香港兒童健康疫苗關注組

致：立法會衞生事務委員會主席及各委員

增加兒童疫苗政策問題透明度，讓公眾討論

香港兒童健康疫苗關注組近日留意到除 1 月 30 日的立法會會議上，余若薇議員及陳婉嫻議員分別以口頭及書面方式，向政府質詢有關肺炎鏈球菌及兒童免疫接種計劃的政策之外，李國麟議員亦於 2 月 18 日的立法會會議上以書面方式，再次向政府質詢兒童免疫接種計劃，顯示香港疫苗政策的落後及肺炎鏈球菌的問題，已在議員、傳媒及社會間引起廣泛關注及討論。

食物及衞生局局長在回答議員時多次引用的一些數據，明顯與早前香港兩所大學所公布的研究數據有很大的出入。

周一嶽局長所引述 2000 年至 2004 年期間醫院管理局部轄下全港所有公營醫院的實驗室對血液、腦脊液及取自其他無菌部位的樣本進行的肺炎鏈球菌分離結果數據顯示，本港兩歲以下及六十五歲以上人士的入侵性肺炎球菌疾病發病率，每年平均為 10 萬人中有 7.7 人。

但港大微生物學系副教授何栢良於 2007 年 7 月發表的研究報告顯示，2000 年至 2005 年底，每 10 萬名兩歲以下兒童的發病率為 23.7 人。而這六年間，共 17,868 宗肺炎入院，當中已確定由肺炎鏈球菌引致的肺炎有 447 宗、10 名幼兒因入血或腦膜炎死亡、57 宗入血致敗血病、及 22 人腦膜炎。

中大藥劑學院教授及副院長(外務)李炯前教授亦曾於 2007 年 8 月 1 日發表亞洲首項「肺炎鏈球菌接合疫苗香港藥物經濟效益」的研究，顯示肺炎鏈球菌接合疫苗符合世界衞生組織訂定的成本效益準則，如為所有本港初生嬰兒接種肺炎鏈球菌接合疫苗乃符合成本效益。如全港所有幼童均接種肺炎鏈球菌接合疫苗的話，該疫苗延長每一人一年壽命的成本約為港幣 385,000 元。如同時計算群體保障，則該疫苗在延長每一人一年壽命的成本為港幣 26,275 元，遠較世衞的準則為低。如獲納入本港兒童免疫接種計劃內，該疫苗可為港府大幅減低數以億計醫療開支。

另外，周一嶽局長於 1 月 30 日的立法會會議上表示，政府委託本地一所大學有關將肺炎鏈球菌疫苗納入本地兒童免疫接種計劃的成本效益研究，將於本年第一季內完成，並提交控制傳染病研究基金秘書處。衞生署衞生防護中心轄下的「疫苗可預防疾病科學委員會」會研究有關結果，並就肺炎鏈球菌疫苗向衞生署衞生防護中心作出建議。政府將會參考委員會的建議，衡量各項因素後作出決定。

香港兒童健康疫苗關注組

兒童免疫接種計劃關乎香港每一位市民、每年 5 萬名新生嬰兒的健康及保障，關注組認為政府有必要將整個報告研究公開，進行公眾諮詢，讓市民有機會參與討論，為每位小生命爭取他們應有的保障。

香港兒童健康疫苗關注組曾兩次致函委員會，促請委員會盡快討論兒童疫苗接種計劃。關注組深信主席及各委員會發揮積極的監察作用。

現隨函附上下列文件供主席和各委員參考：

（一） 中大藥劑學院教授及副院長(外務)李炯前教授於 2007 年 8 月 1 日發表的「肺炎鏈球菌接合疫苗香港藥物經濟效益」資料及新聞稿

（二） 港大微生物學系副教授何栢良於 2007 年 7 月發表的研究及有關研究的剪報

議員對我們的要求有任何查詢，請與本人或關注組聯絡。

祝身體健康，工作愉快！

賴仁彪
香港兒童健康疫苗關注組召集人
2008 年 2 月 21 日

新聞稿

2007 年 8 月 1 日

中大研究顯示肺炎鏈球菌接合疫苗符合成本效益
建議納入本港兒童免疫接種計劃

香港中文大學於 2006 年在本港進行亞洲首項《*肺炎鏈球菌接合疫苗香港藥物經濟效益*》研究。報告顯示肺炎鏈球菌接合疫苗符合世界衛生組織訂定的成本效益準則，如爲所有本港初生嬰兒接種肺炎鏈球菌接合疫苗乃符合成本效益。如獲納入本港兒童免疫接種計劃內，該疫苗可爲港府大幅減低數以億計治療肺炎鏈球菌疾病的醫療開支。

