malnutrition	2 (2.47)	3 (2.54)	1.000§
Intestinal Parasitism	0	3 (2.54)	0.002§
Caustic Ingestion	0	2 (1.69)	0.272§
Hypoxic Ischemic Encephalopathy	10 (12.35)	4 (3.39)	0.015
Multiple Congenital Anomalies	3 (3.70)	3 (2.54)	0.689
Infective Endocarditis	0	1 (0.85)	1.000§
Septic Shock	0	4 (3.39)	0.147§
Endocrine Abnormalities	0	1 (0.85)	1.000§
Dextroscoliosis	0	1 (0.85)	1.000§
Status Epilepticus	0	1 (0.85)	1.000§
Acute Gastroenteritis	0	1 (0.85)	1.000§
Transient tachypnea of the newborn	7 (8.64)	0	1.000§
Duration of nosocomial infection (days)	9 (1 to 23)	14 (1 to 15)	0.001‡
Previous nosocomial infection	38 (46.91)	45 (38.14)	0.217

Statistical Tests Used: Chi Square test; ‡ - Mann-Whitney U test; § - Fisher's Exact test
*Note: * - Multiple Response Variable*

Table 2. Clinical outcomes of the pediatric patients with healthcare-associated Gram-negative infections, Philippine General Hospital (n=199) suggested

	MDR GNB (n=81)	Non MDR GNB (n=118)	P-value
	Frequency (%); Mean ± SD; Median (Range)		
Number of Hospital Stay (days)	25 (3 to 180)	32 (3 to 289)	0.012‡
Days from admission and symptoms (days)	9 (3 to 146)	10 (3 to 279)	0.993‡
Mortality	63 (77.78)	48 (40.68)	0.000

Statistical Tests Used: Chi Square test; ‡ - Mann-Whitney U test; § - Fisher's Exact test

Table 3. Microorganisms isolated from pediatric patients with healthcare-associated Gram-negative infections, Philippine General Hospital (n=199)

	Frequency (%)
B. cepacia	76 (38.19)
K. pneumoniae	61 (30.65)
A. baumanii	35 (17.59)
P. aeruginosa	6 (3.03)
A. iwoffi	5 (2.51)
E. coli	4 (2.01)
Achromobacter sp.	3 (1.51)
S. marcescens	2 (1.01)
E. cloaceae	2 (1.01)
E. aerogenes	1 (0.50)
B. mallei	1 (0.50)
B. gladioli	1 (0.50)
S. paucimonilis	1 (0.50)
A. faecalis	1 (0.50)

Table 4. Multi-Drug Resistant Organisms isolated from pediatric patients with healthcare-associated bacteremia, Philippine General Hospital (n=81)

	Frequency (%)
K. pneumoniae	53 (65.43)
A. baumanii	18 (22.22)
P. aeruginosa	6 (7.4)
A. iwoffi	2 (2.47)
Achromobacter sp.	2 (2.47)

Table 5. Microorganisms isolated from the pediatric patients with healthcare-associated non-MDR Gram-negative infections, Philippine General Hospital (n=118)

	Frequency (%)
B. cepacia	76 (64.4)
A. baumanii	17 (14.4)
K. pneumoniae	8 (6.78)
E. coli	4 (3.39)
A. iwoffi	3 (2.54)
S. marcescens	2 (1.69)
E. cloaceae	2 (1.69)
Achromobacter sp.	1 (0.85)
E. aerogenes	1 (0.85)
B. mallei	1 (0.85)
B. gladioli	1 (0.85)
S. paucimonilis	1 (0.85)
A. faecalis	1 (0.85)

Table 6. Final Model for predicting multi-drug resistance

	Odds Ratio	CI 95%	P-value
Age 0-28 days 29 days and above	2.4538 (reference)	1.0315 to 5.8374	0.042 -
Admission Ward PICU/NICU Wards (Ward 9-11/ Hema ward)	4.1535 (reference)	1.7099 to 10.0888	0.002 -
With Catheterization	2.5582	1.2621 to 5.1852	0.009
With PPN/TTN	2.1029	1.0205 to 4.3334	0.044

P-value = 0.000 ; R^2= 22.42%

CONCLUSION

This study showed that healthcare associated Multi Drug Resistant Gram-Negative infections usually occur in neonates admitted in the ICU, who had a short hospital stay and a higher mortality rate. The most common healthcare-associated MDR gram negative isolates were K. pneumoniae, A. baumanii and P. aeruginosa. The identified risk factors for Multi Drug Resistant Gram-Negative infections were age of 0-28 days, admission in the ICU, intravascular catheterization and use of parenteral nutrition.

Options for treating patients with Healthcare Associated MDRGNB are extremely limited. In this study, MDRGNB isolates were mostly susceptible to Colistin.

RECOMMENDATIONS

A prospective study using a risk assessment tool for predicting MDRO infection can be done based on the results of this study. Diagnostic tools such as molecular based biologic tests can also be done on isolates. There is a need to look into treatment options for MDROs among pediatric patients. Other aspects in the control of MDRGNB infections such as observance of standard and contact precautions, surveillance systems, judicious use of antimicrobials, and education should also be emphasized.

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ORIGINAL ARTICLE

EPIDEMIOLOGY AND OUTCOME OF CHILDREN LIVING WITH HIV IN A TERTIARY HOSPITAL: A 6-YEAR RETROSPECTIVE STUDY

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

2ND PRIZE 2019 PIDSP RESEARCH CONTEST

ABSTRACT

Introduction: Infection with HIV is multi-faceted and involves the interplay of medical, social, and economic factors thus, management of the disease continues to be a challenge to most physicians. The Philippines is experiencing a surge in cases since 2013. Understanding the local epidemiology of pediatric HIV may reveal opportunities to reduce or eliminate transmission through timely diagnosis.

Objective: This study was conducted to identify the features and outcome of children living with HIV in a hospital where a program for HIV treatment and monitoring was implemented.

Methodology: Medical records of all children <18 years of age diagnosed as pediatric HIV based on the World Health Organization case definition and enrolled in the STD/AIDS Guidance Intervention Prevention (SAGIP) Unit were reviewed. Data was analysed using descriptive statistics.

Results: Thirty pediatric HIV patients were included in the study. The most common mode of acquisition is by sexual transmission (57%) and most patients were male (76%), bisexual (47%), and heterosexual (47%). Weight loss (50%), rash (50%), fever (37%) and cough (37%) were the most common clinical findings. The most common opportunistic infections were tuberculosis (47%) and oral candidiasis (34%). Only 27 of 30 patients were started on antiretroviral therapy within 6 months from diagnosis. One patient showed resistance to a non-nucleoside reverse transcriptase inhibitor (NNRTI). There were 11 children who died of various opportunistic infections and its complications, while 2 were transferred to a different treatment hub after 6 months, and 1 lost to follow-up.

