Assessment of the pertinence of a new pneumococcal conjugate vaccine in Québec

INSTITUT NATIONAL
DE SANTÉ PUBLIQUE
DU QUÉBEC

Québec

Assessment of the pertinence of a new pneumococcal conjugate vaccine in Québec

Direction des risques biologiques,
environnementaux et occupationnels

March 2009

Institut national de santé publique Québec

UNDER THE COORDINATION OF

Philippe De Wals, Département de médecine sociale et préventive, Université Laval et Institut national de santé publique du Québec

EDITORS

Nicole Boulianne, Institut national de santé publique du Québec

Geneviève Deceuninck, Centre de recherche, Centre hospitalier universitaire de Québec

Pierre Déry, Département de pédiatrie, Université Laval, Centre hospitalier universitaire de Québec

Maryse Guay, Département des sciences de la santé communautaire, Université de Sherbrooke (chair of the work group) et Institut national de santé publique du Québec

Geneviève Petit, Département des sciences de la santé communautaire, Université de Sherbrooke et Agence de la santé et des services sociaux de l'Estrie/Direction de santé publique

Béatrice Poirier (student), Département des sciences de la santé communautaire, Université de Sherbrooke

Bruce Tapiero, Département de pédiatrie, Université de Montréal, Centre hospitalier universitaire Sainte-Justine

AUTHORS

MEMBERS OF THE COMITÉ D'IMMUNISATION DU QUÉBEC (QUÉBEC IMMUNIZATION COMMITTEE)

Lucie Bédard, Ordre des infirmières et infirmiers du Québec

François Boucher, Département de pédiatrie-infectiologie, Centre de recherche du Centre hospitalier universitaire de Québec - Centre hospitalier de l'Université Laval

Nicole Boulianne, Institut national de santé publique du Québec

Carl Cummings, Association des pédiatres du Québec

Gaston De Serres, Département de médecine sociale et préventive, Université Laval et Institut national de santé publique du Québec

Philippe De Wals, Département de médecine sociale et préventive, Université Laval et Institut national de santé publique du Québec

Réjean Dion, Laboratoire de santé publique du Québec, Institut national de santé publique du Québec

Liette Duval, Centre de santé et de services sociaux de Thérèse-de-Blainville

Charles Frenette, McGill University Health Centre, Montreal General Hospital

Vladimir Gilca, Institut national de santé publique du Québec

Maryse Guay, Département des sciences de la santé communautaire, Université de Sherbrooke (chair of the work group) et Institut national de santé publique du Québec

Fernand Guillemette, Agence de la santé et des services sociaux de la Mauricie et du Centre-du-Québec/Direction de la santé publique

Monique Landry, Direction de la protection de la santé publique, ministère de la Santé et des Services sociaux du Québec

Philippe Ovetchkine, Service des maladies infectieuses, Centre hospitalier universitaire Sainte-Justine

Chantal Sauvageau, Institut national de santé publique du Québec

Bruno Turmel, Direction de la protection de la santé publique, ministère de la Santé et des Services sociaux du Québec

Caroline Quach, Montreal Children's Hospital, Pediatrics Department, McGill University

Louis Valiquette, Département de microbiologie et infectiologie, Faculté de médecine, Université de Sherbrooke

LAYOUT

Marie-France Richard, Institut national de santé publique du Québec

LEGAL DEPOSIT – 2ND TRIMESTER 2009
BIBLIOTHÈQUE ET ARCHIVES NATIONALES DU QUÉBEC
LIBRARY AND ARCHIVES CANADA
ISBN : 978-2-550-55938-2 (FRENCH PRINTED VERSION)
ISBN : 978-2-550-55939-9 (FRENCH PDF)
ISBN : 978-2-550-56226-9 (PRINTED VERSION)
ISBN : 978-2-550-56227-6 (PDF)

