

State of Hong Kong Children

Proceedings of The First Current Topic in Infectious Diseases: Consensus Meeting on Conjugate Vaccines of the Center of Infection, Faculty of Medicine, The University of Hong Kong (Selected Abstracts) 17 February, 2001

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Method and Process of Consensus Building

The consensus meeting on Consensus meeting on conjugate vaccines was held on February 17, 2001, as the first current topic in infectious diseases that was organized by the Centre of Infection, the University of Hong Kong. A panel of experts from the fields of Internal Medicine, Clinical Microbiology, Internal Medicine, Paediatrics and Public Health were provided with the latest scientific papers¹⁻⁸ and were invited to speak and discuss on various aspects concerning the topic.

After the formal presentation, panel discussion was held. All speakers, invited discussants from various aspects of the medical fields and audiences actively participated in the discussion with further elaboration on issues around *S. pneumoniae* and *H. influenzae* disease burden, antimicrobial resistance and conjugate vaccine.

Finally, conclusions were drawn on the basis of the current scientific information and views expressed by the panel and other participants. Drafts in progress and final copies of the manuscript were distributed to panel for comments before submission for publication.

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Invasive *Haemophilus Influenzae b* Disease: Overview and Disease Burden in Hong Kong

YL LAU

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In a position paper on Hib conjugate vaccine, WHO made the following qualified statement: "In view of the demonstrated safety and efficacy of the Hib conjugate vaccines, Hib vaccine should be included, as appropriate to national capacities and priorities, in routine infant immunization programmes." This statement highlights the two major barriers to the implementation of routine infant Hib immunization in Asia: the cost of Hib vaccine and its administration which has to be accommodated by "national capacities"; and the absolute disease burden of Hib diseases and its relative burden in the broader context of total disease burden, which will determine the "national priorities". The disease burden of Hib diseases varies greatly from one country to another in Asia but on a whole may be less than that in North America. Better documentation of burden of disease is not just of academic interest but indispensable as part of a very complex strategy to introduce novel but relatively expensive vaccines, such as Hib and pneumococcal conjugate vaccines. Currently, the high-income countries in Asia should address this issue of whether or not to introduce routine Hib immunization of infants because their "national capacities" could easily accommodate the cost of the vaccine and its administration; and even if the incidence of Hib disease in these countries is low, the benefits of such routine immunization could be substantial because the indirect medical costs and long-term treatment costs of Hib morbidity increase with per capita gross national product (GNP). For example, in Hong Kong Special Administrative Region of China, where the estimated incidence of Hib meningitis and bacteremic pneumonia is only about three per 100,000 children aged under five years; there would still be about 10 cases per year, with perhaps one death and two children suffering sustained permanent neurological sequelae but surviving for decades, and thus in need of long-term health care. The net Hib immunization programme cost could be offset by the savings made in not having to provide care for these handicapped children for the rest of their lives as well as the life saved. However, for low-income countries, the absolute cost involved will be high enough to prohibit implementation of routine Hib infant immunization, despite the demonstrated cost-effectiveness of such programs.

Overview and Disease Burden of *Haemophilus Influenzae* Type b in China

YH YANG

Professor, Beijing Children's Hospital, Beijing

Haemophilus influenzae type b (Hib) infections have been documented in China previously. However, the data are scanty and incomplete. Hib meningitis accounted for up to 16% of all pyogenic meningitis during the 1950s. In the 1900s, it accounted for 30% to 50% of bacterial meningitis in China. The incidence of Hib meningitis in Hefei City was 10.4 per 100,000 children <5 years old.⁹ A study, supported by the World Health Organization, on the epidemiologic information of bacterial meningitis in infants and children with special emphasis on Hib in Beijing Children's Hospital (BCH) and Hefei City was completed in 1992. It has studied 128 patients clinically diagnosed to have bacterial meningitis in BCH from 1988 to 1989. Hib was diagnosed in 37 (29%) of the 128 cases and 84% was <2 years old. Most of the cases occurred in winter and spring. The study done in Hefei City from 1990 to 1992, including 13 hospitals in Hefei City, found that Hib was the most common cause of bacterial meningitis, accounting for 52% of total cases. The incidence of Hib meningitis was 10.4 per 100,000 in children <5 years old. For pneumonia, the yield of culture has been consistently low due mainly to the prior use of antibiotics. By detection of antigens, two studies at BCH found evidence of Hib infection in about one quarter of children with pneumonia.¹⁰ The role of Hib in childhood pneumonia was further highlighted by the finding of a recent study.¹¹ Of 100 children admitted to the BCH for acute lower respiratory infections, 8% of them had serological evidence for Hib etiology. There was no report on other Hib diseases like epiglottitis, sepsis, pyogenic arthritis and osteomyelitis available for China. Further surveillance study in China would be needed in the future.

