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ORIGINAL ARTICLE

Haemophilus Influenzae Type B Conjugate Vaccine (HiBCV) And Heptavalent Pneumococcal Conjugate Vaccine (PCV7) Immunization Status Of Patients 5 Years And Below Hospitalized For Pneumonia

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childhood pneumonia, *Haemophilus influenzae type b* conjugate vaccine, heptavalent pneumococcal conjugate vaccine

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ABSTRACT

Introduction: Community-acquired pneumonia remains to be an important cause of morbidity and mortality among the pediatric age group with Streptococcus pneumoniae and Haemophilus influenzae type B being the predominant bacteria identified. Conjugate vaccines against these organisms are available however, the prevalence of pneumonia in our country continues to be high.

Objectives: The aim of this research is to determine the HiBCV and PCV 7 immunization status of children 5 years and below who were hospitalized due to pneumonia compared to controls. This study also aims to describe the clinical outcome of pneumonia among children who were vaccinated with HiBCV and/or PCV7 compared to those without vaccination.

Methods: This retrospective case-control study was conducted in Makati Medical Center from January 1, 2009 to August 31, 2010. Cases were children five years old and below discharged with the final diagnosis of pneumonia. Controls were patients five years and below discharged without pneumonia during the same study period. Medical records were reviewed for information on age, gender, clinical findings upon admission, laboratory results, vaccination status, interventions and outcomes.

Results: Two hundred twenty seven charts were reviewed (127 cases and 100 controls). The mean age of patients on admission was 1.9 years (SD ± 1.4). In 98.4% of the cases, chest roentgenograms showed infiltrates. The mean white blood cell count for cases was normal with 11.4 x 103/uL (SD + 6.3). None of the case patients had positive blood culture results. Only 34.6% and 5% of the cases completed age-appropriate doses of HiBCV and PCV7, respectively. No statistical difference was found between the length of hospital stay and duration of antibiotic use and the vaccination coverage for the two vaccines. Children without vaccination coverage had the odds of 1.2-1.3 to develop pneumonia compared to children with at least one dose of either vaccine (HiBCV: OR 1.3, 95% Cl 0.8 to 2.3; PCV7: OR 1.2, 95% CI 0.6 to 2.6).

Conclusion: The findings indicated that clinical and radiologically-confirmed pneumonia still occurred among children with complete vaccination with HiBCV and PCV7. Although not statistically significant, those without vaccination had higher odds of having pneumonia.

INTRODUCTION

Community-acquired pneumonia remains as an important cause of morbidity and mortality among children worldwide.[1] It is estimated that each year, over two million children die from pneumonia. The incidence of pneumonia in children younger than five years of age in developing and developed countries is 0.28 and 0.05 episodes per child-year, respectively.[1] In the Philippines, pneumonia is the 3rd leading cause of death in children less than five years of age.[2]

Streptococcus pneumoniae and Haemophilus influenzae type B are the dominant bacterial agents responsible for invasive diseases such as pneumonia, meningitis and bacteremia among children under five years and in older adults.[3,4,5] It is for this reason that the World Health Organization (WHO) recommended routine use of immunization with conjugate vaccines for Streptococcus pneumoniae and Haemophilus influenzae type B.[6,7]

Haemophilus influenzae type B conjugate vaccine (HiBCV) was developed in the United States in 1985. The first improved HiBCV was licensed for use in December 1987. The recommended age of which the vaccine should be given is at 2, 4, and 6 months of age. For those with incomplete schedule (0-2 doses) in the first year of life, it is recommended to give a single dose of HiB vaccine at 1-2 years of age.6

The heptavalent pneumococcal conjugate vaccine (PCV7) was licensed for use in the United States in the year 2000. PCV7 is protective against the seven most common serotypes known to cause invasive pneumococcal disease (IPD); namely, serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. The recommended age for giving the vaccine follows the same schedule as that of HiB vaccine.[7]

Soon after the implementation of routine immunization with conjugate vaccines, numerous studies have reported a dramatic decline in the incidence of invasive diseases caused by Streptococcus pneumoniae and Haemophilus influenzae type B.[1,8,9,10] In 2006, the Center for Disease Control (United States) reported the incidence of pneumonia among children less than two years of age to be 35% lower than during the pre-vaccination period. Rate of pneumonia in developed countries, particularly in the United States, have remained stable since then.[11]

However, because of uncertainties regarding actual disease burden caused by Streptococcus pneumoniae and Haemophilus influenzae type B in Asia, there have been significant delays in the introduction of conjugate vaccines in this region.[4,5]

Two decades after the implementation of universal vaccination with HiBCV and one decade after for PCV7, rates of pneumonia in the Philippines continue to be high. Due to the high cost of these two vaccines, the economic burden of additional vaccination other than those included in the Expanded Program on Immunization (EPI) by the Department of Health (DOH) has limited the use of these two conjugate vaccines. Despite numerous foreign studies confirming the efficacy and safety of giving HiBCV and PCV7, routine use of these vaccines in our setting is far from universal among healthcare practitioners.