SUMMARY

In December 2008, a new pneumococcal vaccine (PCV-10) was licensed in Canada. An older vaccine (PCV-7) is used in Québec for the routine vaccination of children. The ministère de la Santé et des Services sociaux du Québec (Ministry of Health and Social Services (MSSS)) asked the Comité d'immunisation du Québec (Québec Immunization Committee (CIQ)) to rapidly give an opinion on the pertinence of this vaccine and answer the three following questions: (i) Can the old and the new vaccines be considered of equivalent value in preventing invasive infections caused by the seven *streptococcus pneumoniae* serotypes? (ii) Can they be considered interchangeable in terms of primary vaccination? (iii) Is one or the other of the vaccines deemed to have enough benefit to justify considering only this vaccine for the next supply contract?

PCV-7 was licensed on the basis of randomized clinical trials, and a good deal of information is available on the direct and indirect effects associated with its introduction through immunization programs for North American children. PCV-10 is a new vaccine with two attractive characteristics: the presence of three additional pneumococcal polysaccharides (1, 5 and 7F) and the use of the protein D from Hi for the conjugation. PCV-10 was licensed in Canada on the basis of immunogenic data; there is currently no information on the clinical efficacy of the vaccine other than a randomized study on a precursor with a slightly different composition. The principal uncertainties surrounding PCV-10 are related to its effectiveness in practice in a schedule of three doses, and its safety in terms of rare reactions.

In the case of invasive pneumococcal infections caused by the seven serotypes that are in PCV-7-CRM_{197}, the direct protection provided by PCV-10 should be of the same degree. The presence of three additional serotypes in PCV-10 would provide relatively modest added protection in the current Québec context: in the order of six cases of invasive infections prevented per year among children under five years of age, equivalent to about 10% of the total number of residual cases. The indirect protection that could be provided by PCV-10 needs to be assessed, because the antibody levels induced by the new product are usually lower than with the older one. The protection provided by PCV-10 against invasive infections caused by serotype 19A pneumococcus has not been determined and the same is true for rare invasive infections caused by non-encapsulated strains of Hi.

The role played by PCV-10 in preventing community-acquired pneumonia among children should be at least the same as that observed with PCV-7, and the existence of additional protection (extending eventually to empyema and infections occurring in patients suffering from chronic pulmonary disease) related to the presence of type 1 pneumococcal polysaccharide and protein D from Hi may be cited.

Non-encapsulated strains of Hi very likely play an important role in the etiology of acute bacterial otitis in Québec as everywhere else. The fact that PCV-10 induces Hi antibodies represents a definite advantage in terms of the prevention of otitis, but it is difficult to quantify the extent of this advantage with any precision given the many uncertainties related to: the distribution of otopathogenic bacteria in Canada, the protection provided by three versus four doses of PCV-10, and the replacement phenomenon that may arise with any vaccine.

The data at our disposal allow us to predict a very high safety level for PCV-10. This vaccine could be administered simultaneously with other vaccines offered in Québec during two-, four- and 12-month appointments and could also be offered to children who have already been given one or several doses of PCV-7. However, more studies are required to confirm the safety of PCV-10 and the absence of significant interference when it is administered at the same time as Pentacel.

At the same price, PCV-10 appears to be preferable to PCV-7 for the regular child immunization program in Québec. We have tried to put a figure on the price difference between the two vaccines that would tip the balance in favour of one or the other from the perspective of savings for the health system, but the estimates must be taken with much caution, given the many uncertainties existing in the parameters of the model.

The advantage of PCV-10 is especially evident for populations living in the two northern most regions of Québec and who are given four doses of pneumococcal conjugate vaccine. Otitis is very common in these populations and pneumococcus serotypes 1 and 5 are likely to cause outbreaks. PCV-10 should be offered to these populations as soon as possible.

