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ORIGINAL ARTICLE

Population-based incidence of community-acquired pneumonia hospitalization in Hong Kong children younger than 5 years before universal conjugate pneumococcal immunization

Susan S. Chiu [a,*], Pak-Leung Ho [b], Pek-Lan Khong [c], Clara Ooi [c], Lok Yee So [d], Wilfred H.S. Wong [a], Eunice L.Y. Chan [a]

[a] *Department of Pediatrics and Adolescent Medicine, University of Hong Kong, Hong Kong SAR, China*
[b] *Department of Microbiology, University of Hong Kong, Hong Kong SAR, China*
[c] *Department of Diagnostic Radiology, University of Hong Kong, Hong Kong SAR, China*
[d] *Department of Pediatrics and Adolescent Medicine, Pamela Youde Nethersole Eastern Hospital, Chai Wan, Hong Kong SAR, China*

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Objectives: We sought to document the incidence of pediatric hospitalization for bacterial pneumonia before universal childhood conjugate pneumococcal vaccination using two different methods of diagnosis.
Methods: By following the World Health Organization (WHO) chest radiography (CXR) protocol, two radiologists independently read the CXRs of a cohort of systematically recruited children younger than 5 years. The children had acute respiratory infections and were admitted to one of two hospitals that care for 72.5% of all pediatric admissions on Hong Kong Island. Medical records were reviewed for clinical manifestation and to identify bacterial pneumonia diagnosed by pediatricians.
Results: In children younger than 5 years, the incidences of bacterial pneumonia, as diagnosed by pediatricians and by the WHO CXR standard, were 775.7 per 100,000 population [95% confidence interval (CI, 591.8–998.3)] and 439.5 per 100,000 population (95% CI, 304.6–614.5), respectively. The study period was from 2002 to 2004.

* Corresponding author. Department of Pediatrics and Adolescent Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR, China.
E-mail address: ssschiu@hkkucc.hku.hk (S.S. Chiu).

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Conclusion: This study provided a reliable baseline estimate of the hospitalization burden of pneumococcal pneumonia in Hong Kong children before the advent of universal conjugate pneumococcal vaccination.

Introduction

Pneumonia causes significant morbidity in children. *Streptococcus pneumoniae* is the leading cause of bacterial pneumonia and accounts for an estimated 17—44% of pneumonia admissions in young children.[1,2] Routine childhood immunization with conjugate pneumococcal vaccines is associated with a reduction in pneumonia hospitalization in children.[3—6] In Hong Kong, universal conjugate pneumococcal vaccination in children was implemented in 2009. We conducted a study to document the baseline pneumococcal pneumonia hospitalization before the introduction of universal vaccination with conjugate pneumococcal vaccine and to explore the role of common respiratory viruses in children hospitalized for bacterial pneumonia.

In children, the accurate diagnosis of bacterial pneumonia, including pneumonia caused by *S. pneumoniae*, has always been less than certain. A sputum sample is not easily obtained from young children, and the isolation of bacteria from sputum may only reflect colonization. Blood culture has a very low yield because most bacterial pneumonia in children is not bacteremic. Lung aspirate culture is more sensitive and specific, but this procedure is too invasive for routine use in most pediatric practices because of the risk of pneumothorax.[7] To provide an objective endpoint in vaccine trials that evaluate the efficacy of protection against pneumonia, the World Health Organization (WHO) has developed a standardized protocol for diagnosing pneumonia, based on chest radiograph (CXR) findings.[8,9] The finding of alveolar consolidation on CXR by two independent observers is associated with a bacterial cause. The assumption is that *S. pneumoniae* is the major etiology for bacterial pneumonia.

We compared the incidence of hospitalization for bacterial pneumonia as a reflection of pneumococcal pneumonia in Hong Kong children. We used the WHO standardized protocol and the discharge diagnosis by pediatricians to obtain the population-based age-specific incidences as a baseline before the licensing and inclusion of the conjugate pneumococcal vaccines into the universal immunization program in Hong Kong.

