Journal of Paediatric Respirology and Critical Care

Pneumococcal infections pre and post vaccine era in Macao

Shirley Yan LEE 李然[1*] and Kin-Mui IEONG 楊健梅[2]

[1]Attending Physician; [2]Chief Physician, Pediatric and Neonatology Department of CHCSJ, Macao

Abstract

Objective: To analyse the effect of the pneumococcal conjugate vaccine after introduced on 2009 Sept in Macao. ***Method:*** Comparison of pneumococcal infection paediatric population hospitalised in the governmental hospital from 2001 to 2005 that is the pre vaccine era with the 2011 to 2015 post vaccine era. ***Result:*** After the introduction of the vaccine, there is no more invasive streptococcal infection documented in the governmental hospital and the non-invasive streptococcal infection decrease significantly about 91.4% drop.

Keywords: Macau, Pneumococcal infections, Vaccine era

Background

Streptococcus pneumoniae (pneumococcus) is the causative agent of pneumococcal infections. It is a Gram-positive coccus encapsulated with polysaccharides. The difference in the composition of capsular polysaccharides constitutes to at least 90 different serotypes of pneumococci identified thus far. Pneumococcal infection represents a wide range of diseases caused by the bacterium *Streptococcus pneumoniae* (or more commonly referred as pneumococcus). While pneumococcus is a common cause of mild illnesses such as sinus or middle ear infections, it may also cause severe or even life-threatening invasive pneumococcal diseases (IPD) such as pneumonia, sepsis, and meningitis. The outcomes for IPD are usually more severe among young children and elderly persons.

The treatment of pneumococcal infections usually involves the use of antibiotics. But there is a problem of increasing resistance of the bacterium to antibiotics, which makes prevention of pneumococcal infections important. One of the most effective means of preventing pneumococcal diseases is by pneumococcal vaccination.

*Author to whom correspondence should be addressed.

Email: leeshirley@live.com

Pneumococcal disease burden in Macao

In Macao, pneumonia is the second leading cause of death (after cancer and heart diseases) and accounted for 6.7% of total deaths in 2005. The incidence of pneumonia in adults increases with age all over the world.[1] A US study of 46,237 elderly patients reported 18.2 cases per 1,000 person-year among patients aged 65-69 years, rising to 52.3 cases per 1,000 person-years among patients aged ≥85 years.[2] Previous estimates of mortality from CAP range from 5.1% for hospitalised and ambulatory patients to 36.5% for patients in intensive care units.[3] It is estimated that the incidence of pneumonia in Macau under 5-year of age is similar to nearby region of Hong Kong and even US.[4]

Vaccine available in Macau for prevention of IPD

Polysaccharide vaccines

The 23-valent pneumococcal polysaccharide vaccine (PPSV23) effectiveness has ranged from 43%-81%.[5] PPSV23 has been found to be effective in healthy individuals <75 years of age, but protection wanes after 5 years. Unlike conjugate vaccines, PPSVs have not been shown to interrupt carriage and therefore do not have the potential for herd effects.[6] There is no discernible impact of PPSV23 on population incidence of IPD, and the older and high-risk individuals are less likely to benefit. However, based on vaccine efficacy estimates, PPSV23 is still considered a cost-effective intervention for the low-risk elderly.

Conjugate vaccines

In an effort to improve the immunogenicity of vaccines, pneumococcal conjugate vaccines (PCVs) were developed. The advantages of the conjugate vaccines are related to the way the antibodies are produced by the body. PCV induces a T-cell-dependent response which results in plasma cells producing immunoglobulin G but also produces memory B-cells. This T-cell-dependent response elicits immunological memory, and therefore primes the immune system for either natural exposure or subsequent booster vaccination. The latter observation may be considered a surrogate for exposure to the polysaccharide during a "natural" infection.[7] There is no decrease in the immune response seen with revaccination with conjugate vaccines, as they produce immunoglobulin G rather than just immunoglobulin M.[8] Memory B-cells ensure boosting of the effect with revaccination. Memory B-cells are not produced in response to most free polysaccharide vaccines and, in fact, may be depleted post-vaccination, resulting in hyporesponsiveness.[9]