A new 13-valent vaccine is being developed containing serotypes 19A and 7F, which are becoming more prevalent in Québec. Should this vaccine be licensed, it will be critical that a study be conducted immediately, comparing the usefulness of this new vaccine with that of PCV-7 and PCV-10 and to provide maximum flexibility in the choice of product used in Québec.

TABLE OF CONTENTS

LIST OF TABLES ..... **V**

LIST OF FIGURES ..... **V**

1. INTRODUCTION **1**

2. BURDEN OF ILLNESS **3**

3. CHARACTERISTICS OF THE VACCINE **5**

3.1. Composition 5

3.2. Immunogenicity 5

3.3. Clinical efficacy 8

3.4. Safety 9

4. IMMUNIZATION STRATEGIES **11**

5. COST-EFFECTIVENESS OF THE PROGRAM **13**

5.1. Program feasibility 17

5.2. Program evaluation 17

5.3. Research questions 18

5.4. Other considerations 18

6. CONCLUSIONS AND RECOMMENDATIONS **19**

7. REFERENCES **21**

APPENDIX 1: METHODOLOGY OF THE COST-EFFECTIVENESS ANALYSIS **25**

LIST OF TABLES

Table 1: Burden of pneumococcal infections among children under five years of age in Québec, in 2001, prior to the introduction of a pneumococcal conjugate vaccine (Boulianne et al., 2007) 3

Table 2: Composition of pneumococcal conjugate vaccines (PCV-7 and PCV-10 are licensed in Canada) 5

Table 3: Residual burden of the disease in the Québec population and the costs associated with different three-dose vaccination scenarios 13

Table 4: Marginal cost-effectiveness indices for various scenarios 15

Table A1: Distribution (%) of pathogen agents covered by the two vaccines in the basic model 28

Table A2: Maximum efficacy (%) of the two vaccines in the basic model 29

LIST OF FIGURES

Figure 1: Incidence of invasive pneumococcal infections according to serotype in the population under five years of age in Québec, before and after the implementation of the PCV-7 vaccination program (De Wals et al., 2008a) 4

1. INTRODUCTION

The first pneumococcal conjugate vaccine containing seven pneumococcal polysaccharides (PCV-7) was licensed in Canada in June 2001, and recommendations regarding its use were issued by the National Advisory Committee on Immunization early the following year (NACI, 2002). The vaccine was quickly made available in pharmacies and certain medical offices and could be administered by prescription. The first opinion on the establishment of a vaccination program was issued by the Comité d'immunisation du Québec (Québec Immunization Committee (CIQ)) in 2003 (Guay et al., 2003). In October 2002, the ministère de la Santé et des Services sociaux du Québec (MSSS) decided to provide PCV-7 free to children under five years of age with increased risk of invasive infection according to a four-dose schedule (two, four, six and 12 months) as basic immunization. The vaccine was also offered to children living in Québec's two northernmost regions where Cree and Inuit communities are concentrated. In 2004, a second opinion was given by the Comité d'immunisation du Québec (Québec Immunization Committee (CIQ)), taking into account the data available on immunogenicity and the effectiveness of schedules with a reduced number of doses, as well as a financial analysis estimating the marginal cost of invasive infections prevented by adding more doses (CIQ, 2005). In December 2004, the MSSS decided to offer PCV-7 free to all newborns while recommending a schedule of three doses administered at two, four and 12 months respectively. A passive catch-up approach was planned for children between four and 59 months of age. The recommendation of four doses was maintained for high-risk children and those living in northern regions.