Materials and methods

Study design and participants

The Hong Kong Special Administrative Region (SAR) comprises Hong Kong Island, the Kowloon peninsula, the New Territories, and some sparsely populated outlying islands. In 2006, the number of people residing less than 5 years in Hong Kong Island was 37,345 people.[10] The Pamela Youde Nethersole Eastern Hospital (PYNEH) situated at the eastern end and the Queen Mary Hospital (QMH) situated at the south-west, are the only two public hospitals on Hong Kong Island, with a total of 153 pediatric beds. They care for 72.5% of all pediatric admissions on the Island. There are 16 public hospitals with an emergency department for all of Hong Kong SAR and non—Hong Kong Island residents in general do not cross the Harbor to Hong Kong Island for emergency room attendance and admission for an acute general pediatric problem. Census data were used to define the at-risk age-stratified population.

For the purpose of this study, the CXRs of children admitted from 2002 to 2004 were recently retrieved for independent reading by two qualified radiologists who used the WHO protocol. Medical records of these children were also retrieved for review. This period was chosen because this was the closest period before the availability of conjugate pneumococcal vaccine in Hong Kong. All children younger than 5 years old who were admitted with an acute febrile respiratory illness during one 24-hour period each week to PYNEH (Tuesday) and QMH (Wednesday) from September 2002 to August 2004 were specifically included. Children with an underlying condition and a history consistent with apparent aspiration pneumonia were excluded. The CXRs were ordered in the emergency department at the discretion of the emergency department (ED) physicians or ordered after admission by the attending pediatrician if a CXR had not been performed and the child's condition was considered to warrant a CXR.

Definition of pneumonia by CXR (i.e., endpoint consolidation)

The CXRs of the patients for an admission were retrieved and read independently by two radiologists who followed the WHO definition and were unaware of the clinical diagnoses.[8] Endpoint consolidation is the most specific predictor of bacterial pneumonia and is defined as a "dense opacity that may be a fluffy consolidation of a portion or whole of a lobe or of the entire lung, often containing air bronchograms and sometimes associated with pleural effusion." The radiologists also graded the quality of the films as "uninterpretable", "suboptimal" or "adequate". The data manager monitored the disagreement between the radiologists and those films were pulled for a consensus reading in accordance to the WHO guidelines.

Diagnosis of bacterial pneumonia by pediatricians

For the purpose of this study, the subset of children who were treated by the pediatrician with a full course of beta-

lactam antibiotics were assumed to have a diagnosis of bacterial pneumonia by pediatricians. The attending pediatricians made the diagnoses in routine patient care at the time of discharge by using clinical, laboratory, and radiologic information. However, because the endpoint consolidation categorization was conducted for this study several years after the admissions, this information was naturally unknown to the pediatricians.

Statistical analyses

Agreement in the diagnosis of pneumonia by different methods of diagnosis was tested using reliability analysis. A *kappa* value of less than 0.20 denotes poor agreement; 0.20—0.40, fair agreement; 0.40—0.60, moderate agreement; 0.60—0.80 good agreement; and 0.80—1.00, very good agreement.[11] The Chi-square test with Yates' correction was used to detect differences in percentages and an unpaired *t* test was used to detect differences in the counts between two groups. A significance level of *p* less than 0.05 was used for all analyses. All analyses were performed by SAS version 9.1 software (Cary, North Carolina, USA).

The number of population younger than 5 years hospitalized for differently defined pneumonia on Hong Kong Island was calculated by multiplying hospitalizations by 7 for the two categories of pneumonia each week (for one in seven sampling) and then by the reciprocal of the proportion of children served in the two hospitals each year (i.e., $1 \div 0.725$ because the two public hospitals cared for 72.5% of all hospitalizations on Hong Kong Island). Using the age-stratified population on Hong Kong Island, we calculated the exact rates of hospitalization for pneumonia for each age group. These data would be representative of the whole Hong Kong SAR because the Hospital Authority runs all public hospitals throughout all of Hong Kong SAR. The size of the whole SAR is 1.04 km^2 (426 square miles).