Seven-valent PCV (PCV7), which included the purified capsular polysaccharides of seven serotypes conjugated to a nontoxic variant of diphtheria toxin known as CRM197, was developed in 2000.[10] The Macau health Bureau recommends children under 2 years of age to receive PCV under the Macau Childhood Immunisation Programme on September 2009. The standard regimen includes a primary series of 3 doses at 2, 4 and 6 months and a booster dose at 12 months After PCV7 was introduced in the US, rates of IPD caused by the seven serotypes have decreased substantially even among the unvaccinated population.[11] The indirect benefits of vaccination, or herd effects, likely result from reduced nasopharyngeal carriage of pneumococcus in PCV7-vaccinated children and reduced transmission from children to unvaccinated children and adults.[12] Surveillance data has shown reduction in IPD, pneumonia, and acute otitis media in young children after the introduction of PCV7 in many different geographic locations. In order to provide improvements in serotype coverage and potentially reduce the remaining IPD burden, further improvements in conjugate vaccines were released. PCV13 comprises "13" *S. pneumoniae* polysaccharide serotypes, including the existing seven in PCV7 and six additional serotypes. The immunogenicity of PCV13 has been evaluated in a number of trials in healthy infants in comparator studies versus PCV7 and when coadministered with other vaccines.[13] Noninferiority in terms of the proportion of responders 1 month after the final dose of the primary series of PCV13 versus PCV7 has been demonstrated for six of the seven common serotypes in one pivotal study[14] and in five of the seven in another.[15] The remaining six serotypes in PCV13 also demonstrated robust immune responses. Importantly, functional antibodies were elicited against all 13 serotypes contained in PCV13 after primary vaccination. Recently, the results of first randomised PCV13 versus PCV7 pediatric trial results were published. PCV13 resulted in lower acquisition and prevalence of nasopharyngeal colonisation than PCV7 for four additional PCV13 serotypes, and serotypes 6C and 19F. It was comparable with PCV7 for all other common serotypes. Evidence for PCV13 protective effectiveness against IPD is also beginning to emerge in many industrialised countries such as England, Wales, Germany, and the US.[15] These findings predict vaccine effectiveness through both direct and indirect protection. PCV13 immunogenicity and safety was also demonstrated either alone or with concomitant administration of a trivalent inactivated influenza vaccine in adults aged ≥65 years who were naive to PPSV23.[16]

A meta-analysis of all available published data from controlled clinical trials of PCV (any valency) found the efficacy of PCV in the reduction of IPD was 89% for disease due to vaccine serotypes and 63%-74% for disease due to all serotypes. The efficacy to prevent acute otitis media by vaccine serotypes was 55%-57% and 29% to prevent otitis media involving all serotypes. However, the efficacy to prevent clinical pneumonia was only 6%-7%, although it was 29%-32% to prevent radiograph-confirmed pneumonia.[17]

How about the effectiveness of vaccine in Macao? After introduction of PCV for 6 year, we would like to compare the pneumococcal infection Paediatric population hospitalised in Macau governmental hospital from 2001 to 2005 that is the pre vaccine era with the 2011 to 2015 post vaccine era.

Methods

Study design. ICD9-coded hospitalisation data for the selected cases in the Macau governmental hospital (Centro Hospitalar Conde de S Januario Macau) bear the majority of inpatients in Macau was chosen. We compared both IPD and pneumococcal pneumonia hospitalisations between the year 2001-2005 with the data between 2011-2015. We chose the period on 2001 to 2005 for comparison because of our previously published paper on 2009. We extracted the numbers of hospitalisations for each outcome from among all of the

listed diagnosis codes. We defined IPD as ICD9 code 320.1 or 038.2 or as codes 320.8, 790.7, or 038.9 and 041.2; pneumonia with diagnosed S. *pneumoniae* infection as ICD9 code 481. We scanned across discharge diagnoses in each patient record for any mention of these disease codes.

Results

From 2001 to 2005 we found out there were 4 invasive PD with 2 cases lobar pneumonia complicated with empyema, one case streptococcal meningitis and one case streptococcal bacteremia. There are also 35 cases with respiratory tract infection, their sputum culture growing streptococcus pneumoniae. According to the drug sensitivity, there are no penicillin resistant strains of streptococcus pneumoniae but almost 44.4% are intermediate penicillin sensitive.[18] While for the data from 2011 to 2015, there are no documented cases of invasive pneumococcal diseases. There are only 3 cases diagnosed with respiratory tract infection, their sputum culture growing streptococcus pneumoniae. That is almost 91.4% drop of pneumococcal infection. On 2015, the pneumonia drop from the second to the third position leading cause of death in Macao.

Discussion

After routine PCV vaccination in the Macau, hospitalisation rates for pneumococcal infection decreased significantly. There is 91.4% drop of pneumococcal infection was found out in our hospital. Compared with the situation in US, 66% reduction observed in national rates of pneumococcal meningitis hospitalisations in children aged <2 years, the target population for the PCV7 program, is consistent with reports from other population-based studies of pneumococcal meningitis in selected areas, including a 59% decrease in children aged <2 years by 2001 in 7 geographic areas and a 69% decrease in children aged <5 years by 2003 in Massachusetts. Similarly, a 56% reduction in pneumococcal meningitis was observed between 1994 and 2004 in 8 children's hospitals in the United States. In addition, a 40% decrease in invasive pneumococcal disease cases was seen in infants aged 0-90 days after the introduction of PCV7.[19]

Findings from this study need to be interpreted in light of some potential limitations. We identified pneumoccoccal hospitalisations on the basis of the ICD-9-CM codes listed as primary discharge diagnoses, which are considered to be the main reasons for hospital admission and are limited to one hospital. Furthermore, information on pneumococcal serotype distribution or antimicrobial susceptibility of the bacterial isolates is not available in Macau. Before PCV7 introduction, the vaccine serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) accounted for 73% of pneumococcal meningitis in US children aged <6 years. Although invasive disease caused by these serotypes has been reduced dramatically, the incidence of invasive disease caused by nonvaccine serotypes has been increasing in recent years.[20] Although to date these increases have been small compared with overall disease reductions, continuous monitoring of changes in serotype distribution is necessary.