肺炎鏈球菌可致命

肺炎鏈球菌是公認惡菌，嚴重威脅幼童及長者的性命，可引致腦膜炎、肺炎、菌血症及中耳炎等嚴重疾病；其中腦膜炎極具威脅性，帶給患者失聰或神經紊亂等深遠影響，甚至死亡。兩歲以下幼童最受威脅。一項在 2001 年進行的研究顯示，本港約兩成二至六歲幼童的鼻腔內帶有肺炎鏈球菌，屬高危一族。由於肺炎鏈球菌早在 60 年代已對盤尼西林及其他主要抗生素產生抗藥性，醫生在治療肺炎鏈球菌疾病時倍感困難。

十七個國家已將肺炎鏈球菌接合疫苗納入兒童免疫接種計劃

世界衛生組織已將肺炎鏈球菌疾病列為五歲以下幼童致命疾病中能以疫苗預防之首位。由於肺炎鏈球菌接合疫苗能透過群體保障作用 （herd protection）減低已接種疫苗兒童及沒有接種疫苗人士患上肺炎鏈球菌疾病的風險，全球十七個國家之政府已將肺炎鏈球菌接合疫苗納入幼童免疫接種計劃內。不少其他國家亦考慮在未來數年資助該疫苗納入幼童免疫接種計劃。

亞洲首項研究肺炎鏈球菌接合疫苗的經濟效益研究

該項由香港中文大學藥劑學系於 2006 年進行全亞洲首項針對香港社會的研究結果，剛於 2007 年 5 月國際藥物經濟及成果研究學會 (The International Society for Pharmacoeconomics and Outcomes Research 簡稱 ISPOR) 的週年會議上發表。

該項研究的中期結果顯示，肺炎鏈球菌接合疫苗符合世界衛生組織訂定的成本效益準則，爲所有本港初生嬰兒接種肺炎鏈球菌接合疫苗乃非常合符成本效益的方法，以減低肺炎鏈球菌疾病為本港所帶來的負擔。

研究顯示肺炎鏈球菌疾病的治療成本高昂

研究採用來自威爾斯親王醫院、聯合醫院、香港中文大學醫學院兒科學系及私家醫生門診收費的本地醫療數據計算肺炎鏈球菌疾病的治療成本，其中包括住院費、門診費、醫護人員診金、深切治療部、藥物、檢驗及併發症的長期醫療費用等。另外，研究也計算患者家人在照顧患者時付出的間接開支，包括往來醫院/診所及家中的交通費等。

肺炎鏈球接合疫苗符合成本效益

研究顯示肺炎鏈球菌接合疫苗有助減低已接種疫苗兒童的肺炎鏈球菌帶菌率，因而減低將疾病傳染給沒有接種疫苗人士的風險。這種效果稱爲「群體保障」，是在疫苗被納入兒童免疫接種計劃後帶給成年人的非直接但重要的好處，有助節省相當的醫療開支。

研究顯示，如全港所有幼童均接種肺炎鏈球菌接合疫苗的話，該疫苗延長每一人一年壽命的成本約爲港幣 385,000 元。如同時計算群體保障，則該疫苗在延長每一人一年壽命的成本爲港幣 26,275 元，遠較世衛的準則爲低。