Factors to Consider in the Routine Use of Hib in Hong Kong

Thomas HF TSANG

Community Physician, Department of Health

The routine use of conjugate Hib vaccine is a public health decision, which should only be made after a careful assessment of a number of factors, related to the disease and the vaccine. A major issue concerns the burden of invasive Hib disease in Hong Kong. Available data suggested that the disease is much less common locally than in other industrial countries such as the United States, Canada, Australia and Finland. Hib is not a notifiable disease. Notwithstanding this, the department of Health only received between one to six cases of Hib meningitis per year. The conjugate Hib vaccine is highly efficacious (>95%) with relative few and minor side effects (5-30%). It is accustomed to use one or more of the following quantitative tools to assess the cost and benefit of a vaccination program: cost-benefit analysis (CBA), cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). Of the CBA performed overseas, the B:C ratio for routine Hib range between 1.2 to 5.1. In Australia, one study reported the cost per QALY saved of a routine Hib program to be between AUS \$1231 to 9136. A CBA of routine Hib program in Hong Kong is difficult to perform because there is no local consensus on how to calculate the cost of some parameters such as the long term medical care, loss in productivity and death. On the basis of an estimated incidence of five invasive Hib per 100,000 children age ≤ 5 years, the cost per case of invasive disease prevented is about 1.6 million. In conclusion, quantitative assessment of a routine Hib program in Hong Kong is difficult to perform, due mainly to the lack of certain data. A consensus economic model on which to base decision should be developed and validated.

Burden of Pneumococcal Disease in Hong Kong

CB CHOW

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Streptococcus pneumoniae causes a spectrum of diseases. The general breakdown of diseases caused by pneumococcus is as follows: meningitis (4.1%), bacteremia without focus (38.7%), bacteremic pneumonia (53.4%). The incidence of invasive pneumococcal disease (IPD) is more well defined in the US, the UK and Australia. In general, the incidence is highest in children ≤ 2 years of age, although the absolute incidence varies with countries and risk factors. The incidence in the US was 165.3/100,000 population <1 year of age, 203.3/100,000 <2 years, and 37.1-48.1/100,000 and 96.4/100,000 population <1 year in the UK and Australia, respectively. Children with sickle cell disease and HIV infection also had extremely high incidence of IPD. Population-based data from Hong Kong are lacking. The incidence of pneumococcal septicemia appears low. One study reported that 22% of septicemia in infants and preschoolers were due to pneumococcus although the incidence is not known. In Hong Kong, one study reported an incidence of 5.2/100,000/year for bacterial meningitis in children <5 years.¹² Data from Princess Margaret Hospital between 1976 and 1991 revealed that 76.9% of bacterial meningitis were culture negative and 5.9% grew *S. pneumoniae*. Another study documented 6.4 episodes of community-acquired pneumonia per 1000 children <5 years of age in Hong Kong, with pneumococcus accounting for 5%-17%.¹³ Putting available information together leads to a rough "guesstimate" of the pneumococcal disease burden in Hong Kong for children <5 years would be: 20/100,000 for bacteremia, $\sim 1/100,000$ for meningitis, 1/1000 for pneumonia. Better studies to ascertain the disease burden in Hong Kong is much needed.

