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Malaysian Health Technology Assessment Section

Pneumococcal Conjugate Vaccine for Children Below Five Years Old Executive Summary

[Adapted from the report by NOORMAH MOHD DARUS]

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Background

The human nasopharynx is the reservoir of *Streptococcus pneumoniae*, which is usually carried asymptomatically, and is transmitted to other individuals by respiratory droplets. The carrier rate is highest in young children, who most likely carry pneumococci in the nasopharynx at least one time, and are the primary source for its spread within a community. In the host, pneumococci can spread locally from the nasopharynx to cause otitis media or sinusitis, or to the lungs to cause pneumonia. Pneumococci can also cause invasive infections with high mortality. Pneumonia with empyema or bacteraemia, septicaemia and meningitis are invasive pneumococcal diseases (IPD). In Europe and the US, the risk of infection is greatest in children younger than two years old.

Pneumococcal conjugate vaccines (PCVs) containing polysaccharide antigens connected to carrier proteins have been found to be effective in developing an immune response and in reducing nasopharyngeal carriage of vaccine-type pneumococci in infants and children.

Streptococcus pneumonia is the most common cause of acute otitis media (AOM) and invasive bacterial disease in children, including bacteraemia, meningitis, and pneumonia. With integration of 7-valent pneumococcal conjugate vaccine (PCV7) into the routine childhood immunization schedule, incidence of invasive pneumococcal disease (IPD) in US children declined dramatically. Similar decreases have been noted in Canada, Australia, the United Kingdom, Norway, Spain, Germany, and France after routine PCV7 infant immunization. Another positive impact of PCV7 is indirect protection against vaccine-type pneumococcal carriage among family members living with PCV7-vaccinated children and a reduction in the rate of vaccine-type IPD in the nonvaccinated population. Nevertheless, *S pneumoniae* remains a major cause of morbidity and mortality in children worldwide, particularly in countries in which nonvaccine serotypes such as 1, 3, 5, 6A, and 19A are common. Data collected before and after PCV7 introduction showed that serotypes in PCV7 provided coverage of approximately 80% of IPD-causing isolates in children younger than 5 years in North America, 68% in Europe and up to 65% in Latin America. In Asia, PCV7 coverage ranges from 41.2% in Bangladesh to 81% in China, 76.2% in Japan, and 62% in Thailand.

In Malaysia, the overall under 5 years old death incident rates in 2006 was 0.6 per thousand age specific population and 3.5 per thousand live births. Meanwhile it was reported in 2010 that there were 6 deaths per 1000 live births. Crude birth rate in 2010 was 17.5.

Currently in Malaysia there is no policy on the use of pneumococcal conjugate vaccines to protect against invasive pneumococcal disease, such as meningitis, and acute otitis media among infants and children.

In 2011, the majority of paediatricians from public and private sectors have come to an agreement to introduce PCV into the National Childhood Immunization programme due to its high efficacy. However, the Committee for Vaccine Use and Cost has suggested that the introduction of PCV into the National Immunization Programme should be further studied in terms of cost-effectiveness. Hence, the information on the cost-effectiveness of two pneumococcal vaccines in the market (PCV10 & PCV13) with different antigenic composition and comparable efficacy is needed.

Therefore this HTA is conducted to review the evidences on the efficacy, safety, effectiveness, cost effectiveness and organizational aspects of PCV10 & PCV13 before introducing them into the National Childhood Immunization programme.

Technical Features

PCV7 is licensed in the United States as Prevnar (Wyeth Pharmaceuticals, Philadelphia, PA). The 10- and 13-valent pneumococcal conjugate vaccines (PCV-10 and PCV-13 respectively) are used to protect against invasive pneumococcal disease, such as meningitis, and acute otitis media among infants and children. Recently the indication for protecting against pneumonia among children was added for PCV 13. PCV-10 provides coverage against pneumococci and the non-typeable *H. influenzae* (NTHi) protein which may provide protection against otitis media (see table 1 below). The vaccine include serotypes contained in PCV 7 (4,6B,9V,14,18C,19F,23F) plus serotypes:(1,5,7F). PCV-13 includes the serotypes contained in PCV 10 plus serotypes: (3, 6A, 19A). As with PCV7, each of the polysaccharides is covalently conjugated to a common carrier protein, CRM197, a nontoxic variant of diphtheria toxin. PCV13 contains 2.2 µg of each saccharide, except for 4.4 µg of serotype 6B, in 5.0 mM succinate buffer with 0.125 mg of aluminum as aluminum phosphate per 0.5-mL dose.