Conclusion: Sexual means of HIV transmission among adolescents is evident in this study. Weight loss, cough, rash, fever, and lymphadenopathy are common presenting features. Tuberculosis and oral candidiasis are the most common opportunistic infections and should alert physicians on possible HIV infection. A mortality rate of 37% was noted mostly in the first 6 months of initiating ART treatment.

KEYWORDS: *Pediatric HIV, Outcome, Profiles*

INTRODUCTION

The scale-up efforts on the program on prevention of maternal to child transmission (PMTCT) has contributed to the global decrease in pediatric HIV, with 2 million new infections averted since the year 2000. Although prevention of pediatric HIV has shown some success, based on the 2017 UNAIDS report where a steep decline in pediatric AIDS-related illness to about half from 2010 to 2016 (210,000 vs 120,000 cases) was seen, the same report showed a lag in pediatric HIV testing and treatment[1]. Global HIV trends have been decreasing, but the Philippines is experiencing an exponential increase of about 138% in cases since 2013[2]. Increase in pediatric HIV can be attributed to the following: increasing HIV infection in females of reproductive age leading to vertical transmission, lack of accessible testing facilities for infants <18 months thereby causing a delay in treatment, and earlier age of sexual debut in adolescent patients[1].

Clinical manifestations of pediatric HIV are varied and often non-specific[3]. A local study by Aro et.al. showed that 48% of children living with HIV (CLHIV) were 0-6 years old and majority were infected through vertical transmission (73%). The most common presenting signs and symptoms were cough, skin lesions and weight loss[4].

Understanding the local epidemiology of pediatric HIV and knowledge on the natural progression of the disease may reveal opportunities to reduce and eliminate transmission[3]. Identification of children infected with HIV will allow for timely and appropriate treatment and significantly improve quality of life. Knowledge of the epidemiologic and clinical profile may help clinicians meet the diagnostic and management challenges presented by CLHIV. There is paucity of data on the clinical profile and outcome of CLHIV in the Philippines and as HIV cases are increasing, data on CLHIV need to be updated. This study aimed to look into the epidemiology and outcome of children living with HIV in a hospital where an improved HIV diagnosis, treatment and monitoring program was implemented in the STD/AIDS Guidance Intervention Prevention (SAGIP) Unit of the University of the Philippines-Philippine General Hospital (UP-PGH).

METHODOLOGY

Ethics: Data was collected after approval of the study from the institutional Ethics Review Board.

Study Design and Population: A retrospective chart review of all pediatric cases <18 years of age at the time of HIV diagnosis and reported in the UP-PGH SAGIP Unit from January 1, 2012 to December 31, 2017 was done. HIV/AIDS diagnosis is based on the World Health Organization (WHO) case-definition of pediatric HIV/AIDS[5]. The SAGIP Unit is the hospital's facility which caters to STD/HIV/AIDS patients from all areas and facilitates inter-hospital and inter-departmental referrals.

Exclusion Criteria: Patients more than 18 years of age at the time of HIV diagnosis and those enrolled in the prevention of mother-to-child transmission (PMTCT) program who are born to HIV-positive mothers but with negative HIV-DNA PCR were excluded from the study.

Data Collection: Demographic and clinical data were obtained and recorded in a case report form. Data collected were age, sex, sexuality, residence, educational attainment and presenting signs and symptoms. Information on the child's HIV status, and marital status and respective professions of parents were noted. Maternal and birth history, mode of infant feeding, previous hospitalizations and relevant social history were collected. Pertinent laboratory tests (i.e., CD4, viral load, complete blood count, liver function tests) at the time of diagnosis and on follow-up were obtained. Information on Anti-Retroviral Therapy (ART) regimen including date started and duration of use, and occurrence of adverse events and its management were also obtained. Concomitant use of medications such as Cotrimoxazole and Isoniazid were noted. Clinical course and outcome of individual patients up to 6 months post-diagnosis were described.

Case Definition: HIV infection in patients >18 months to 18 years of age is defined as a positive

HIV antibody test confirmed by a second HIV antibody test and/or a positive virological test for HIV or its components confirmed by a second virological test obtained from a separate determination[5]. HIV status of patients <18 months was confirmed by at least one positive DNA-PCR test[5].

Mode of HIV transmission was determined by establishing maternal HIV status, as well as history of blood transfusion, use of injectable drugs and unsafe sexual practices.

Patients were stratified based on the WHO Staging System for pediatric HIV which classified an individual's status from asymptomatic to severely symptomatic.[5]WHO immunological classification for established HIV infection using CD4% based on age was also used to stage individual patients.[5]

Descriptive statistics was used for the following: demographic profile of patients, mode of HIV transmission, clinical presentation and clinical stage of the disease at the time of diagnosis. Quantitative variables were described using mean and standard deviation, while responses to qualitative variables were summarized as frequencies and percentages.

RESULTS

A total of 30 children were included in this study and median age at diagnosis was 16 years (2months being the youngest and 18 years being the oldest).

Sexual means was the most common mode of transmission in 57% of cases, with a mean age at diagnosis of 17.5 years (n=17). Perinatal transmission accounted for the remaining 40% (n=12). The mode of transmission was unknown in a 5-year-old male child who tested positive to 2 rapid HIV antibody tests and 1 HIV-ELISA test. He presented with prolonged fever, weight loss, cough and multiple lymphadenopathies. During his hospital stay, he had progressive respiratory distress with hypoxemia. He eventually died and autopsy revealed the presence of disseminated tuberculosis involving the lungs, pericardium, liver, spleen, pancreas, adrenals and kidneys. HIV testing of both parents and other siblings were negative.

In patients infected through sexual transmission (Table 1) majority were males (76%), mostly heterosexual (47%) or bisexual (47%). Sixty five percent came from urban areas. Their parents were mostly married (70%), high school graduates (47%), with unknown HIV status.