Overview and Disease Burden of Streptococcus Pneumoniae in China

YH YANG

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There were limited data about *Streptococcus pneumoniae* infections in China. The first study on the epidemiology of *S. pneumoniae* was performed in collaboration with World Health Organization during 1982-1985. It included 27 hospitals from 18 provinces, with more than 400 cases of pneumococcal infections. The rates of pneumococcal pneumonia, meningitis and otitis media were 14 cases, 79 cases and 68 cases per 1000 homologous disease cases respectively. Most of the cases were in children less than or equal to three years old. The mortality rates for pneumococcal pneumonia and meningitis were 16.4% and 16% respectively. Majority of them were patients less than 1 year old or more than 50 years old. Overall, the six commonest serotypes found in this study, in descending order, were 5, 6, 1, 19, 2 and 14. They accounted for 59% of all *S. pneumoniae* identified in the study. In descending order of frequency, the "pneumonia-related" serotypes were 1, 5, 14, 6, 21 and 28 while the "meningitis-related" serotypes were serotypes 2, 5, 6, 1, 27 and 14. Compared to overseas data, the incidence of type 5 pneumococcal infections in China was higher. Another study on acute bacterial meningitis in children was conducted in Hefei from 1990 to 1992. Of all the bacterial meningitis in children between the age of one month to five years old, 8.3% were caused by *S. pneumoniae*. The case fatality rate was up to 20%. Nonetheless, no pneumococcal etiology was detected in a recent study of 100 children hospitalized for acute lower respiratory infection.¹¹ Meanwhile, the data is still incomplete and further studies are now actively undergoing in China.

Resistance in Pediatric Isolates of Pneumococci. Results from a Territory-wide Carriage Study

Susan SS CHIU

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Resistance to penicillin and multiple antibiotics among *Streptococcus pneumoniae* strains is becoming increasingly problematic worldwide and in Asia.^{14,15} To determine the prevalence of carriage of these penicillin-nonsusceptible *Streptococcus pneumoniae* isolate in young children, we obtained nasopharyngeal swab specimens from 1978 children (ages, two to six years) attending 79 daycare centers or kindergartens. Three hundred and eighty-three strains of *Streptococcus pneumoniae* were isolated from these children. Fifty-eight percent of these isolates had reduced susceptibility to penicillin; 123 (32.1%) were intermediate and 100 (26.1%) were resistant. Very high MICs to penicillin (MIC >2 µg/ml) and cefotaxime (MIC >2 µg/ml) were found in 3.3% and 0.3% of the isolates, respectively. The isolates also demonstrated high rates of resistance to other antibiotics (51.2% to cefaclor, 50.2% to cefuroxime, 42.8% to cefotaxime, 80.7% to trimethoprim-sulfamethoxazole, 77% to erythromycin, 60% to clindamycin and 33.7% to chloramphenicol). No isolate was resistant to quinolone. However, 58.7% were resistant to multiple antibiotics, with extremely high prevalence of 79% in penicillin resistant isolates. Risk factors for the carriage of penicillin-nonsusceptible *Streptococcus pneumoniae* were multiple physician visits in the preceding three months, and use of antibiotics by the individual or by household members in the preceding three months. In the logistic regression analysis, only the use of antibiotics in the preceding three months was an independent risk ($P=0.004$, OR 2, 95% CI 1.2-3.2). This study demonstrated the high prevalence of antibiotic resistant *Streptococcus pneumoniae* in healthy young children in the community in Hong Kong.

Serotype Distribution of Invasive and Noninvasive Strains of Pneumococci in Hong Kong