In December 2008, a second product (PCV-10) was licensed in Canada. This new vaccine has different characteristics in terms of composition and coverage of pathogens that cause invasive infections, pneumonia and acute otitis media. It in fact contains three *streptococcus pneumoniae* serotypes more than PCV-7, and the conjugating protein induces the appearance of *haemophilus influenzae* (Hi) antibodies. The MSSS asked the CIQ to immediately provide an opinion on the pertinence of this vaccine and answer the following three questions: (i) Can the two vaccines be considered of equivalent value in preventing invasive infections caused by the seven *streptococcus pneumoniae* serotypes that the two vaccines have in common? (ii) Can they be considered interchangeable in terms of primary vaccination? (iii) Is one or the other of the vaccines deemed to have enough benefit to justify considering only this vaccine for the next supply contract? To provide a second opinion and answer these questions, a working group was formed and an assessment conducted, taking into account published and unpublished data from the producer of the new vaccine, the GlaxoSmithKline (GSK) company, following the analysis framework proposed by Erickson et al. (2005). The report has been discussed, modified and approved by the CIQ.

2. BURDEN OF ILLNESS

An estimate of the burden of pneumococcal infections among children under five years of age in Québec was carried out before the introduction of PCV-7 (Boulianne et al., 2007). The key results are presented in Table 1. Invasive infections present the heaviest burden, but they are few in number compared to community-acquired pneumonia and acute otitis media, this latter category representing nearly 80% of total costs. To this, sinusitis, pharyngitis, bronchitis, empyema and other more rare clinical diseases for which there are no accurate statistics must be added. The estimated number of deaths is low thanks to the effectiveness of antibiotic treatment.

Table 1: Burden of pneumococcal infections among children under five years of age in Québec, in 2001, prior to the introduction of a pneumococcal conjugate vaccine (Boulianne et al., 2007)

Clinical disease	Number of cases	Number of deaths	Societal cost*
Meningitis	19	1	$594 000
Bacteremia	284	2	$627 000
Pneumonia	2 800	-	$1 896 000
Acute otitis media	80 791	-	$10 851 000
Total	83 894	3	$13 968 000

* Including the direct costs of the disease and sequelae (neurological sequelae and serous otitis media) to the health system and families, but excluding indirect costs.

The coverage rates reached with PCV-7 following the universal program's implementation are high. A survey among a representative sample of children born in 2005 after the program was announced shows that close to 90% of the subjects had been given at least three doses of PCV-7 before the age of two years (Boulianne et al., 2007). A more recent survey conducted in 2008 indicates vaccination coverage of 91% with three doses or more by the age of two years (Boulianne, written communication).