The objective of the study was determine the HiBCV and PCV 7 immunization status of children 5 years and below who were hospitalized due to pneumonia compared to controls. This study also aims to describe the clinical outcome of pneumonia among children who were vaccinated with HiBCV and/or PCV7 compared to those without vaccination. This study also aimed to determine the clinical outcome of pneumonia among children who were vaccinated with HiBCV and/or PCV7 compared to those without vaccination.

MATERIALS AND METHODS

Study design

This case-control study was performed using review of medical records from pediatric patients admitted at the Makati Medical Center, an urban, private, tertiary hospital with a 717-bed capacity.

Selection of Participants:

The study included children aged five years and below discharged Makati Medical Center with a final diagnosis of pneumonia from January 1, 2009 to August 31, 2010. Cases were children five years and below with clinically and radiographically confirmed pneumonia. Controls were patients five years and below discharged without pneumonia at the Makati Medical Center during the same study period. Clinical case definition of community-acquired pneumonia was established according to the signs present upon hospital admission following the WHO guidelines[12], which mainly includes rapid or difficult breathing and presence of chest wall retractions. Radiologic pneumonia was defined by the presence of consolidation and/or focal infiltrates on chest roentgenogram.

Patients were excluded if they had co-morbid conditions such as congenital heart disease or immunodeficiency (neoplasia, undergoing chemotherapy or on long-term steroid use).

Patients who had been treated for pneumonia within four weeks of admission and those who developed pneumonia more than 48 hours after admission (nosocomial or hospital-acquired pneumonia) were not included in this study.

Data Collection:

Medical records were reviewed using a standard form. Information on age, gender, clinical findings upon admission, laboratory results, vaccination status, interventions and outcomes were recorded. Vaccine records were further verified from attending physicians' clinic records. Children having complete immunization were defined as those with full age-appropriate series of HiBCV and/or PCV7 vaccination following the 2009 Childhood Immunization Schedule recommended by the American Academy of Pediatrics. Clinical outcomes were measured in terms of length of hospital stay, duration of antibiotic use, and response to antibiotic treatment (i.e. improved or unimproved).

Data Analysis:

The required sample size was 100 cases and 100 controls, assuming a 20% reduction in pneumonia between the vaccinated and unvaccinated groups, with statistical power of 80%, confidence level of 95% (two-tailed), and ratio of controls per case of 1:1. Mean and standard deviation were used to describe study variables. Mann Whitney U test and $\chi 2$ test were used to determine significant differences between cases and controls. The risk of developing pneumonia was estimated using odds ratio (OR).

RESULTS

Between January 1, 2009 to August 31, 2010, 127 charts were reviewed with a final diagnosis of pneumonia. Clinical and demographic characteristics of these patients are shown in Table 1. The mean age of patients admitted was 1.9 years (SD ± 1.4). Cough was the presenting symptom of 99.2% of children with pneumonia and 26.8% had concomitant difficulty of breathing during the time of admission.

Among the cases, only 34.6% and 5% completed age-appropriate doses of HiBCV and PCV7, respectively. There was, however, no statistical significance when compared to the control group (HiBCV 34.6% vs. 45%; PCV7 5% vs. 6%; $p > 0.05$) (Table 1).

In all, 125 cases had chest roentgenogram with infiltrates (98.4%). One patient had atelectasis (0.8%) and another patient had no chest roentgenogram done (0.8%). Mean white blood cell count for cases was 11.4 x 10^3/uL (SD + 6.3). Of the 127 cases, 21 (16.5%) had blood culture and sensitivity done. None of these patients had positive blood culture (Table 2).

Among those children with pneumonia, there was no statistical difference found between the length of hospital stay and duration of antibiotic use and their vaccination status. All children with pneumonia improved upon discharge regardless of the completeness of their immunization for the two vaccines (Table 3).