Results

A total of 441 children younger than 5 years old were admitted at the two sites in the 2 year period with 1-in-7 days systematic sampling: 292 children were from PYNEH and 149 children were from QMH. Three hundred and forty-four (78%) children underwent a CXR, but 30 (8.7%) films were missing. A review of discharge diagnoses indicated that none of the 97 children who did not have a CXR performed was diagnosed as having pneumonia by pediatricians. This indicated the group of children who had upper respiratory tract infection, based on physical examination.

The median age of the 314 children who had an available CXR was 2 years (range, 0.08—4 years). Of these children, 53 children received a discharge diagnosis of pneumonia by the attending pediatricians. They were treated for bacterial pneumonia with a full course of beta-lactam antibiotics. When the CXRs of these children were retrieved for endpoint consolidation categorization, 31 children were diagnosed as having pneumonia by the study radiologists. Of the 64 children diagnosed by either method, 20 children were considered to have bacterial pneumonia by pediatricians and by the study radiologists using the WHO CXR protocol, with an agreement of 86.0% (*kappa* = 0.40). Eight (25.8%) children with endpoint consolidation did not receive treatment that was appropriate for community-acquired bacterial pneumonia: four children never received any antibiotics before or during hospitalization, two children received less than 2 days of a beta-lactam antibiotic treatment, and two children were treated with a course of macrolide only, which would unlikely be effective because of the extremely high incidence of macrolide resistance in pneumococcus in Hong Kong. These children all defervesced and were well at discharge.

There was no difference in the clinical manifestations in children diagnosed as having bacterial pneumonia by a pediatrician or by endpoint consolidation—with the exception that 100% of children diagnosed by pediatrician were prescribed with a course of beta-lactam antibiotics, compared to only 74.2% of children diagnosed by endpoint consolidation ($p = 0.0005$) (Table 1). Sputum culture was performed in only five patients and was positive in two patients. One culture grew *Branhamella catarrhalis* and the other culture grew *S. pneumoniae*. Blood culture was performed in 157 (50%) of 314 patients, and none of these cultures grew *S. pneumoniae*.

Thirty CXRs were missing from our recruited patients. We projected our finding that 31 (9.9%) of 314 available CXRs would indicate pneumonia, based on endpoint consolidation. We were able to have a pro rata estimation for calculating the incidence of pneumonia defined by endpoint consolidation. A chart review of the 30 children with missing CXRs revealed an additional six children diagnosed by pediatricians as having bacterial pneumonia. Table 2 presents the projected age-specific incidences of pneumonia hospitalization on Hong Kong Island using various criteria. Children from 2 years to up to 5 years old

Table 1 Comparison of the evidence of bacterial involvement in 84 children with an available chest radiograph who were diagnosed as having bacterial pneumonia by a pediatrician or by endpoint consolidation

	Bacterial pneumonia ($N = 53$)	Endpoint consolidation ($N = 31$)	*p*
Mean maximum temperature (°C)	39.47 ± 0.94	39.49 ± 0.98	NS
Focal crepitation, no. (%)	24 (45.3%)	14 (45.2%)	NS
Mean respiratory rate/min	38.57 ± 11.49	39.23 ± 10.73	NS
Percentage with neutrophilia	33/53 (62.3%)	18/30 (60.0%)	NS
Antibiotic before presentation	23/53 (43.4%)	8/31 (25.8%)	NS
Percentage treated with a course of beta-lactam antibiotics	53/53 (100%)	23/31 (74.2%)	0.0005

Table 2 The mean annual age-specific rate of pneumonia per 100,000 children (95% confidence interval) in Hong Kong Island, according to different criteria (2002–2004)

	<2 y	2 y to <5 y	Overall <5 y
Population (no.)	14,525	22,818	37,343
Discharge diagnosis of bacterial pneumonia by pediatrician	365.6 (182.5–653.8)	1036.7 (766.9–1370.3)	775.7 (591.8–998.3)
Endpoint consolidation by radiologists	232.7 (94.1–479.6)	571.2 (376.4–831.0)	439.5 (304.6–614.5)

The data are presented as the number or as the number (confidence interval).

had a higher incidence of pneumonia hospitalization, compared to children younger than 2 years old who had been diagnosed by both groups. The incidences of bacterial pneumonia in children younger than 5 years old, as diagnosed by pediatricians and by the WHO CXR standard, were 775.7 per 100,000 population (95% CI, 591.8–998.3) and 439.5 (95% CI, 304.6–614.5) per 100,000 population, respectively.