Table 1. Demographic Profile and Mode of Transmission of Children Living with HIV

Demographic Profile	N=30 (%)	Mode of transmission N=30(%)		
		Sexual 17(57%)	Perinatal 12 (40%)	Unknown 1 (3%)
Median Age at diagnosis (Range)	16 (0.17-18)			
Mean Age at diagnosis (range)		17.5 (15-18)	3.45 (0.17 – 7)	
Sex				
Male	21 (70.00)	13 (76%)	7 (58%)	1 (100%)
Female	9 (30.00)	4 (24%)	5 (42%)	-
Sexuality				
Bisexual	8 (26.67)	8 (47%)		
Heterosexual	9 (30.00)	8 (47%)		
Homosexual	1 (3.33)	1 (6%)		
N/A	12 (40.00)	-		
Residence				
Urban	18 (60.00)	11 (65%)	6 (50%)	1 (100%)
Rural	12 (40.00)	6 (35%)	6 (50%)	
Educational attainment (care givers)				
Elementary	2 (6.67)	1 (6%)	1 (8%)	-
Highschool	11 (36.67)	8 (47%)	2 (16%)	1 (100%)
College	3 (10.00)	1 (6%)	2 (16%)	-
N/A	14 (46.67)	7 (41%)	7 (60%)	-
Occupation of parents/guardian				
both unemployed	1 (3.33)	-	1 (8%)	-
1 parent employed	14 (46.67)	6 (35%)	8 (67%)	-
both parents employed	6 (20.00)	2 (12%)	3 (25%)	1 (100%)
N/A	9 (30.00)	9 (53%)	-	-
Marital Status of parents/guardian				
Not married				
Married	1 (3.33)	1 (6%)	-	-
Cohabiting	15 (50.00)	12 (70%)	2 (17%)	1 (100%)
Separated	3 (10.00)	-	3 (25%)	-
Widowed	5 (16.67)	2 (12%)	3 (25%)	-
N/A	5 (16.67)	1 (6%)	4 (33%)	-
	1 (3.33)	1 (6%)	-	-
HIV Status of Father				
Negative	8 (26.67)	5 (30%)	2 (17%)	1 (100%)
Positive	8 (26.67)	-	8 (67%)	-
Unknown	14 (46.67)	12 (70%)	2 (17%)	-
HIV Status of Mother				
Negative	7 (23.33)	6 (35%)	-	1 (100%)
Positive	12 (40.00)	-	11 (92%)	-
Unknown	11 (36.67)	11 (65%)	1 (8%)	-

In those infected through vertical transmission (Table 1), mean age at diagnosis was 3.45 years. Fifty eight percent were males, with an equal number of cases in urban and rural areas. Most patients have at least 1 employed parent (67%). Most parents were initially married (n=9) but 4 got widowed, 3 separated, and 2 remained married. Eleven out of 12 (92%) mothers were HIV positive except for one who was not tested because of non-disclosure of the HIV positive husband due to poor marital relationship. As for the fathers 8 out of 12 were HIV positive (67%), 2 (17%) were negative and 2 (17%) were of unknown status.

The most common presenting features (Table 2) in those infected through vertical transmission were fever (42%), cough (34%), weight loss (50%) and rash (67%). Most common physical findings (Table 2.1) were rashes (42%), weight loss (58%), fever (67%), and presence of abnormal chest findings (67%).

There is no significant difference on the clinical signs and symptoms in those infected through sexual transmission from those infected through vertical transmission, however, CNS symptoms and signs (18% and 29%) were more common in those who got infected sexually, and so is the presence of anal warts (12%), as seen in Table 2.

Table 2. Clinical Symptoms of Children Living with HIV (N=30)

Clinical Presentation	Vertical Transmission n(%)	Sexual Transmission n(%)	P-value (<0.05)
Fever	5 (42%)	6 (35%)	0.9302
Rashes	8 (67%)	7 (41%)	0.3292
Weight loss	6 (50%)	9 (53%)	0.8759
Cough/Chest findings	4 (34%)	7 (41%)	0.9679
Abdominal distention/ Organomegaly	2 (17%)	2 (17%)	1.000
Lymphadenopathy	5 (42%)	5 (29%)	0.7740
Jaundice	-	1 (6%)	1.000
Seizures/ CNS	-	3 (18%)	0.2436
Oral lesions	3 (25%)	2 (12%)	0.1626
Anal Warts	-	2 (12%)	0.1626

Table 2.1. Physical Examination Findings of Children Living with HIV (N=30)

Clinical Presentation	Vertical Transmission n(%)	Sexual Transmission n(%)	P-value (<0.05)
Fever	8 (67%)	8 (47%)	0.5050
Rashes	5 (42%)	9 (47%)	0.8250
Weight loss	7 (58%)	12 (70%)	0.7740
Cough/Chest findings	8 (67%)	9 (53%)	0.7216
Hepatomegaly	0	3 (18%)	0.3587
Lymphadenopathy	1 (8%)	2 (12%)	1.000
Seizures	0	5 (29%)	0.0588
Easy fatigability	0	5 (29%)	0.0588
Diarrhea	4 (33%)	5 (29%)	0.8221
Ear discharge	2 (17%)	1(6%)	1.000
Oral lesions	2 (17%)	0	0.1626
Vomiting	2 (17%)	0	0.1626
Abdominal distention	2 (17%)	0	0.1626

Nutritional status (Table 3) upon initial chart review were unknown in almost 30% of patients. In those with available data and where weight was obtained, 10 (34%) showed a normal weight for age, 7 (23%) were severely underweight and 4 (13%) were underweight. Height for age measurements in those with available data revealed that 13 (43%) had normal height for age, 7 (23%) were severely stunted, 2 (7%) were stunted and 8 (27%) were unknown due to lack of data.

Table 3. Nutritional Status of Children Living with HIV (N=30)

	N=30	%
Weight for Age		
Normal	10	34%
Underweight (Z score below -2)	4	13%
Severely Underweight (Z score below -3)	7	23%
Unknown	9	30
Height for Age		
Normal	13	43%
Stunted (Z score below -2)	2	7%
Severely Stunted (Z score below -3)	7	23%
Unknown	8	27%

Baseline laboratory tests were done in majority of patients prior to initiation of ARTs, however, follow-up diagnostics after initiation of ART was lacking (Table 4). The median CD4 count in patients infected through vertical transmission was 523.3 cells/mm3 and in those infected through sexual means, 161 cells/mm3 (Table 4).