Table 1. Clinical and Demographic Characteristics of Cases and Control Patients included in the study

Characteristics	Cases (n =127)	Control (n = 100)	p value
Age in years (mean± SD)	1.9 ± 1.4	2.6 ± 1.7	0.0001
Sex			
Male Female	72 (56.7%) 52 (52.0%)	55 (43.3%) 48 (48.0%)	0.48
Clinical Features			
Cough	125 (99.2%)	37 (37.0%)	< 0.0001
Difficulty of breathing/Dyspnea	34 (26.8%)		
Grunting	0 (0.0%)		
Alar flaring	8 (6.3%)		
Retractions	29 (22.8%)		
Respiratory Rate (mean± SD)	33.9 ± 11.2	25.2 ± 3.5	< 0.0001
Chest Auscultation			
Clear breath sounds Crackles Decreased breath sounds (DBS) Harsh breath sounds (HBS) Rhonchi Wheeze DBS + wheeze HBS + wheeze HBS + rhonchi HBS + DBS	1 (0.8%) 99 (78.0%) 1 (0.8%) 20 (15.7%) 2 (1.6%) 0 (0.0%) 1 (0.8%) 1 (0.8%) 1 (0.8%) 1 (0.8%)	99 (99.0%) 1 (1.0%)	
Immunization Status			
Complete HiB immunization	44 (34.6%)	45 (45.0%)	0.11
Incomplete/No HiB immunization	83 (65.4%)	55 (55.0%)	
Complete PCV7 immunization	6 (5.0%)	6 (6.0%)	0.67
Incomplete/No PCV7 immunization	121 (95.0%)	94 (94.0%)	

In terms of vaccination coverage and the odds of developing pneumonia, there were no significant differences found between the two groups for the two vaccines. Children without vaccination coverage had odds of 1.2-1.3 to develop pneumonia compared to children with at least one dose of either vaccine (Table 4).

DISCUSSION

Implementation of universal vaccination with HiB and pneumococcal vaccines in industrialized countries has shown promising results in decreasing the incidence of pneumonia. Numerous studies have documented the efficacy of HiBCV and PCV7 in preventing invasive infections such as meningitis, pneumonia, and bacteremia.[8,10,13,14] This retrospective case-control study investigated the HiBCV and/or PCV7 immunization status of children who were hospitalized for pneumonia. Among those children without vaccination with either HiBCV or PCV7, the odds of developing pneumonia were 1.2-1.3 compared to children with at least one dose of either vaccine.

Table 2. Laboratory results of cases and control patients

Laboratory Test	Cases (n =127)	Control (n = 100)	p value
White cell blood count (mean± SD)			
Total Segmenters Lymphocytes	11.4 x 10^3/uL (± 6.3) 47.0 % (± 21.4) 41.8% (+ 21.0)	10.6 x 10^3/uL (± 5.4) 52.5 % (±21.4) 37.2% (± s0.3)	0.46 0.05 0.08
Blood Culture and Sensitivity			
Positive Negative/no growth	0 21 (16.5%)		
Chest X-ray			
No Chest X-ray Atelectasis Bronchopneumonia Pneumonia	1 (0.8%) 1 (0.8%) 112 (88.2%) 13 (10.2%)		

Although not statistically significant, the occurrence of pneumonia among children under five years with complete HiBCV and PCV7 was slightly lower than the control group (HiBCV 34.6% vs. 45%; PCV7 5% vs. 6%; p > 0.05). One possible explanation for this non-significance is that the percentage of vaccinated children was lower than what was estimated in computing for the sample size. Significant differences were also detected on the ages of cases and controls. A bigger population would have been necessary to reflect a significant difference between these two groups.

Another possible explanation for the above results is the possibility that community-acquired pneumonia in this age-group may be due to organisms other than pneumococcus and *H. influenzae* type B. Information on population-based incidence of pneumonia caused by *S. pneumoniae* and *H. influenzae* type B in the Philippines is insufficient.

Table 3. Comparison of clinical progress of children with pneumonia (Cases) and their immunization status (n=127)

	HiB Vaccine			PCV7		
	Complete Vaccine (n = 44) (mean± SD)	Incomplete/ No Vaccine (n = 83) (mean± SD)	p value	Complete Vaccine (n = 6) (mean± SD)	Incomplete/ No Vaccine (n =121) (mean± SD)	p value
Length of hospital stay	4.1 ± 1.4 days	4.9 ± 3.2 days	0.14	4.2 ± 1.9 days	4.7 ± 2.8 days	0.68
Duration of Antibiotic Use	6.9 ± 0.3 days	7.4 ± 2.5 days	0.29	6.6 ± 0.8 days	7.3 ± 2.1 days	0.50
Improved	44	83		6	121	
Not improved	0	0		0	0	

Table 4. Estimated effect of HiBCV and PCV7 vaccination and the odds of developing pneumonia (n=227)

Immunization Status	**Cases** N= 127	**Control** N = 100	p value	**Odds ratio (95% CI)**
With HiB	52 (40.9%)	48 (48.0%)	0.29	1.3 (0.8, 2.3)
Without HiB	75 (59.1%)	52 (52.0%)		
With PCV7	17 (13.4%)	16 (16.0%)	0.67	1.2 (0.6, 2.6)
Without PCV7	110 (86.6%)	84 (84.0%)		

Attempts to identify the etiologic agents of community-acquired pneumonia are limited by the low yield of blood culture. Lupisan et al. reported the blood isolation rate of *S. pneumoniae* and *H. influenzae* was only 1.3% and 1.2%, respectively, among children less than five years old in a tertiary hospital in Bohol.[15] In our study, none of the 21 patients with blood cultures showed positive result. Likewise, the technical difficulty of doing sputum cultures in children younger than six years has limited our knowledge of the real prevalence of *S. pneumoniae*, *H. influenzae* type B and other pathogens in community-acquired pneumonia.

