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Prevnar™: A Pneumococcal Conjugate Vaccine for Infants and Young Children

Introduction

- Streptococcus pneumoniae infections in infants and young children most commonly result in otitis media, sinusitis, pneumonia, bacteremia, and meningitis.
- Prevnar™ vaccine is an effective, but expensive, preventative measure against several forms of pneumococcal infection for infants less than two years of age.
- The projected cost effectiveness of a Prevnar™ vaccination program for healthy infants and small children is dependent upon: manufacturer's sales price; prevalence and trends of *S. pneumoniae* and its antibiotic resistant strains in Canadian infants and young children; vaccine efficacy; and the target populations selected for a pneumococcal conjugate vaccine program.

The Technology

Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM197 Protein) is the generic name for Prevnar™ (Wyeth Lederle, Philadelphia, Pennsylvania). It is the first conjugate vaccine for the *Streptococcus pneumoniae* bacteria (also known as pneumococcus) which causes a number of infections including otitis media, sinusitis, pneumococcal pneumonia, meningitis and bacteremia.¹

The polysaccharide capsule that surrounds *S. pneumoniae* protects the bacteria from destruction by white blood cells and therefore is important in its ability to produce disease.² There are about 90 serotypes of *S. pneumoniae*, classified on the basis of their antigenic differences in the capsular polysaccharide.³

The currently licensed polysaccharide vaccine contains 23 serotypes, but children under two years of age do not mount an effective immune response to it.³ Prevnar™ enhances the immune response of the standard vaccine using conjugation technology.

To make a conjugate vaccine, individual capsular saccharides are conjugated to a carrier protein. In the case of Prevnar™ the carrier protein is CRM197, a nontoxic mutant of diphtheria toxin. The saccharide conjugates are then combined to create the final preparation. The Prevnar™ formulation includes saccharides of seven common pneumococcal serotypes: 4, 6B, 9V, 14, 18C, 19F, and 23F.⁴ Approximately 80% of invasive pneumococcal disease in infants is attributable to these strains.⁵ The vaccine contains only seven serotypes because each must be individually conjugated to the carrier protein, which is an expensive and time-consuming process.

Regulatory Status

Health Canada has fast-tracked the review of Prevnar™ with high priority status, however, as of February 20, 2001 Prevnar™ had not been approved in Canada.⁶ In February 2000 the US Food and Drug Administration approved Prevnar™ for the prevention of invasive pneumococcal diseases in infants aged less than two years.¹⁵ In October 2000 the Advisory Committee on Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention added the vaccine to the Childhood Immunization Schedule.^{7,8} In November 2000 the Committee for Proprietary Medicinal Products (CPMP), a European advisory panel, recommended the use of Prevenar™ (European brand name) in infants and children up to two years old.⁹

Patient Group

The advantage of Prevnar™ over existing pneumococcal polysaccharide vaccines is primarily the enhancement of the immune response to the polysaccharide shell in children less than 24 months old. This is the age of highest susceptibility to encapsulated bacteria such as *S. pneumoniae*.⁴ The increased prevalence of bacterial strains resistant to antibiotics for children under two years is another factor that has stimulated the development of pneumococcal conjugate vaccines.¹⁰

The human nasopharynx is the primary reservoir for *S. pneumoniae* and the main source of person-to-person transmission. Pneumococcal infections are preceded by bacterial colonization of the nasopharyngeal mucosa, where the bacteria can persist without causing disease. Nasopharyngeal carriage is more common in young children than adults.³ Carriage tends to persist for weeks to months, but usually antibodies to the colonizing strain are developed and symptoms do not develop.

The most common bacterial cause of otitis media in children under six is *S. pneumoniae*.¹¹ Otitis media (OM) is a disease in which fluid is present in the middle ear, and is one of the most frequently diagnosed diseases in children, with most children experiencing at least one episode. Also, *S. pneumoniae* is the leading cause of invasive bacterial infections in children under two years of age in Canada.^{10,12} The primary goal of the vaccine is to decrease invasive disease in children under two, with a secondary goal to decrease carriage. Decreasing carriage could decrease the spread of pneumococcus to other children and adults.¹³

Canadian epidemiologic data are limited, as *S. pneumoniae* infection is not a reportable disease in Canada.¹⁴ In Vancouver over the period 1994-1998 the average annual incidence rate of invasive pneumococcal infection was 112.2 per 100,000 among children 0 to 23 months old. The 6 to 17 month age group accounted for most of the cases in the first two years (161.2 per 100,000). For the 2 to 5 year age group the average annual incidence rate was 36.1 per 100,000 and for 6 to 12 years it was 3.0 per 100,000.¹² A recent population-based survey of Vancouver, Halifax, and Quebec City indicates a cumulative risk to age five years for invasive pneumococcal infection of 1 in 300 children.¹⁵ The IMPACT group (Canadian Paediatric Society and Laboratory Centre for Disease Control Immunization