Table 4. Laboratory Results before and after ART Treatment in CLHIV

	Sexual Transmission		Vertical Transmission	
Laboratory Tests	**Laboratory Results at the time of Diagnosis Median (n)**	**Laboratory Results after initiation of ART treatment Median (n)**	**Laboratory Results at the time of Diagnosis Median (n)**	**Laboratory Results after initiation of ART treatment Median (n)**
Viral Load	14, 512 (2)	12 (2)	2,542,229 (2)	39.4 (2)
CD4	161	264 (9)	523.3 (10)	1,149 (6)

Hem	120.9	133 (7)	104.1 (9)	97.8 (6)
Hema	0.36	0.39 (7)	0.31 (9)	0.29 (6)
WBC	7.0 (16)	7.77 (7)	9.8 (9)	5.42 (6)
Neutr	0.66	0.58 (7)	0.49 (9)	0.46 (5)
Lymp	0.21	0.32 (7)	0.38 (9)	0.43 (5)
Mono	0.11	0.084 (5)	0.06 (9)	0.086 (5)
Eosin	0.04	0.047 (4)	0.05 (9)	0.016 (5)
Platel	333	263 (6)	326 (9)	291.6 (5)
AST	45.18	42.19 (4)	59 (8)	34 (4)
ALT	34.99	39.26 (4)	56 .68 (8)	19.2 (4)
BUN	2.85 (8)	3.15 (2)	4.06 (5)	2.64 (3)
Crea	55.69	76.95 (6)	44.9 (6)	41.67 (3)
Total Chole	5.30 (8)	6.99 (3)	-	-
Trigly cerid	2.52 (7)	5.83 (3)	-	-
HBsAg n(%)	Non-reactive 13 (76.5) Reactiv	N/A	Non-reactive 6 (50) Reactive (0)	N/A
RPR n(%)	Non-reactive 11 (65)	N/A	Non-reactive (0) Reactive	N/A

Screening tests for other STIs in those infected sexually showed that only 1 in 17 (6%) was reactive to HBsAg and 3 (17.5%) were reactive to RPR. The laboratory findings before and after initiation of ART cannot be compared due to incomplete data.

Majority of patients infected by vertical transmission were at WHO clinical Stage I and II at the time of diagnosis (Table 5). In contrast, majority of those infected by sexual transmission were at WHO clinical Stage IV (53%). Using the CDC Surveillance staging which is based on initial CD4 count, most patients were at Stage 3 for both groups at the time of diagnosis, 77.78% and 67% respectively.

Follow-up staging after initiation of ART treatment showed that majority were at WHO Stage 1 (45%) and CDC Stage 1 (50%) in those infected through vertical transmission; the other group were mostly on WHO Stage IV (47%) and CDC Stage 3 (56%).

Table 5. Clinical and Immunological Staging of CLHIV before and after initiation of ART

	Sexual Transmission n=17		**Vertical Transmission n=12**	
CDC HIV Surveillance staging (based on CD4 count)	**At time of Diagnosis n (%)**	**After Treatment n (%)**	**At time of Diagnosis n (%)**	**After Treatment n (%)**
1	2 (16.5)	3 (33%)	1 (11.11)	3 (50.00)
2	2 (16.5)	1 (11%)	1 (11.11)	2 (33.33)
3	8 (67)	5 (56%)	7 (77.78)	1 (16.67)
Total	12	9	9	6
WHO Clinical and Immunologic staging	**At time of Diagnosis n (%)**	**After Treatment n (%)**	**At time of Diagnosis n (%)**	**After Treatment n (%)**
I	6 (35%)	6 (35%)	4 (33.33)	5 (45.46)
II	2 (12%)	3 (18%)	4 (33.33)	-
III	0	0	1 (8.33)	3 (27.27)
IV	9 (53%)	8 (47%)	3 (25.00)	3 (27.27)
Total	17	17	12	11*

**1 patient was lost to follow-up hence no clinical staging done*

A total of 42 opportunistic infections were recorded at the time of HIV diagnosis. The most common opportunistic infections as seen in Table 6 were were tuberculosis (35%), oral candidiasis (26%), Pneumocystis jiroveci pneumonia (14%), Toxoplasmosis (10%), and Cytomegalovirus infection (5%).

Table 6. Opportunistic Infections Present at the Time of Diagnosis

	Sexual Transmission N=22	**Vertical transmission** N= 20 (%)	**Total N=42 (%)**
Tuberculosis	9 (53%)	6 (50%)	15
Candidiasis	5 (29%)	6 (50%)	11
PCP pneumonia	3 (18%)	3 (25%)	6 (14%)
Toxoplasmo	3 (18%)	1 (8%)	4 (10%)
Others	2 (12%)	2 (17%)	4 (10%)
CMV	0	2 (17%)	2 (5%)

Only 27 of 30 patients (90%) were started on highly active antiretroviral therapy (HAART) as seen in Table 7. Twenty-five patients were started on treatment within 6 months from diagnosis while 2 patients started treatment after 6 months from diagnosis. Three patients who were not started on HAART were diagnosed with disseminated tuberculosis at presentation, hence, anti-tuberculous regimen was given first. These patients eventually died 2-3 days after the diagnosis of HIV infection was made.

Table 7. Highly Active Antiretroviral Treatment Regimens Used in Children Living with HIV (N=30)

HAART Regimens	**N (%)**
Lamivudine, Tenofovir, Efavirenz	14 (47%)
Lamivudine, Abacavir, Efavirenz	5 (17%)
Lamivudine, Zidovudine, Navirapine	3 (10%)
Lamivudine, Zidovudine, Efavirenz	2 (6.5%)
Lamivudine, Abacavir, Nevirapine	2 (6.5%)
Lamivudine, Abacavir, Lopinavir/ritonavir	1 (3%)
HAART not started	3 (10%)

Eighteen children were on Cotrimoxazole chemoprophylaxis for Pneumocystis jiroveci pneumonia (PJP). Seven patients who were >7 years old with CD4 count more than 200 cells were not given cotrimoxazole prophylaxis, while 5 patients were given Cotrimoxazole as treatment for PJP pneumonia. The diagnosis of PJP pneumonia was based on a high index of suspicion coupled with findings of respiratory distress and hypoxemia. One patient developed an adverse drug reaction to cotrimoxazole and prophylaxis was shifted to dapsone.

A total of thirteen patients (43%) were treated for tuberculosis, 7 (54%) were classified as Pulmonary TB and 6 (46%) diagnosed to have Disseminated Tuberculosis (Gastrointestinal, liver, lymph nodes, CNS). Six of 13 (46%) patients were classified as treatment completed, 1 (8%) as relapse after treatment, 3 (23%) with ongoing treatment and 3 (23%) died of complications of TB. One patient with disseminated tuberculosis developed multi-drug resistant TB and had secondary bacterial peritonitis; another patient with TB meningitis died of brain herniation; still another patient with unknown mode of HIV transmission died of probable bacterial pneumonia on top of disseminated tuberculosis.