PL Ho

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The capsular polysaccharide is a major virulence factor in the pathogenesis of invasive pneumococcal disease. On the basis of the capsular specificity, the pneumococci can be grouped into about 90 serogroups and serotypes (SGTs). While much is known about the SGT distribution of *S. pneumoniae* isolates in the Western countries, the situation in Asian countries is unclear.¹⁶ To determine the coverage of the 7-valent conjugate vaccine for invasive and noninvasive isolates in Hong Kong, the capsular SGT of 721 nonduplicate isolates of *S. pneumoniae* from diverse sources were determined by the Quellung method.¹⁵ Of the 721 isolates, 383 isolates were obtained from the nasopharynx (NP) of children age between two to six years, attending day care centers or kindergartens during a territory-wide surveillance in 2000, 140 isolates were obtained from respiratory tract specimens of hospitalized patients in seven hospitals in 1998, and 199 isolates were obtained from blood (187) or CSF (12) of patients hospitalized in four hospitals between 1996 to 2000. SGT included in the 7-valent pneumococcal conjugate vaccine were 4, 6B, 9V, 14, 18C, 19F and 23F. At all age groups, the most common serotypes were 6B, 19F and 23F. Of the isolates from young children, the 7-valent conjugate vaccine respectively covered 65%, 88% and 88% of the NP, respiratory and invasive isolates. Our data showed that distribution of SGT among invasive and noninvasive isolates among young children in Hong Kong is similar to those reported in the United States. On the basis of the SGT distribution, the recent 7-valent pneumococcal conjugate vaccine could offer protection against many of the invasive pneumococcal infections among children in this locality.

Overview of Conjugate Pneumococcal Vaccine: Serotype Coverage, Efficacy and Status of Usage in other Countries

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Streptococcus pneumoniae remains a major cause of morbidity and mortality even in the developed countries. It is one of the commonest causes of community-acquired pneumonia, bacteraemia, meningitis, acute otitis media, sinusitis, and postsplenectomy sepsis.⁶ Currently available vaccines target the polysaccharide capsule, whose antiphagocytic property is a major virulence factor. Of the 90 described capsular types, the 23 commonest types are included in the polysaccharide vaccine, which provides coverage against 80% to 90% of bacteraemic isolates.^{7,8} The polysaccharides, however, are poorly immunogenic in children less than two years of age that are most susceptible to invasive pneumococcal infections. Pneumococcal polysaccharides are therefore conjugated to proteins to improve their immunogenicity in young children and infants. A heptavalent conjugate pneumococcal vaccine was licensed in 2000 in the United States, which contains serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. CRM₁₉₇, a non-toxic variant of diphtheria toxin, is used as the protein conjugate. These seven serotypes accounted for 86% of bacteraemia, 83% of meningitis, and 65% of acute otitis media in children less than six years of age in the United States. In a randomized, double-blinded clinical trial in which ~37,000 children were recruited, the heptavalent vaccine is ~100% effective in preventing invasive pneumococcal infections caused by vaccine serotypes and 89% against all serotypes. There is a 7.0%-22.8% reduction in the incidence of otitis media and a 5.3% reduction in antibiotic use in the vaccinees. The vaccine is presently licensed for use in infants older than six weeks and is given at two, four, six months, with a booster dose at 12-15 months. It is recommended for children less than 23 months old; for children aged 24-59 months, it should be considered for those who are predisposed to severe pneumococcal disease. A 40%-50% reduction in nasopharyngeal pneumococcal carriage of vaccine serotypes is found in field trials of a 9-valent conjugate vaccine.

Consensus Statements

Disease burden of paediatric *Haemophilus influenzae* type b infections in Hong Kong

1. The incidence of *Haemophilus influenzae* type b (Hib) diseases in Hong Kong appears to be low. Multiple confounding factors, such as prior antibiotic usage, might be the causes for the apparent low recorded prevalence.
2. Further study to collect epidemiological data in Hong Kong would be difficult due to the following factors:
 - a) Some children might have been given Hib vaccination on an individual basis.
 - b) There are quite a number of patients taking antibiotics prior to collection of specimens for cultures and the recovery rate of any microorganisms in these situations is relatively low.
3. Gaps in existing data should be addressed in future studies using new research methodology, such as the WHO rapid assessment tool.

Use of conjugate *Haemophilus influenzae* type b vaccine

1. Conjugate Hib vaccine has proven safety and efficacy in prevention of invasive Hib disease.
2. Thorough cost-effective/benefit/utility analysis and comparison of existing program would be very helpful in supporting recommendation for universal vaccination in this locality. Broader discussion/consultation on what constitute the "acceptable" cost is required.