Monitoring Program, Active) conducted a study of 11 pediatric centers in Canada. It found the case fatality rate for invasive pneumococcal disease for children less than two years of age was 2%.¹⁵

In the US, the ACIP recommends all infants under the age of two be vaccinated with Prevnar™. The ACIP also recommends that all children 24 to 59 months of age be considered for vaccination. Priority is given to children at moderate risk of invasive pneumococcal disease such as children aged 24 to 35 months, children of certain minority groups, and children who attend out-of-home group childcare.⁸

The risk of invasive *S. pneumoniae* infection is greatly increased in children attending childcare centers.¹⁶ A point prevalence survey of 1322 children from 59 childcare centers in Toronto was carried out (1995-96).¹⁶ On the day of the study, 44.3% of the children had nasopharyngeal carriage of *S. pneumoniae*. This is much higher than the carriage rate in children cared for at home and increases their risk of developing invasive disease. In the carriers, 17.0% of the pneumococcal isolates they were carrying were penicillin resistant, and 13.7% were resistant to multiple antibiotics.¹⁶ Disease caused by these resistant isolates may not respond to commonly used antibiotics.

Although Prevnar™ offers protection against only seven serotypes of pneumococcus, this includes the majority of the antibiotic resistant serotypes collected from 1995 to 1998 in a large US study.¹⁷ Therefore, it is possible that Prevnar™ will decrease the proportion of pneumococcal disease which is caused by antibiotic resistant pneumococci.

Prevnar™ is not indicated for use in adults and does not provide a substitute for other pneumococcal polysaccharide vaccines that are approved for adults and for children aged over two years who are at high risk of infection.⁵ It is not yet clear if Prevnar™ has any advantages over the polysaccharide vaccine in anyone over two years of age.

Current Treatments

Current preventive measures for pneumococcal infections in Canada include understanding individual and familial risk factors, avoidance of environmental risk factors, the polysaccharide vaccine against 23 common *S. pneumoniae* serotypes, and antibiotic prophylaxis. As well, specifically for otitis media, there is myringotomy with tympanostomy tubes, and adenoidectomy.

Tympanostomy tubes are beneficial in chronic otitis media with effusion, but of less value in recurrent acute otitis media.^{12,18,19} The polysaccharide vaccine against 23 common *S. pneumoniae* serotypes does not induce an effective immune response in children less than 2 years old, an age group with a high burden of disease. Since it has no effect on pneumococcal carriage, the polysaccharide vaccine has little potential to control the spread of resistant pneumococci.^{3,12} Antibiotic prophylaxis is challenged by increased prevalence of antibiotic resistant strains of *S. pneumoniae*.¹² A US study of the epidemiologic features of invasive pneumococcal infections found that over the period 1995 to 1998 the proportion of isolates that were resistant to penicillin went from 25% to 29%, and the proportion resistant to three or more classes of drugs increased from 9% to 14%. It concluded that because a limited number of serotypes account for most infections with drug resistant strains, Prevnar™ offers protection against most drug resistant strains of *S. pneumoniae*.¹⁷

Dosage and Potential Cost

In the US, under a typical schedule, infants are given the vaccine at 2, 4, and 6 months of age followed by a fourth shot at 12 to 15 months of age. The dosing schedule will vary for those children previously unvaccinated who are beyond the age of the routine infant schedule.²⁰ Unvaccinated infants aged 7 to 11 months are given a total of three doses; unvaccinated children aged 12 to 23 months are given a total of two doses; and healthy, unvaccinated children aged 24 months or older receive one dose.⁸

The manufacturer's list price for Prevnar™ is US\$58 (C\$88) per dose.¹⁰ The normal four-dose schedule would cost US\$232 (C\$353) per patient. (Exchange rate as of Feb. 13, 2001) The injection schedule will also result in extra nursing costs. It is estimated that over the next decade over 300,000 babies will be born each year in Canada,²¹ implying a potential annual expenditure of around C\$100 million for a national Prevnar™ vaccination program.

Projected Rate of Diffusion

If the US experience is an indicator, the potential diffusion of Prevnar™ in Canada could be rapid. Since its US launch in February 2000, by the third quarter 2000 the coverage in US managed-care plans was about 90% in children under 5 years. The

manufacturer expects full penetration of the US market some time in 2001.⁷

Concurrent Developments

In addition to Prevnar™ some other formulations of pneumococcal conjugate vaccines have recently been developed and are being tested in clinical trials.³ Aventis Pasteur (Lyon France) has produced an 11-valent pneumococcal vaccine conjugated to diphtheria and tetanus toxoids (PCV-DT).²² It is a potential competitor since it covers the same serotypes as Prevnar™ plus serotypes 1, 3, 5, and 7F. Also, a 9-valent formulation is being developed by Wyeth Lederle, with serotypes primarily applicable to the developing world.²³ There is evidence that the proposed 9-valent formulation would improve coverage minimally over Prevnar™ in any age group. The 11-valent formulation would provide a modest increase in coverage of 3.7% in children aged less than six months and 6 to 16 years.²⁴