For clinical course and outcomes during treatment, there were 3 reported adverse events for patients <10 years old and 2 events in those older than 10 years old (Table 8). Two events were attributed to zidovudine which manifested as severe and persistent anemia with a mean hgb of 70mg/dL; 1 related to nevirapine which presented as urticarial rash; 1 related to efavirenz which presented as severe headache and 1 with abacavir which presented as acute pancreatitis with abdominal pain, elevated serum lipase and amylase. Only one patient showed resistance to an NNRTI, Efavirenz.

The occurrence of opportunistic infections was noted to be high for all patients during the first 6 months of HAART. The most common diagnosis was tuberculosis in 4 patients followed by clinical

diagnosis of PCP (n=4), cryptococcal meningitis (n=2), CMV disease (n=1), oral candidiasis (n=1) and cerebral toxoplasmosis (n=1).

Eleven out of 30 (37%) HIV positive children succumbed to death secondary to AIDS-related infections and complications such as secondary bacterial infections, tuberculosis, and PJP pneumonia. There were 2 patients transferred to another treatment hub after more than 6 months of follow-up while 1 patient was lost to follow-up. The rest of the patients are continuously being seen and managed at the SAGIP Clinic.

Table 8. Clinical course, treatment and outcome of Children Living with HIV

Outcome	Vertical transmission	Sexual Transmission	Total (N=30)
Adverse Drug Reaction* (n=5) (HAART)	3 (60%)	2 (40%)	5 (17%)
Opportunistic Infection * (n=13)	6 (46%)	7 (54%)	13 (43%)
Mortality (n=11)	4 (36%)	7 (64%)	11 (37%)

** 1 patient may have 1 or more adverse event or opportunistic infection*

As seen in Table 9, baseline CD4 count as well as hemoglobin levels had significant negative correlation with the WHO clinical and immunologic staging (-0.4026, p-value=0.0061 and -0.4215, p-value=0.0014 respectively). The rest of the laboratory findings did not show any association with the clinical and immunological stage of HIV at the time of diagnosis.

Table 9. Association of Laboratory Findings with Clinical and Immunological Staging of CLHIV

Laboratory Findings	CDC HIV Surveillance staging		WHO Clinical and Immunologic staging	
	Kendall Tau	**p-value**	**Kendall Tau**	**p-value**
HIV Viral Load	*	*	*	*
CD4 Count	-0.4561	0.0015	-0.4026	0.0061
Hemoglobin	-0.2288	0.1354	-0.4215	0.0014
Hematocrit	-0.0523	0.7585	-0.1446	0.2800
WBC	-0.0523	0.7587	-0.0892	0.5119
Neutrophils	0.1765	0.2528	0.4000	0.0025
Lymphocytes	-0.2484	0.1042	-0.3877	0.0034
Monocytes	-0.0083	1.0000	-0.0290	0.8533
Eosinophils	-0.1538	0.4265	-0.2762	0.0671
Bands	-0.3571	0.1310	-0.1209	0.4668
Platelet count	0.1242	0.4287	0.0800	0.5579
AST	0.4667	0.0037	0.3587	0.0100
ALT	0.2417	0.1383	0.1558	0.2695
Total Bilirubin	0.0000	1.000	0.0000	1.000
Direct Bilirubin	0.0000	1.000	0.3000	0.5791
Indirect Bilirubin	0.0000	1.000	-0.3000	0.5791
Albumin	0.0000	1.000	0.1389	0.6102
BUN	-0.2857	0.2433	-0.4066	0.0323
Creatinine	0.1758	0.3504	-0.1368	0.3859
LDH	*	*	*	*

Total cholesterol	-0.4364	0.0508	-0.0545	0.8623
Triglycerides	-0.4222	0.0803	-0.2222	0.3774

DISCUSSION

Pediatric HIV has become a global public health problem affecting mostly children in resource poor areas of the world. In the Philippines, based on the latest report from the National Epidemiology Bureau of the Department of Health, from January 2013 to March 2018, there were 92 pediatric cases in those <15 years old with an increasing proportion of HIV positive cases in the 15-24-year age group (25% in 2006-2010 to 29% in 2011 to 2018).

Presence of HIV in the family can significantly impact on interpersonal relationships especially in a setting where family ties are strong. In a study done in Malawi on HIV status, gender and marriage dynamics showed that HIV status is a predictor of marital change and the relative risk of a divorce is three times higher for HIV positive compared to HIV negative women[6]. In this study, most parents of children affected by perinatal transmission were married (n=9/12), 4 were widowed, and 3 separated. Our data suggest that HIV positive individuals face risks of union dissolution from widowhood or separation.

Sixty percent of patients came from urban areas consistent with the report of Aro et.al. in 2012[4]. This may be attributed to the availability and accessibility of diagnostic and treatment facilities in urban centers.

Mother to child transmission (MTCT) is the most important source of HIV infection in children as seen in most studies[3,9]; however, in our study, sexual transmission outweighed MTCT, 57% vs 40%. This is in contrast to the findings of Aro et al. where MTCT was found to be the major mode of HIV transmission (73%)[4]. Results in this study is comparable with a UNAIDS report, where the number of adolescents 10-19 years living with HIV has risen by 30% between 2005 and 2016[1]. This may be due to various factors that puts the adolescents at an increased risk for HIV - early sexual debut, non-use of condoms, and preference for older sexual partners – all posing a greater risk for sexually transmitted infections and unintended pregnancies[10].

Risk factors found in a study done in Africa by Fernandez et al. include tobacco (34%), marijuana (28%), and alcohol use (22%) either on a weekly or daily basis[11]. In the Philippines, a study done in 2013 on adolescent sexual attitudes and behavior involving 1,412 participants showed that 27.7% engaged in premarital sex (PMS), compared to 18% back in 2000. Of those who engaged in PMS, 80% did not use a condom. Still in 2015 in an Integrated HIV Behavioral and Serologic Surveillance in the Philippines involving 9,498 males/transgenders having sex with males, 17% were in the 15-17-year age group while majority were 18-24 years of age (49%). More than half of the study population (58%) did not practice condom use and only 14% know their HIV status.

In this study, the mean age of diagnosis for patients infected through MTCT is 40 months with a median of 36 months. A later age of diagnosis was noted in India with a mean of 54 months, in Cameroon 71 months, and in Nepal 58 months [12-14] For patients infected through sexual transmission the mean age is 17.5 years with a median of 18 years. The youngest who became infected with HIV was at 15 years of age. In this study, 76% were males, 47% of which were bisexuals, 47% were heterosexuals and 6% homosexuals. This is in contrast to the findings in South Africa, where majority of adolescent patients were females (57%) and heterosexuals (83%)[15].