研究支持將疫苗納入本港兒童免疫接種計劃

負責該項研究的香港中文大學藥劑學院教授及副院長(外務)李炯前教授表示：「研究顯示，肺炎鏈球菌接合疫苗有助減低大部份現時本港用於治療肺炎鏈球菌疾病的直接醫療開支。爲所有嬰兒接種疫苗乃合乎世界衛生組織的標準。香港生活環境擠逼，易於傳播疾病，研究所用的群體保障計算較爲保守，實際的群體保障效應較大。因此，如將肺炎鏈球菌接合疫苗納入本港兒童免疫接種計劃可能更符合成本效益，是一項非常值得的投資。爲保障本港市民免受肺炎鏈球菌疾病威脅，港府有必要將肺炎鏈球菌接合疫苗納入香港兒童免疫接種計劃內。」

- 完 -

傳媒聯絡：精信醫療保健

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Short communication

Pediatric hospitalization for pneumococcal diseases preventable by 7-valent pneumococcal conjugate vaccine in Hong Kong

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Abstract

In a population-based study, we use ICD-9-CM codes to estimate the hospitalization rates for pneumococcal disease among young children in Hong Kong, 2000–2005 and the preventable burden using several outcome indicators. For children aged ≤2 years, the average admission rates (per 100,000 person-years) were 23.7 for invasive pneumococcal disease (IPD), 1047.5 for clinical pneumonia and 213 for radiological pneumonia. For this group of children, the disease burden potentially preventable by vaccination, per 100,000 person-years, were estimated to be 19.3 (95% CI, 16.7–21.9) for IPD, 58.5 (95% CI, 57.3–59.6) for clinical pneumonia and 40.6 (95% CI, 59–82.2) for radiological pneumonia.

Keywords: Pneumococcal disease; *Streptococcus pneumoniae*; Children

1. Introduction

Streptococcus pneumoniae is the leading cause of pediatric meningitis, bacteremia and pneumonia. Recently, a heptavalent pneumococcal conjugate vaccine (PCV-7) was approved for prevention against pneumococcal disease in young children. In clinical trials, it has efficacies of 97.4% against serotype-specific invasive infections and 20.5% against radiological pneumonia [1]. In the United States where PCV-7 has been adopted for universal immunization of children since 2000, encouraging public health benefits were reported recently [2]. According to a surveillance in 2004, it has been shown that the disease burden for invasive pneumococcal disease (IPD) has reduced by 45%; and cases that were caused by antibiotic resistant strains have decreased by 51% [2]. In Asia, limited information for pneumococcal disease burden is perceived as one important obstacle for wider application of PCV-7. In Hong Kong, our previous studies estimated that the incidence rates for IPD was 18.3 and 15.6 per 100,000 for children aged ≤2 and ≤5 years, respectively; and the expected serotype coverage for PCV-7 is 89.7% [3,4]. This study examines the possibility that IPD is under-represented in hospital discharge diagnoses. It also estimates the in-patient burden of pediatric pneumonia and the annual incidence of pneumococcal diseases that could potentially be prevented by a widespread use of PCV-7.

2. Materials and methods

In Hong Kong, the Hospital Authority (HA) is a statutory body responsible for provision of all public hospital services for the 6.7 millions population. The organization manages a total of 19,505 hospital beds and accounts for

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90% of all hospital admissions in the region [5]. For every in-patient discharge (alive or dead), information on the hospitalization diagnosis and procedures is included in a central computerized database, accordance to the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) system. Data quality and consistency in the computerized system is ensured through training and a manual prepared for use by hospital personnel responsible for entering the information. This database was used as the data source in the enquiry for discharge diagnoses. The search strategy was as follows: (1) only discharge diagnoses listed in the first five positions were included; (2) the ICD-9-CM codes used in the search include unspecified pneumonia (code 486), pneumococcal pneumonia (code 481), pneumococcal septicemia (code 038.2) and pneumococcal meningitis (code 320.1) and (3) each hospital admission was only counted once. The search covered a 6-year period from January 2000 to December 2005. For calculation of the annual unadjusted age-specific rates, the mean annual number of cases was divided by the total population in each age band and expressed as number per 100,000 persons at specified ages per year [4]. The sum of cases for pneumococcal septicemia (code 038.2) and pneumococcal meningitis (code 320.1) was used to estimate the unadjusted hospitalization rates for IPD. The population figures obtained in the 2001 census by the Census and Statistics Department was used in all calculations. The number of children aged 0–2 years and 3–5 years were 149,092 and 206,105, respectively. Age was defined by the number of complete years a person has passed since birth (i.e. the age in the last birthday).