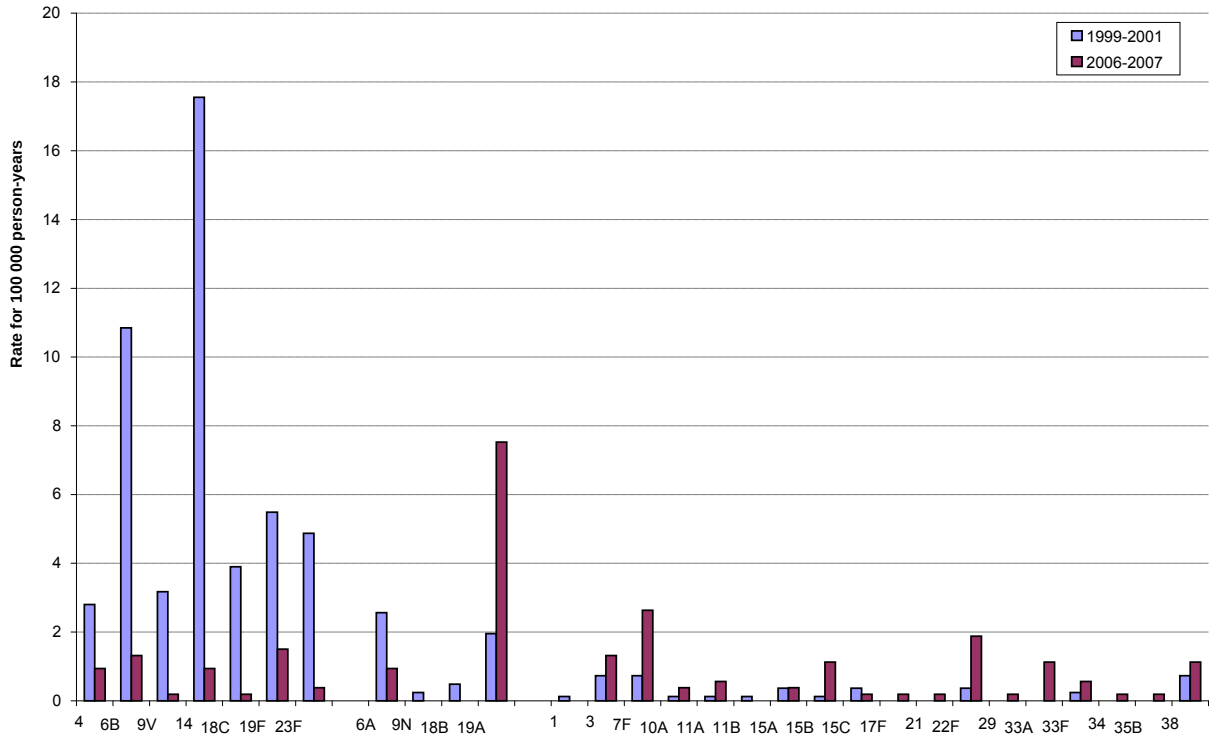
The implementation of this routine vaccination program and the catch-up associated with it had an important epidemiological impact. Among children under five years of age, the incidence rate of invasive infections caused by the seven serotypes contained in PCV-7 went from 54.9 per 100 000 per year in 2001-2004 to 4.6 per 100 000 in 2006-2007, a 90% reduction (De Wals et al., 2008a). This decline has been counterbalanced, in part, by an increase in the incidence of invasive infections caused by serotypes not covered or incompletely covered by PCV-7 (serotypes of the same serogroups as those included in the vaccine). Thus, among children under five years of age, the decline in the incidence rate of all invasive infections was only 61% (67.3/100 000 vs. 26.1/100 000). This paradox, which is largely attributable to replacement of an ecological nature, was mainly caused by strains belonging to serotype 19A and, to a lesser extent, by other serotypes including 7F (Figure 1). An indirect effect of the program in the older, non-vaccinated portion of the population was also observed with a 47% decline in the incidence of infections caused by vaccine serotypes (5.4/100 000 vs. 2.9/100 000) and a 10% reduction in infections of all serotypes (9.0/100 000 vs. 8.3/100 000). Other analyses have also shown a 72% reduction in the frequency of hospitalized lobar pneumonias and a 13% reduction in the frequency of all

pneumonias (De Wals et al., 2008c). In the case of otitis media, the introduction of PCV-7 led to a 13% decline in the frequency of medical consultations in this same age category (De Wals et al., unpublished manuscript).

In Canada, an increase in the frequency of hospitalizations with a diagnosis of empyema has been observed since 1995 among children between the ages of one and 14 years (Finley et al., 2008). Serotype 1 pneumococcus is a pathogen that is frequently found in community-acquired empyemas (Hausdorff et al., 2005). However, we have no precise data on the etiology of empyema in Canada.

There are no recent Canadian statistics on the role of non-encapsulated strains of Hi in the etiology of respiratory infections and acute otitis media. Non-encapsulated and non-typeable strains of Hi rarely cause invasive infections. In a series of cases diagnosed in Manitoba in 2002-2004, invasive infections caused by non-typeable strains were observed mainly in adults and less among infants (Tsang et al., 2006). Non-encapsulated strains are known to cause non-bacteremic pulmonary infections among adults and a significant proportion of acute otitis media among children, with the proportions varying between 16% and 61% according to the study (Murphy, 2003; Liebovitz et al., 2004; Murphy et al., 2009).