Only one case of HIV acquired thorugh MTCT received maternal ARV during her 2nd trimester. The infant received prophylaxis with Nevirapine for 6 weeks. Maternal viral load prior to ART was at 1,000,000 copies/ml and no repeat viral load was done prior to delivery. Maternal transmission of HIV has been well documented especially in the absence of effective intervention[13]. The implementation of

the PMTCT program has greatly reduced the incidence of HIV infection through vertical transmission. Failure of PMTCT program is usually attributed to late antenatal care, delay or omission of maternal ART initiation, and maternal seroconversion (or an initial false-negative HIV screening which later becomes positive prior to or during or after delivery) which leads to subsequent delay in maternal ART initiation[16]. ART started >24 weeks age of gestation may not allow adequate time for viral suppression by the time of delivery[17]. Although maternal ARV was started before the 3rd trimester for this case, the presence of high viral load may have contributed to the failure of PMTCT. Maternal illness may also contribute to insufficient levels of antibodies and inability to provide children with adequate natural passive immunity before birth[16], although in our case, there was no documented illness in the mother.

In this study, 11 out of 12 fathers of CLHIV infected perinatally were tested for HIV and 8 were positive. Paternal risk factors for HIV infection noted were multiple sexual partners, non-use or inconsistent use of condoms and IV drug use.[18]

There is a wide spectrum of clinical presentation of HIV infection in children. The common clinical findings in a study carried out in 4 hospitals in Yaoundé in 2002 were anemia (85%), prolonged fever (63%), chronic diarrhea lasting >1 month (46%), and weight loss or cachexia (43%)[19]. In India, the main clinical manifestations were pulmonary tuberculosis (55%), oral candidiasis (43%), recurrent respiratory tract infections (26%), and skin infections (21%)[20]. In our study, the most common clinical features were weight loss, cough, fever, and rashes. Presenting features in our study are almost similar and comparable with other studies done in resource limited settings [21-23].

Undernutrition is an important feature in HIV infected children in the developing world and remains to be one of the major causes of child morbidity[24]. Children with HIV infection can manifest with poor weight gain and may have failure to thrive[25]. In this study, majority presented with weight loss in 50% in those infected by vertical transmission and 53% in those infected by sexual transmission (Table 2). This can be due to multiple factors - poor nutrition, repeated bouts of infection or immunosuppression, along with poverty. Data in this study were comparable to the study by Sunguya et al. who found that among 213 HIV positive children 6-60 months old, 36.6% were stunted, 22.1% were underweight, and 13.6% were wasted[22].

Tuberculosis is the most common opportunistic infection seen in HIV infected children in developing countries[26]. Tuberculosis was also the most common opportunistic infection in our study at 47%. Mortality was higher in patients with disseminated TB at 67% comparable with reports of higher mortality in HIV co-infected TB patients in Ethiopia in 2016 (8.3% vs 2.5%, P=0.014) [26]. Oral candidiasis may be the first sign of HIV infection[27]. This was the second most common opportunistic infection noted in this study at 33%. Various studies have reported higher prevalence of candidiasis. Pruthvi et al. reported candidiasis in 71% of HIV positive patients, Nagalingeswaran et al. in 70%, Singh et al. in 65% and Anupriyawadhwa et al. in 50% of HIV positive patients[27-29]. Candidiasis has been used as a clinical marker of the disease as its frequency correlates with a low CD4 + T Lymphocyte count and a high viral load[30]. In our study, patients with oral candidiasis at HIV diagnosis had a higher mortality rate of 75%, and all of these patients had tuberculosis. In a local study by Manicad et al. on the prevalence of HIV infection in children using clinically directed selective HIV screening, there was a 1.6% prevalence of HIV in patients with tuberculosis and oral candidiasis[31].

Only 23 patients had initial hemoglobin determination and anemia was present in 53% of those tested. A study done in Ethiopia concluded that anemia was more prevalent and severe in patients with low CD4 T cell counts, patients infected with intestinal parasites, and HAART naïve patients[32-33]. However, another study in Ethiopia showed conflicting results[34]. In this study, 68% of those with anemia at the time of HIV diagnosis died.

However, a direct relationship between anemia and mortality cannot be established from this study due to presence of other comorbidities. Hemoglobin determination 6 months post ART was done in only 13 patients; hence, a significant correlation cannot be established with regard to improvement of anemia after ART.

CD4 count data in this study showed that majority had a CD4 counts of 0-199 (37%) followed by 200-399 (13%). CD4 cell count is a strong predictor of subsequent risk of AIDS or death in both untreated HIV-infected individuals and in those initiating combination ART (cArt)[35], although, the use of CD4 count along with viral RNA provides more information[36]. The higher the viral load and the lower the CD4 counts, the more susceptible the patient is to opportunistic infections such as pneumocystis jiroveci pneumonia, TB, oral candidiasis, toxoplasmosis, and cryptococcosis.

A significant negative correlation exists between the CD4 count and WHO Clinical Staging with a p value of 0.0061 as seen in this study. However, many patients who had complications of HIV/AIDS and those who died did not have baseline CD4 level and viral load in the data collected. Ideally, testing for viral load and CD4 should be part of the routine monitoring of patients with HIV, however, limiting factors in this study include the price and availability of the test, especially since baseline testing is not covered by the insurance system in the Philippines. Although baseline viral load was done in only 4 patients, CD4 count determination at the start of ART was done in majority of patients (63%). Because of the insufficient number of data obtained on follow up after initiating ART, CD4 count, viral load, level of immunosuppression, and development of symptoms cannot be correlated in this study.

The use of Cotrimoxazole as prophylaxis for various opportunistic infections in patients with HIV has been well documented[37]. In our study, cotrimoxazole prophylaxis was given to 60% of patients and it was withheld in 7 patients all with CD4 count of >200 cells. WHO treatment guidelines 2006 on the use of cotrimoxazole prophylaxis recommend the use of cotrimoxazole for CLHIV younger than 1 year of age regardless of CD4 percentage, children >1-year-old who are symptomatic or children with CD4 of <25%, and in children >5 years of age with CD4 <200 cells/mm3. The most common AIDS-defining condition in children is PJP pneumonia[37]. In this study, five patients were clinically diagnosed to have PJP pneumonia. This is noted to be high when compared to a study done in Nepal with only 1 case of PJP pneumonia out of 39 HIV-infected children[3]. The high incidence of PJP in this study could mean overdiagnosis due to lack of funds to have the diagnostics done as well as lack of readily available laboratory facilities for a definitive diagnosis.