Since discharge coding data is known to be imprecise [6], medical records for the subsets of children hospitalized in one large Hospital Authority hospital, the Queen Mary Hospital (QMH) was reviewed to assess the sensitivity of the coding data as surrogate for IPD and to obtain the proportion of radiological pneumonia within code 486, unspecific pneumonia. This hospital has all the clinical disciplines, including a pediatric department with 138 beds. In this hospital, all pediatric febrile admissions were vigorously investigated with blood cultures; chest radiograph findings and clinical information were entered to a computerized database. Most chest X-rays (>90%) were reported by radiologists. Coding data, using pneumococcal septicemia (code 038.2) and pneumococcal meningitis (code 320.1) as search terms, and culture records in the microbiology department were used as data sources for IPD case identification. Cases of IPD were defined by the isolation of *S. pneumoniae* from a normally sterile body site [4]. All the culture-confirmed cases were matched with those identified by the two discharge diagnoses for omission, and vice versa. Sensitivity for the coding data obtained was used to calculate the adjusted hospitalization rates for IPD.

To obtain the proportion of radiological pneumonia within code 486, unspecified pneumonia, we reviewed the hospital charts and radiology reports for the subset of children aged ≤5 years who were admitted to QMH. Radiological pneumonia was defined by: (1) onset before or within two days of hospitalization; (2) a compatible clinical picture such as presence of respiratory symptoms and (3) positive chest radiograph, defining as having either alveolar consolidation or pleural effusion according to the WHO criteria [1,7]. Historical reporting of chest radiograph was used in making the diagnosis of radiological pneumonia. Radiographs with perihilar infiltrates or other non-end-point shadows were regarded as negative. Afterwards, the proportion of radiological pneumonia obtained for the QMH subset was used to calculate the burden estimate within all code 486, unspecified pneumonia for all children.

Risk factors for pneumococcal diseases were categorized according to the Advisory Committee on Immunization Practices (ACIP) [8]. The preventable proportion of pneumococcal diseases was calculated on the basis of a 90% share by the Hospital Authority for hospitalization and an assumed vaccine uptake of 93%. PCV-7 is assumed to cover 89.7% of the invasive isolates from children [3], to have efficacies of 97.4% for IPD caused by vaccine serotypes [9], 20.5% for radiological pneumonia and 6% for code 486, unspecified pneumonia [1,10].

3. Results

During the 6-year period, the total numbers of in-patient discharges from the HA hospitals for children aged ≤5 years were 17,868 for unspecified pneumonia, 447 for pneumococcal pneumonia, 57 for pneumococcal septicemia and 22 for pneumococcal meningitis. Table 1 showed the average unadjusted hospitalization rates according to discharge coding. The hospitalization rates for the surrogate diagnoses in children aged 0–2 years were consistently higher than those for the older children aged 3–5 years. Pneumococcal meningitis and septicemia were associated with fatal outcome for 10 children; 5 each for aged 0–2 years and 3–5 years.

Table 1
Unadjusted hospitalization rates for unspecified pneumonia and pneumococcal pneumonia, septicemia and meningitis in Hong Kong, 2000–2005

Discharge diagnosis and age groups[a]	Hospitalization rate (per 100,000 person-years)	95% Confidence interval
Unspecified pneumonia		
0–2 years	1047.5	1026.4–1068.6
3–5 years	847.7	831.6–863.9
Pneumococcal pneumonia		
0–2 years	31.3	27.6–35.0
3–5 years	17.5	15.2–19.6
Pneumococcal septicemia		
0–2 years	4.2	2.9–5.6
3–5 years	2.1	1.3–2.9
Pneumococcal meningitis		
0–2 years	1.9	1.0–2.8
3–5 years	0.6	0.2–1.1

[a] According to ICD-9-CM codes for unspecified pneumonia (code 486), pneumococcal pneumonia (code 481), pneumococcal septicemia (code 038.2) and pneumococcal meningitis (code 320.1).