Disease burden of pneumococcal infections in Hong Kong

1. Disease burden of pneumococcal disease is still unclear and further study would be needed for different at-risk groups.
2. Penicillin-resistant and multiple antibiotic-resistant pneumococci are a major problem in Hong Kong.

Use of conjugate pneumococcal vaccine

1. The heptavalent conjugate vaccine provides good coverage of the serotypes causing invasive pneumococcal disease in Hong Kong at present.
2. Conjugate pneumococcal vaccine is effective in decreasing vaccine strain carriage, and preventing invasive pneumococcal disease in young children from published experience.

Acknowledgement

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References

1. Yang Y, Shen X, Jiang Z, et al. Study on *Haemophilus influenzae* type b diseases in China: the past, present and future. *Pediatr Infect Dis J* 1998;17:S159-S165.
2. Lau YL, Yung R, Low L, Sung R, Leung CW, Lee WH. *Haemophilus influenzae* type b infections in Hong Kong. *Pediatr Infect Dis J* 1998;17:S165-S169.
3. Lau YL. *Haemophilus influenzae* type b diseases in Asia. *Bull. World Health Organ* 1999;77:867-8.
4. Levine OS, Schwartz B, Pierce N, Kane M. Development, evaluation and implementation of *Haemophilus influenzae* type b vaccines for young children in developing countries: current status and priority actions. *Pediatr Infect Dis J* 1998; 17:S95-S113.
5. Heath PT. *Haemophilus influenzae* type b conjugate vaccines: a review of efficacy data. *Pediatr Infect Dis J* 1998;17:S117-S122.
6. American Academy of Pediatrics. American Academy of Pediatrics. Committee on Infectious Diseases. Policy statement: recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis. *Pediatrics* 2000;106: 362-6.
7. Hausdorff WP, Bryant J, Kloek C, Paradiso PR, Siber GR. The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use, part II. *Clin Infect Dis* 2000; 30:122-40.
8. Hausdorff WP, Bryant J, Paradiso PR, Siber GR. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part I. *Clin Infect Dis* 2000;30:100-21.
9. Yang Y, Leng Z, Lu D. Pediatric *Haemophilus influenzae* type b meningitis in Hefei city: an epidemiologic study. *Chung Hua I. Hsueh Tsa Chih* 1998;78:251-3.
10. Levine OS, Liu G, Garman RL, Dowell SF, Yu S, Yang YH. *Haemophilus influenzae* type b and *Streptococcus pneumoniae* as causes of pneumonia among children in Beijing, China *Emerg Infect Dis* 2000;6:165-70.
11. Yang Y, Shen X, Vuori-Holopainen E, et al. Sero-etiology of acute lower respiratory infections among hospitalized children in Beijing. *Pediatr Infect Dis J* 2001;20:52-8.
12. Lau YL, Low LC, Yung R, et al. Invasive *Haemophilus influenzae* type b infections in children hospitalized in Hong Kong, 1986-1990. Hong Kong Hib Study Group. *Acta Paediatr* 1995;84:173-6.
13. Sung RY, Cheng AF, Chan RC, Tam JS, Oppenheimer SJ. Epidemiology and etiology of pneumonia in children in Hong Kong. *Clin Infect Dis* 1993;17:894-6.
14. Ho PL, Que TL, Tsang DN, Ng TK, Chow KH, Seto WH. Emergence of fluoroquinolone resistance among multiply resistant strains of *Streptococcus pneumoniae* in Hong Kong. *Antimicrob. Agents Chemother* 1999;43:1310-3.
15. Ho PL, Yam WC, Cheung TKM, et al. Rapid rise of fluoroquinolone resistance among *Streptococcus pneumoniae* in Hong Kong linked to acquisition of fluoroquinolone resistance by the locally dominant Spanish 23F clone. *Emerg Infect Dis* 2001. In press.
16. Luey KY, Kam KM. Vaccine coverage of *Streptococcus pneumoniae* in Hong Kong with attention to the multiple-antibiotic-resistant strains. *Vaccine* 1996;14:1573-80.