In conclusion, this study provides a comprehensive assessment of changes in pneumococcal disease after a routine PCV immunisation program began in Macau. Results from this study contribute to the evidence supporting the overall nationwide beneficial effects of PCV on pneumococcal infection, the most common cause of community-acquired bacteria.

References

1. Nuorti JP, Martin SW, Smith PJ, Moran JS, Schwartz B. Uptake of pneumococcal conjugate vaccine among children in the 1998-2002 United States birth cohorts. Am J Prev Med 2008;34(1):46-53.
2. Grijalva CG, Poehling KA, Nuorti JP, Zhu Y, Martin SW, Edwards KM, et al. National impact of universal childhood immunization with pneumococcal conjugate vaccine on outpatient medical care visits in the United States. Pediatrics 2006;118(3):865-73.
3. Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ, et al. Influenza-associated hospitalizations in the United States. JAMA 2004;292:1333-40.
4. Lee Y, Lao UL, Leong IH, Chan SF, Lam K, Lam ML. Pneumococcal infection in Macau. Health Science Journal of Macao December 2009 Vol. 9 No.4.
5. Fedson DS, Guppy MJ. Pneumococcal vaccination of older adults: conjugate or polysaccharide? Hum Vaccin Immunother 2013;9(6):1382-4.
6. Fletcher MA, Laufer DS, McIntosh ED, Cimino C, Malinoski FJ. Controlling invasive pneumococcal disease: is vaccination of at-risk groups sufficient? Int J Clin Pract 2006;60(4):450-6.
7. Paradiso PR. Pneumococcal conjugate vaccine for adults: a new paradigm. Clin Infect Dis 2012;55(2):259-64.
8. Richmond P, Borrow R, Miller E, Clark S, Sadler F, Fox A, et al. Meningococcal serogroup C conjugate vaccine is immunogenic in infancy and primes for memory. J Infect Dis 1999;179(6):1569-72.

9. Torling J, Hedlund J, Konradsen HB, Ortqvist A. Revaccination with the 23-valent pneumococcal polysaccharide vaccine in middle-aged and elderly persons previously treated for pneumonia. Vaccine 2003;22(1):96-103.
10. Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. Pediatr Infect Dis J 2000;19(3):187-95.
11. Millar EV, Watt JP, Bronsdon MA, Dallas J, Reid R, Santosham M, et al. Indirect effect of 7-valent pneumococcal conjugate vaccine on pneumococcal colonization among unvaccinated household members. Clin Infect Dis 2008;47 (8):989-96.
12. Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med 2003;348(18):1737-46.
13. Duggan ST. Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) (Prevenar 13®) Drugs 2010; 70(15):1973-86.
14. Kieninger DM, Kueper K, Steul K, Juergens C, Ahlers N, Baker S, et al. Safety, tolerability, and immunologic noninferiority of a 13-valent pneumococcal conjugate vaccine compared to a 7-valent pneumococcal conjugate vaccine given with routine pediatric vaccinations in Germany. Vaccine 2010;28(25):4192-203.
15. Plosker GL. 13-valent pneumococcal conjugate vaccine: a review of its use in infants, children, and adolescents. Paediatr Drugs 2013;15(5):403-23.
16. Schwarz TF, Flamaing J, Rumke HC, Penzes J, Juergens C, Wenz A, et al. A randomized, double-blind trial to evaluate immunogenicity and safety of 13-valent pneumococcal conjugate vaccine given concomitantly with trivalent influenza vaccine in adults aged ≥65 years. Vaccine 2011;29(32):5195-202.
17. Pavia M, Bianco A, Nobile CG, Marinelli P, Angelillo IF. Efficacy of pneumococcal vaccination in children younger than 24 months: a meta-analysis. Pediatrics 2009;123(6): e1103-10.
18. Cheang TF, Lee Y, Ieong KM, Lui KM. An introduction and resistance analysis of 37 cases of Penumococccal Disease in children of Macao. Health Science Journal of Macao June 2009 Vol.9 No.2.
19. Hsu K, Pelton S, Karumuri S, Heisey-Grove D, Klein J; Massachusetts Department of Public Health Epidemiologists. Population-based surveillance for childhood invasive pneumococcal disease in the era of conjugate vaccine. Pediatr Infect Dis J 2005;24:17-23.
20. Hicks LA, Harrison LH, Flannery B, Hadler JL, Schaffner W, Craig AS, et al. Incidence of pneumococcal disease due to non-pneumococcal conjugate vaccine (PCV7) serotypes in the United States during the era of widespread PCV7 vaccination, 1998–2004. J Infect Dis 2007;196:1346-54.