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Table 2
Q4 Population-based estimation of pneumococcal disease potentially preventable with 7-valent PCV using different outcome measures, Hong Kong, 2000–2005

	Hospitalization rates, per 100,000 person-years (95% confidence interval, CI)		
	0–2 years	3–5 years	0–5 years
Disease burden estimates			
Invasive pneumococcal diseases (adjusted)[a]	23.7 (20.5–26.9)	10.5 (8.7–12.3)	16.1 (14.4–17.8)
Unspecified pneumonia	1047.5 (1026.4–1068.6)	847.7 (831.6–863.9)	931.6 (918.7–944.5)
Radiological pneumonia[b]	213 (208.7–217.3)	205.3 (201.4–209.2)	206.2 (203.4–209.1)
Potentially preventable with PCV-7			
Invasive pneumococcal diseases[c]	19.3 (16.7–21.9)	8.5 (7.1–10)	13.1 (11.7–14.5)
Unspecified pneumonia[d]	58.5 (57.3–59.6)	47.3 (46.4–48.2)	52.0 (51.3–52.7)
Radiological pneumonia[d]	40.6 (39.8–41.4)	39.1 (38.4–39.9)	39.3 (38.8–39.9)

[a] This was estimated by using two discharge diagnoses (ICD-9-CM codes 320.1 and 038.2) as a surrogate. The rates have been adjusted using the sensitivity (25.6%) identified for this approach through chart review of the patient subset in QMH.
[b] This was estimated from unspecified pneumonia using the proportions identified for children admitted to the QMH in which radiological pneumonia was found for 20.3% (97/477) children aged 0–2 years and 24.2% (100/413) children aged 3–5 years.
[c] Calculated by hospitalization rate (adjusted) × vaccine uptake (93%) × vaccine coverage (89.7%) × vaccine efficacy (97.4%).
[d] Calculated by hospitalization rate × vaccine uptake (93%) × vaccine efficacy (6% for unspecified pneumonia and 20.5% for radiological pneumonia).

In the QMH, the microbiology database registered 39 episodes of culture-confirmed IPD among children aged 0–5 years during the review period. These included positive blood culture alone in 33 episodes, both blood and CSF in 4 episodes, blood and pleural fluid in 1 episode and lymph node in 1 episode. The 39 children with culture-confirmed IPD included 33 (84.6%) who were previously healthy, three (7.7%) with an ACIP-defined high risk medical condition including two malignancy and one congenital heart disease, and three (7.7%) with other chronic medical conditions not defined as conferring a high risk for pneumococcal infection including one asthma, one bilary atresia and one global developmental delay. Matching of cases identified in the two data sources showed that all cases with the two IPD-related discharge diagnosis were captured by the microbiology records. In contrast, only 10 of the 39 culture-confirmed episodes were given discharge diagnosis of pneumococcal septicemia (code 038.2) and/or meningitis (code 320.1). A variety of other discharge diagnoses (e.g. code 038.0 streptococcal septicemia, code 038.9 unspecified septicemia) were listed for the remaining 29 episodes. Therefore, the sensitivity of the two discharge codes as a surrogate for IPD burden is only 25.6% (10/39). This means estimation of hospitalization rate for IPD using discharge diagnoses 038.2 and 320.1 could have underestimated the true burden by a multiplication factor of 3.9 (95% confidence interval (CI), 2.4–6.9).

During the study period, 890 children were discharged from the QMH with code 486, unspecified pneumonia. Radiological pneumonia was found for 97 of 477 children aged 0–2 years (20.3%, 95% CI, 17.0–24.2%) and 100 of 413 children aged 3–5 years (24.2%, 95% CI, 20.3–28.6%). Concerning the underlying health status, 89.8% (177/197) had previously been healthy, 7.1% (14/197) had an ACIP-defined high risk medical condition (nine chronic cardiac diseases, five chronic chest diseases), and 3.1% (6/197) had other chronic medical conditions not defined as conferring a high risk for pneumococcal infection (four neurological diseases, one Klinefelter syndrome, one failure to thrive). During the same period, there were a total of 11 and 8 hospital discharges with code 481 from the QMH for children aged 0–2 years and 3–5 years, respectively.