The use of highly active antiretroviral therapy (HAART) in HIV treatment has led to dramatic improvements in the health of people with HIV/AIDS. ART reduces mortality as well as serious AIDS- and non-AIDS-related complications[35]. Previous recommendations for delayed ART were heavily influenced by drug toxicities, the potential for drug resistance and limited treatment options for patients who failed initial therapy. At present, therapeutic options have expanded, and the available agents are more potent, better tolerated, with lower toxicities compared to older agents. Most patients in this study (83%) were started with ART within 6 months from diagnosis and 2 patients after 6 months from diagnosis.

Various reports showed that adverse drug reactions (ADR) are associated with non-adherence to treatment, discontinuation of ART, treatment failure, and changes in ART regimens. ADRs in the form of anemia, rash, severe headache and acute pancreatitis were reported in 5 patients in our study. In Nicaragua where data on 692 HIV patients on ART were reviewed, there was a 6.4% incidence of ADRs, and the most common adverse events involved the central nervous (57%), gastrointestinal (27%) and dermatologic systems (18 %)[38].

The presence of opportunistic infections during the first 6 months of HAART was noted in 40% of patients in this study. Most common opportunistic infections noted were tuberculosis, cryptococcoma, CMV and PJP pneumonia among others. The pattern of opportunistic infections may be affected by the availability of ART to children infected with HIV. In a Nepalese study involving all age groups, oral candidiasis was the predominant opportunistic infection followed by streptococcal pneumonia, salmonella infection, cryptosporidial infection and tuberculosis[37].

From this data collected (2012-2017), there were 11 mortalities noted due to complications of AIDS. The most common cause of death was PJP and tuberculosis and most deaths occurred within 6 months from diagnosis.

This is comparable with reports of high mortality in children living with HIV within the first 6 months of initiating ART in Africa and Asia, with deaths resulting from TB and PJP [39-40]. However, a recent study done in Nigeria on the causes of death among HIV-infected children within the first 6 months of HAART cited tuberculosis (70%), sepsis/ undernutrition (10%) and severe pneumonia as contributing factors (6.7%)[41].

LIMITATIONS OF THE STUDY

The retrospective nature of the study was a major limiting factor. The forms used within the SAGIP Unit were also tailored for adult patients, and data pertinent to the pediatric population were found to be lacking. Due to limited advanced diagnostic facilities, recognition of opportunistic infections was mainly done by assessment of clinical features and indirect markers where applicable, which may have led to over or under diagnosis of various opportunistic infections. Lastly, because of the small number of HIV positive children reviewed in a single center, as well as the descriptive nature of this study, our findings may not be generalizable to similar settings.

CONCLUSION

In this study, sexual mode of transmission is the more common mode of acquiring HIV infection in children. Fever, weight loss, rash, cough and lymphadenopathy were the most common presenting features. Tuberculosis and oral candidiasis are the most common opportunistic infections present at the time of HIV diagnosis. HIV mortality is more common during the first 6 months of HAART initiation.

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Dengue Disease Bulletin
A Disease Awareness Campaign for Pediatricians

(A Joint Statement by the Philippine Pediatric Society and the Pediatric Infectious Disease Society of the Philippines)

The Philippines is continuously facing an alarming rise in dengue cases at the present time. Reported through the Philippines Integrated Disease Surveillance and Response (PIDSR) system, there have been 106,630 dengue cases in the country from January 1 to June 29, 2019, reflecting an 85% increase in cases compared to 2018. There were 456 reported deaths for this period, giving a case fatality rate (CFR) of 0.43%, with the greatest number of both cases and deaths seen in the 5-9-year age group. While this CFR is lower compared to the rate in the previous year (0.55%), it is still higher than the average 0.22% CFR in the Western Pacific region. The regions that have been most affected are II, IVA, V, VI, VII, VIII, IX, XII, BARMM, and NCR, while the provinces that have already declared an outbreak and seek access to calamity funds include Iloilo, Capiz, Aklan, Antique and Guimaras in the Western Visayas.[1] It has recently been reported that a number of provinces are already seeing dengue way beyond an epidemic threshold.

Dengue is a viral illness transmitted to humans thru the bite of an infected mosquito, *Aedes aegypti*. Most infections are asymptomatic, but is often suspected when high fever associated with two or more of the following symptoms are present: headache, pain behind the eyes, muscle and joint pains, marked body weakness, significant loss of appetite, nausea, vomiting, diarrhea, or a rash, which is usually seen on the lower limbs, arms, and trunk. Physicians should be vigilant in recognizing the following 'warning signs': persistent vomiting, abdominal pain or tenderness often on the right upper quadrant, clinical fluid accumulation (abdominal enlargement, difficulty of breathing or decreased breath sounds on auscultation over the right lung field), mucosal bleeding such as profuse gum or nose bleeding, lethargy, restlessness, liver enlargement, and an increase in hematocrit with or without a decreasing platelet count.[2,3] A potentially lethal complication of the disease known as severe dengue occasionally develops. This is characterized by severe plasma leakage leading to shock and fluid accumulation, severe bleeding, and organ impairment.

While there is no specific anti-viral treatment, early recognition and prompt access to medical care lower mortality rate.[2] Among hospitalized patients, judicious use of intravenous fluid should be observed as over hydration places the patient at risk for pulmonary edema and other grave complications.[3,4] Local guidelines (the PPS "*Revised Guidelines on Fluid Management of Dengue and Dengue Hemorrhagic Fever 2012*" and

PIDSP's "*Clinical Practice Guideline on Dengue for Children"*) on fluid management of children with dengue are available and can be accessed through https://www.scribd.com/doc/316006977/PPS-Revised-Dengue-Guidelines-Fluid-Management-Oct-2012; http://www.pidsphil.org/home/wp-content/uploads/2017/06/2017_Dengue_CPG_Final.pdf . [5, 6]

An effectively implemented and sustained vector control measure is one key strategy for dengue prevention. As the number of dengue cases in the country continues to escalate, the Department of Health (DOH) constantly reminds the public to practice the '4S against Dengue' that includes the following strategies: (1) Search and Destroy: eliminate mosquito larvae breeding sites in your surroundings and cover containers with collection of stagnant water; (2) Self-Protection Measures: use mosquito repellent and cover yourself up to avoid mosquito bites; (3) Seek Early Consultation: consult a medical specialist at once for fever and rash of 2 days duration; and (4) Say No to Indiscriminate Fogging: fogging only during outbreaks.[7]

Another integral component in the global strategy for Dengue prevention and control is vaccination.[2] In April 2019, the World Health Organization has included the Dengue vaccine in the Model List of Essential Medicines for Children recommended for use in certain high-risk populations. Based on currently available data, the vaccine has been proven safe and efficacious most especially to those who had prior dengue infection. Unfortunately, this vaccine is no longer available in the country.