Using local pneumococcal serotype data, only a fraction of *Streptococcus pneumoniae* would be prevented by PCV7. In 1994, Capeding et al. reported 20 invasive *Streptococcus pneumoniae* serotypes cultured from blood, cerebrospinal fluids and lung aspirates among hospitalized Filipino children less than five years old in Metro Manila.[16] They reported that serotypes 1, 6, 23, and 19 were responsible in 52.6% of all the infections. Lankinen et al. similarly reported that among Filipino children under five years with acute lower respiratory tract infection, the seven most common types of pneumococci isolated from nasopharyngeal aspirates were 6,14,19,23,15,7, and 11, which accounted for an overall 64%. In 30 to 40% of the samples, *H. influenzae* was the most frequently isolated pathogen.[17] O'Grady et al. reported limited evidence in the reduction of radiologically diagnosed pneumonia among indigenous infants in Australia who received PCV7 and were followed up until 18 months of age. They explained this finding to the serotype coverage of PCV7 and the declining nasopharyngeal carriage targeted by the vaccine since its introduction in the country.[18] Rodrigues et al. supported these findings among children in Portugal who received PCV7. They found that non-vaccine type pneumococci were predominant among the nasopharyngeal swabs of children who were vaccinated with PCV7.[19]

Atypical organisms (*Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Legionella pneumophila*) have also been implicated as important causative agents for community-acquired pneumonia. Data from Makati Medical Center and Cardinal Santos Medical Center have shown that 22-25% of pneumonia cases among children younger than five years

may be due to *Mycoplasma pneumoniae.*[20,21] In this study, two children were found to have *Mycoplasma pneumoniae* positive IgM (data not shown). Moreover, Saikku et al. described acute lower respiratory tract infection associated with *Chlamydia pneumoniae* (TWAR) in Metro Manila. They reported serologic evidence of chlamydia infection in 21 children (9.1%) with acute lower respiratory tract infection.[22] It is important to note that the pneumonia cases in our study presented with normal white blood cell counts with 11.4 x 10^3/uL (SD $\pm$ 6.3). This could support earlier findings that community-acquired pneumonia due to atypical organisms present with normal WBC counts and differentials.[20, 21]

Lastly, viruses are major causative organisms in community-acquired pneumonia. Tupasi et al. reported in a longitudinal study in Metro Manila that the prevalence of viral infection was 32.8 per 1,000 children less than five years old with acute lower respiratory tract infection. Respiratory syncytial virus was the predominant viral pathogen with a prevalence of 12.9%. Other viruses isolated were adenovirus (3.5%), parainfluenza B virus (1.9%), influenza B virus (1.9%), parainfluenza 2 virus (0.6%), and influenza A virus (0.3%).[23]

This study was limited by the small sample size that did not successfully show significant difference among the vaccinated and unvaccinated groups. Moreover, the vaccination status of the study population was based on recall upon history taking on admission. Not all of the vaccination records were made available for verification in the admitting physicians' clinic records. Of the 227 charts reviewed, only 130 charts were verified. Lastly, cultures for blood, sputum, or lung aspirates are not part of routine diagnostic work-ups for community-acquired pneumonia. These data are not available to provide evidence on the real etiology pneumonia.

Decisions to routinely give HiBCV and PCV7 among healthcare practitioners are based on available estimates on disease burden and the affordability by the general population. Although this study did not show significant difference between vaccinated and unvaccinated children and the odds of developing community-acquired pneumonia, the potential impact of universal HiBCV and PCV7 vaccination was reflected by the lesser occurrence of community-acquired pneumonia among those with vaccine.

CONCLUSIONS AND RECOMMENDATIONS

Among children aged five years and below with clinical and radiologically-confirmed pneumonia only 34.6% and 5% had complete vaccination with HiBCV and PCV7, respectively. Although not statistically significant, children without vaccination with HiBCV or PCV7 were noted to be 1.2-1.3 times likely to develop community acquired-pneumonia compared to those children with immunization with either vaccine. No significant difference was likewise found in terms of the clinical outcome of children who received complete vaccination compared to those without or with incomplete vaccination.

For future studies, increase in the sample size and inclusion of cultures other than blood for viral, bacterial as well as atypical organisms are recommended.

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