Table 2 showed the hospitalization rates for IPD, the two pneumococcal pneumonia surrogates and disease burden estimates potentially preventable through PCV-7 vaccination using different outcome measures. After correction for the coding data sensitivity, the number of IPD admissions for the period were estimated to be 212 (95% CI, 132–373) and 130 (95% CI, 81–229 episodes for children aged 0–2 and 3–5 years, respectively. The 10 IPD-related deaths translated into case-fatality rates of 2.4% (5/212) and 3.8% (5/130) for children aged ≤2 years and 3–5 years, respectively. The average annual incidences of pneumococcal disease hospitalizations preventable in children aged 0–5 years in Hong Kong were 13.1 (95% CI, 11.7–14.5) per 100,000 person-years for IPD, 52 (51.3–52.7) per 100,000 for unspecified pneumonia and 39.3 (38.8–39.9) per 100,000 for radiological pneumonia. Approximately two IPD-related mortalities among young children would be preventable every year.

4. Discussion

This study shows how a universal infant and early childhood immunization program with PCV-7 in Hong Kong would have impact upon the hospitalized burden of pneumococcal infection in young children. As in previous studies, we used discharge diagnoses and microbiology database for retrospective surveillance of pneumococcal disease burden [11,12]. Culture results are highly specific for IPD but could lack sensitivity because of antibiotic use, techniques and disparities in blood culture practice. Therefore, the higher IPD rates in the United States than in Europe have been attributed to better detection of milder cases [11]. In Italy, estimates of IPD were shown to be affected greatly by the number of blood cultures performed [13]. These studies indicate the potential for underestimation if only culture results were used in

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surveillance [4]. By using the findings from a regional hospital to validate the ICD-9-CM codes commonly used for IPD, our data reaffirms the poor sensitivity of coding data as an outcome measure. As reported previously, the sensitivities of commonly used ICD-9-CM codes in detecting laboratory-confirmed pneumococcal pneumonia were 11.3–58.3% [6]. Accordingly, this study corrects the IPD rates derived from coding data using the sensitivity data obtained from chart review for one regional hospital. The adjusted rates for IPD and the case-fatality ratios were similar to those previously reported for children in Hong Kong using other methodologies [4,14].

In the absence of a gold standard for confirming the diagnosis of pneumococcal pneumonia, we assessed the vaccine-preventable burden by two indicators. The results show that the preventable burden is approximately 30% greater when clinical pneumonia (i.e. code 486, unspecified pneumonia) rather than radiological pneumonia is used as the outcome measure. As suggested by Madhi et al., these results may be explained by the inability of radiograph-confirmed alveolar consolidation in identifying cases of pneumococcal pneumonia that have not progressed to radiographically-confirmed alveolar consolidation possibly because of a number of factors [15,16]. Despite the relatively low IPD rates in Hong Kong, our population-based hospitalization rates for both pediatric pneumococcal (code 481) and unspecified pneumonia (code 486) are largely similar to those reported in the United States before the widespread use of PCV-7 [17]. In estimating the PCV-7 preventable burden, we assumed the efficacy to be 6% for clinical pneumonia according to clinical trial estimates [1,10,16] whilst surveillance after universal use has recently found a 37% decline in all-cause pneumonia admissions; suggesting a substantially greater benefit [17].

This study has several limitations. In defining radiological pneumonia, we used the historical reporting of alveolar consolidation or pleural effusion for making the diagnosis instead of independent reading of films by two observers, with discordant readings sent to another radiologist. Since the data were derived from a large computerized database involving many hospitals, variations in coding practice and inter-observer differences in chest radiograph interpretation are potential confounders. Although duplicate counts were excluded by using anonymous patient identifiers, it would not have overcome marginal repetitions from readmission and multiple coding. Nonetheless, the effect of this on the total PCV-7 preventable admissions is likely to be small. Because hospitalization rates could be influenced by socio-economical and cultural factors, caution should be exercised in making comparison with rates reported in other studies.

In conclusion, this study found that a significant proportion of the pneumococcal disease in Hong Kong children could be preventable by a widespread use of PCV-7. Further studies to address disease burden in outpatients, impact on antibiotic prescription and resistance pattern, as well as cost-effectiveness analysis are necessary to inform vaccine policy decision.

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