Discussion

Our overall pneumonia hospitalization incidence for children younger than 5 years was 775.7 per 100,000 population (by pediatrician diagnosed bacterial pneumonia) and 439.5 per 100,000 population (by endpoint consolidation) was in general agreement with estimates based on the 2004 WHO pneumonia disease burden data from around the world: 836 per 100,000 population for the Americas and 462 per 100,000 population for Europe; however, it was lower than the 1775 per 100,000 population for the Western Pacific Region.[12] The incidences were not directly comparable because our data pertained to hospitalization. It is surprising that we documented a lower hospitalization incidence in the less than 2 years. This was evident for both years by the pediatricians and by the WHO criteria. A possible explanation may be the incidence in this study only reflected hospitalization, and not all pneumonia incidences. Younger children with pneumonia in Hong Kong may have been brought to a doctor and received treatment sooner, thereby deterring admission. Studies from Taiwan have also shown that suspected or definite pneumococcal pneumonia were more likely in children 1 year up to 5 years old, compared to other pediatric age groups.[13,14] Therefore, this may reflect a true phenomenon in Asia.

The WHO CXR protocol has been used to study community-acquired pneumonia in hospitalized children in Fiji, although this definition of pneumonia has been challenged as possibly underestimating the burden of pneumococcal pneumonia.[15–18] Bacterial pneumonia diagnosed and treated by attending pediatricians seemed well supported by clinical and laboratory parameters and may provide a better estimation of pneumococcal pneumonia, compared to the WHO CXR protocol. As Madhi et al had indicated, clinically diagnosed pneumonia is a more sensitive endpoint than radiographic endpoint: in two clinical trials evaluating the efficacy of PCV9 (Wyeth, Dallas, USA) in South Africa and in the Gambia, the radiographic endpoint detected only 58% of the burden of pneumonia, based on clinical diagnosis in the first trial and 88% of clinical pneumonia in the second trial.[18–20] The population-based incidences of bacterial pneumonia hospitalization of children in Hong Kong Island, as defined by endpoint consolidation, was indeed 58% of the incidence as defined by the pediatrician in charge. In this study, the specificity of endpoint pneumonia for the diagnosis of bacterial pneumonia is also challenged. More than 25% of children with endpoint consolidation recovered without appropriate treatment for pneumococcal pneumonia, which suggests a possible overdiagnosis of pneumococcal pneumonia.

The reports of the incidence of community-acquired pneumonia can be quite confusing when all-cause pneumonia is used and is compared to pneumonia, as defined by the endpoint consolidation of the WHO CXR standard, which is supposed to reflect a bacterial etiology. The strengths of this study include diagnosis by pediatrician, based on clinical findings and laboratory investigation at an individual level. In addition, the set up of the public hospital system in Hong Kong Island allowed the derivation of the age-specific population-based pneumonia incidences.

There are limitations to this study. A small number of CXRs could not be retrieved. Additional tests such as C-reactive protein (CRP) or procalcitonin that may have a role in diagnosing community-acquired pneumonia were not used.[21–23]

With the availability and inclusion of conjugate pneumococcal vaccines into government immunization policies, it is important to define the pneumococcal pneumonia hospitalization burden before and after the implementation of such policies. The seven-valent conjugate pneumococcal vaccine was licensed in Hong Kong and available to the private sector in 2005, and was incorporated into the universal vaccination scheme in September 2009. It was followed by the switch to the 10-valent vaccine in October 2010 and the 13-valent vaccine in December 2011. This study provided a reliable baseline estimate of the hospitalization burden of pneumococcal pneumonia in Hong Kong children before the introduction of any conjugate pneumococcal vaccination into the community, which allows the study of the impact of the conjugate vaccines after their introduction and universal usage.

Conflicts of interest

The authors reported no conflict of interest.

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