Streptococcus pneumoniae (the pneumococcus) is one of the major bacterial causes of acute otitis

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media (AOM) in children, being responsible for between 30 and 50% of all cases. *Streptococcus pneumoniae* is an antigenically diverse species in which more than 90 serotypes have been identified. However, the prevalence with which the serotypes are recovered from patients with invasive disease varies greatly, presumably because some serotypes have a much greater propensity to cause invasive disease than others.The association of the common childhood serotypes (e.g., types 6B, 9V, 14, 19F, and 23F) with AOM is not necessarily evidence for any special propensity of these to cause AOM, as these serotypes are the ones most commonly carried in the nasopharynx of children and their association with AOM could merely reflect the fact that they are the most likely to gain access to the middle ear from the nasopharynx. Thus, even if all serotypes are equally able to cause AOM, the majority of episodes of this disease would be caused by the most frequently carried childhood serotypes.

Policy Question

Which pneumococcal conjugate vaccine should be recommended into the National Childhood Immunisation programme for children below 5 years old?

Objective

a) Is 10-valent and 13-valent pneumococcal conjugate vaccine comparable in effectiveness and in reducing the development of IPD, pneumonia and otitis media in infants and children?
b) Are the adverse events of 10-valent and 13-valent pneumococcal conjugate vaccine comparable?
c) Is 10-valent and 13-valent pneumococcal conjugate vaccine comparable in cost-effectiveness?

Methods

Major electronic databases such as Medline, Embase, Pubmed, EBM reviews, HTA databases, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Review, Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) databases were searched up to February 2014. Studies were reviewed separately according to the research questions. Retrieved records were screened for relevance. The search was limited to publication year from 2000-2014. Additional articles were identified by reviewing the bibliographies of retrieved articles and hand searching of journals. Potentially relevant papers were retrieved and independently checked against predefined criteria for inclusion by two reviewers. Included reviews and primary papers were critically appraised using the Critical Appraisal Skills Programme (CASP) and evidence was graded based on guidelines from U.S./Canadian Preventive Services Task Force and data were extracted and narratively presented.

Result and conclusion

Thirty-six studies were included in this review, where one of the studies was a systematic review; one study was a heath technology assessment, eleven RCT's, three cross sectional studies and twenty economic evaluation studies. For efficacy/effectiveness, fourteen articles were included, whereby thirteen studies involved PCV13 as the main intervention, with only one study involving PCV 10 as the main intervention and only two studies directly comparing PCV13 and PCV10. For safety, nine articles were included, out of which eight studies had PCV 13 as the main intervention, with only one study that involved PCV 10 as the main intervention and only one study directly comparing PCV13 and PCV10. For cost effectiveness, twenty articles were included with twelve studies that included PCV 13 as the main intervention, six studies that involved PCV 10 as the main intervention while six studies were directly comparing PCV13 and PCV10.

There was fair to good level of evidence to show that PCV7 is no longer cost effective because of increases in uinvasive diseases caused by nonvaccine serotypes, which reduces the overall direct effects of vaccination. The 10-valent and 13-valent pneumococcal vaccines showed better net health benefits than PCV7. Total programme costs can be lowered by reduction in vaccine prices.

A national immunization program with PCV10 or PCV13 was found to be good value for money and estimated to prevent additional cases of disease among children and save additional costs due to treatment of acute otitis media (AOM) and pneumococcal diseases. Choosing between the PCV10 and PCV13 vaccines will depend on the preference of the decision maker either to prevent the severe invasive pneumococcal diseases (IPD) cases only, or prevention of AOM. There was fair to good level of evidence to show that PCV13 was predicted to provide a higher impact on IPD and CAP, while PCV10 was expected to provide a substantially greater reduction in AOM.

Recommendations

Based on the above review, it is recommended that regular surveillance is conducted since changes in serotypes may occur naturally with time and serotypes replacement by nonvaccine serotypes in response to vaccine pressure. The surveillance data is required to determine the usefulness of available pneumococcal vaccines and the need for new vaccine. It is also recommended that local

economic evaluation and research should be conducted considering our healthcare systems as well as local costing that will further provide more evidence to support the above strategies.

Choosing between the PCV10 and PCV13 vaccines will depend on the preference of the decision maker / policy maker either to prevent the severe IPD cases only, or prevention of AOM. PCV13 was predicted to provide a higher impact on severe invasive pneumococcal diseases (IPD) and community acquired pneumonia (CAP), while PCV10 was expected to provide a substantially greater reduction in acute otitis media (AOM). PCV13 may be the choice to prevent death due to pneumococcal diseases in order to achieve Millenium Development Goal 4 (MDG4). Cost of PCV10 and PCV13 are expensive and our low less than 5 mortality need also to be considered before embarking on the national pneumococcal conjugate vaccination programme. Affordability and sustainability is also an important issue for any national programme. Hence, taking into account our current Malaysian scenario, PCV13 should be given for high risk group first before considering giving it for all children below 5 years old.