Assessing the Evidence

A randomized, double blind clinical trial involving 37,868 children under two years old was carried out at 23 medical centers within Northern California Kaiser Permanente (NCKP).²⁵ The objective was to determine the efficacy, safety and immunogenicity of Prevnar™ against invasive disease caused by the seven Prevnar™ vaccine serotypes and to determine the effectiveness against clinical episodes of otitis media. Infants in the treatment group received Prevnar™ and the control group received the meningococcus type C CRM197 conjugate vaccine. The study reported 39 cases of invasive pneumococcal disease in the control group and one case in the treatment group, for an efficacy of 97.4% (95% C. I. 82.7% to 99.9%). The efficacy of Prevnar™ with respect to physician visits for otitis media, episodes of OM, and ventilatory tube placement was 8.9%, 7.0%, and 20.1% respectively, ($P < 0.04$). The serotype-specific effectiveness was 66.7% for spontaneously draining ears. The study concluded that Prevnar™ appeared to be highly effective in preventing invasive pneumococcal disease in young children and has a significant impact on otitis media.

Normally, studies using primary health outcomes are preferred for assessments. In the case of vaccines, however, immunogenicity is often used as

an intermediate outcome since the sample size needed for primary outcomes is very large. For example, a study to determine the safety and immunogenicity of Prevnar™ was carried out in four US cities.²⁶ Two hundred and twelve healthy 2-month-old infants were randomized to receive either four consecutive doses of Prevnar™ or the control meningococcus type C CRM197 conjugate vaccine. The study concluded that Prevnar™ seemed to be acceptably safe and resulted in significant rises in antibody to all seven serotypes in the Prevnar vaccine.

A cost effectiveness analysis on Prevnar™ has been done using the Northern California Kaiser Permanente randomized trial and published sources of disease epidemiology.¹⁰ The study considered routine vaccination with four doses at 2, 4, 6 and 12-15 months, and a single dose catch-up vaccination for children aged 2 to 4.9 years. The authors concluded that pneumococcal conjugate vaccination of all healthy US infants has the potential to be cost effective. They found that the US\$58 price per dose would have to be dropped to US\$18 before the vaccine would result in cost savings to governments, and to US\$46 to result in net savings for society.¹⁰ The reported incremental cost per life-year saved from a health system perspective of \$176,000 exceeds conventionally accepted benchmarks for cost effectiveness.²⁷ Other researchers have argued that in an era of competing health care priorities, promotion of the use of this expensive vaccine without solid data on the use of Prevnar™ as a "catch-up" vaccine for children over two years of age may not be cost effective.²⁸ A simulation study on the cost effectiveness of Prevnar™ in Canada concluded that at the estimated purchase price the program will probably not save money for society, but it would avoid significant morbidity.²⁹

Adverse Effects

Evidence suggests adverse effects from Prevnar™ are minor and should not affect diffusion. The most frequently reported adverse effects include injection site reactions, fever, irritability, drowsiness, restless sleep, and decreased appetite. Prevnar™ appears to be well tolerated with a safety profile similar to the routine pediatric vaccines.^{1,4,25,26,30}

Implementation Issues

The first use of conjugate vaccine technology was the Hib vaccine. Its introduction in the early 1990s virtually eliminated Haemophilus influenzae type b infections among immunized populations of children.²⁶ However, because there are about 90 serotypes of *S. pneumoniae*, development of the pneumococcal conjugate vaccines is considerably more difficult and expensive than the conjugate Hib vaccines, making its implementation a more complicated policy issue.²⁶ Also, there are several potential benefits to Prevnar™ that analysts will have trouble valuing until there have been some years of experience with the vaccine.³¹ These include: reduced spread of resistant organisms, reduced transmission of pneumococci to unvaccinated persons, and simplified management of febrile infants.^{24,31}

An observational study conducted by the Canadian Paediatric Society and the Laboratory Centre for Disease Control Immunization Monitoring Program, Active (IMPACT) stated that Prevnar™ has considerable potential to reduce invasive pneumococcal infections in children, but important information gaps remain.²⁴ For example, it is unknown whether widespread use of the vaccine would result in increasing the prevalence of carriage of the invasive serotypes that are not contained in the vaccine.

Knowledge of the epidemiology of pneumococcal disease will aid in planning the use of pneumococcal vaccines. Evidence indicates that invasive pneumococcal disease varies by serotype, age, and country, emphasizing that its epidemiology is heterogeneous and requires continued surveillance.³² Since pneumococcal infection is not a reportable condition in Canada,¹⁴ Canadian epidemiologic data in this area is limited.

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