Some activities that clinicians can engage in to augment the health department's efforts in disease control include:

1. Early recognition and timely management of dengue cases
    - Watch out for warning signs in suspected patients.
    - Close monitoring of patients' clinical condition (i.e. vital signs, urine output, peripheral pulses, level of consciousness) especially during the critical phase of the illness.
    - Judicious administration of IV fluids. Know when to decrease or stop IV hydration.
    - Refer to a higher level of care (preferably in centers with intensive care units) when necessary.
    - Coordinate with specialty societies who can provide training of health workers in the recognition and management of cases.

2. Engage in hospital and community activities that promote the education of patients and caregivers on dengue prevention:
    - Proper waste disposal and eliminating possible breeding habitats for mosquitoes.
    - Regular cleaning, emptying and covering of water containers.
    - Practice personal protective measures: screening of doors and windows, use of mosquito nets, wearing appropriate clothing (e.g. jogging pants, long-sleeved shirts), use of insect repellents,

- Active surveillance and reporting of cases.

Lastly, for those children who were previously given partial (1-2) or complete (3) doses of the dengue vaccine, the same precautions are advised, since just like any other recommended vaccine, it may not provide 100% efficacy or protection.

A coordinated effort from the different sectors is needed to battle this pervading disease. The Philippine Pediatric Society and the Pediatric Infectious Disease Society of the Philippines (PIDSP) are in support of making the vaccine available to individuals who will benefit best from this. Likewise, the society through its module on pediatric dengue diagnosis and management can help increase disease awareness among physicians. Visit www.pidsphil.org for more information.

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A Position Statement from the
PHILIPPINE PEDIATRIC SOCIETY and PEDIATRIC INFECTIOUS DISEASE SOCIETY OF THE PHILIPPINES
on the Dengue Vaccine

In July 15, 2019, the Philippine Department of Health (DOH) has declared a National Dengue Alert with a total of 106,630 dengue cases nationwide from January 1 to June 29, 2019, which is 85% higher compared to the same period in 2018. To date, a total of 491 deaths due to dengue has been reported by DOH.

The WHO has set objectives to reduce the burden of dengue by 2020. These objectives include reducing dengue mortality by >50% by 2020, reducing dengue morbidity by ≥25% by 2020, and estimating the true burden of disease by 2015. In order to achieve these objectives, there are five (5) technical elements that focus on diagnosis and case management, surveillance and outbreak preparedness, sustainable vector control, future vaccine implementation, and basic operational and implementational research.

There is no specific antiviral treatment for dengue and clinical management is mainly based on supportive therapy. Prompt diagnosis and early detection plays a vital role in its management. Prior to the licensure of the first dengue vaccine, the only approach to control and prevention was intervention through vector control.

The first licensed live attenuated recombinant dengue vaccine was approved for use in the Philippines by the FDA on December 22, 2015; following the approval in Mexico on December 08, 2015. It was subsequently licensed in Brazil on December 28, 2015. However, the Philippine Food and Drug Authority (FDA), for reasons not related to safety issues, decided to revoke the vaccine's license through a legal order signed by Director General Puno on December 21, 2018.

Results of two large scale Phase III studies (CYD 14 and 15) consisting of more than 30,000 participants showed that the vaccine reduced symptomatic dengue disease by 65.6%, reduced hospitalization by 80.8 % and a 93.2% reduction in cases of severe dengue during the first 25 months in participants 9-16 years old. WHO, in 2018, stated that overall, the number of severe* cases prevented in those who had evidence of prior dengue infection or tested positive with dengue antibody, was substantially greater than the additional cases that occurred in those who tested negative.

Only one out of 4 patients who get dengue will be symptomatic. Majority of cases are asymptomatic.

In its September 2018 Position Paper on the Dengue vaccine, the WHO has acknowledged the public health role of the dengue vaccine and its protective benefit in seropositive individuals (those who tested positive for dengue antibody) against subsequent dengue infection, but that it carries an increased risk of severe dengue in those who experience their first natural dengue infection after vaccination for individuals who have not had dengue infection or tested negative for dengue antibody.

In order to maximize the public health impact and minimize risk with dengue vaccination, the WHO has recommended two main approaches for countries considering vaccination as part of dengue control programme:

1. Preferred Approach: Pre-vaccination Screening
    - Do serological screening prior to vaccination
    - Dengue IgG ELISA could potentially be used for screening
    - Currently available Rapid Diagnostic Tests could be considered in high transmission settings.

    With this strategy, only persons with evidence of a past dengue infection would be vaccinated (based on an antibody test, or on a documented laboratory confirmed dengue infection in the past).

2. Alternative Approach: Population Seroprevalence without Pre-vaccination Screening
    - Subnational or national mass vaccination strategy in areas of high transmission intensity (seroprevalence ≥ 80% in individuals from 9 years of age)
    - Population surveys to identify areas with high seroprevalence where public impact is maximized and harm minimized
    - Mass vaccination in identified high seroprevalence areas without serological screening

According to the study by L'Azou et al, dengue seroprevalence in the Philippines was at 89% by the age of 9 years old. Furthermore, a systematic review done by Agrupis et al. in 2019 showed that current incidence and seroprevalence data confirm the high endemicity of dengue infections in the country resulting to a heavy socio-economic burden.

As of June 2019, the dengue vaccine has been approved in 20 countries (including the US) plus Europe. The vaccine has also been added into the WHO List of Essential Medicine** in July 2019, which further attests to the benefit and value of the vaccine.

The vaccine however, is not used nor indicated for outbreak response. The vaccine has been shown to be efficacious for those who had dengue and tested positive for dengue antibody. However, the availability of the vaccine will help individuals who had previous dengue infection from getting severe disease. The vaccine can be made available to those who are interested and are known to have had the infection or are documented to be positive for dengue antibody. Physicians and caregivers must inform recipients about the benefits and possible risks of the vaccine so that informed decisions can be made.

The vaccine will be of benefit to the Filipino population when used appropriately.

* “Severe dengue” in the clinical trials and in the WHO position paper refers to Virologically Confirmed Dengue Fever PLUS any of the following:

1. Low platelet count (less than 100,00))
2. Shock (pulse pressure ≤20mmHg in child; low BP with increased Heart rate, weak pulse)
3. Bleeding that requires blood transfusion
4. Organ impairment (neurologic, renal, hepatic or cardiac)

** The core list presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost–effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

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