Figure 1: Incidence of invasive pneumococcal infections according to serotype in the population under five years of age in Québec, before and after the implementation of the PCV-7 vaccination program (De Wals et al., 2008a)



3. CHARACTERISTICS OF THE VACCINE

3.1. COMPOSITION

PCV-10 contains 10 pneumococcal polysaccharides that are conjugated with three different protein carriers, the most important being protein D (Table 2). This vaccine is derived from another 11-valent vaccine whose development was interrupted, which included serotype 3 and used protein D for the conjugation only (PCV-11). Protein D is a surface lipoprotein that is antigenically stable and produced by practically all strains of *haemophilus influenzae* (Forsgren et al., 2008). In humans, this protein induces the development of specific serum antibodies that are active against non-encapsulated strains of Hi and that, in a clinical trial, demonstrated its ability to prevent otitis caused by non-typeable strains of Hi and to reduce the prevalence of nasopharyngeal carriage of this bacterium (Prymula et al., 2006). Tetanus toxoid for the conjugation of serotype 18C and diphtheria anatoxin for serotype 19F are used to enhance the range and quality of the immune response. In comparison to PCV-7, PCV-10 contains three additional pneumococcal polysaccharides (1, 5 and 7F). Serotypes 1 and 5 have been linked to outbreaks of severe respiratory infections in Aboriginal and underprivileged populations, in Canada especially (Hausdorff et al., 2005; Proulx et al., 2002; Romney et al., 2008). Serotype 7F is part of those for which an increase in incidence has been observed since the introduction of PCV-7 among children in Québec (De Wals et al., 2008a).

Table 2: Composition of pneumococcal conjugate vaccines (PCV-7 and PCV-10 are licensed in Canada)

Vaccine	Pneumococcal polysaccharide serotype	Conjugation proteins
PCV-7	4, 6B, 9V, 14, 18C, 19F, 23F	CRM_{197}
PCV-11	1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F	Protein D
PCV-10	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F	Protein D Tetanus toxoid Diphtheria anatoxin

3.2. IMMUNOGENICITY

PCV-7 was licensed on the basis of two randomized trials that demonstrated its efficacy in preventing invasive pneumococcal infections among children, as well as pneumonia and otitis (Black et al., 2000; Black et al., 2002; Eskola et al., 2001). Henceforth, all new pneumococcal conjugate vaccines for children will be licensed according to immunogenicity criteria. In the case of PCV-10, the following arguments were made to Health Canada in favour of licensing: (i) achievement of a specific IgG antibody threshold (measured by ELISA) in a large proportion of those receiving the vaccine and for all serotypes included in the vaccine following administration of a primary series of three doses; (ii) the non-inferiority of PCV-10 compared to PCV-7 in immune response for serotypes shared by the two vaccines; (iii) the existence of functional antibodies measured by *in vitro* opsonophagocytic activity (OPA); (iv) demonstration of an immune memory following administration of a booster dose.

It should be noted that the method used for measuring the doses of antibodies is not the same in the two companies that produce PCV-7 and PCV-10. GSK presented data that support the hypothesis according to which a 0.20 µg/mL titre of IgG is equivalent to a 0.35 µg/mL titre measured by the company that produces PCV-7 and which is proposed by the World Health Organization as a standard for licensing pneumococcal conjugate vaccines (WHO, 2005). However, there is no consensus as to the validity of these titres for predicting the level of protection against invasive infections in people who have received a vaccine (Lee et al., 2003; Jódar et al., 2003). In the absence of clinical trial results on the protection offered by PCV-10, we have data from an *in vitro* dose of serum antibody OPA. The OPA titre appears to be a better marker for protection than the IgG measurement by the ELISA method (Schuerman et al., 2007).

PCV-10 was tested in more than 10 phase-III immunogenicity trials, and the schedule used for infants generally consisted of three doses of primary vaccination with, in some studies, a booster shot around the first birthday. This type of schedule was used to make comparisons between PCV-7 and PCV-10 (007 and 010 trials). A schedule of three doses of PCV-10 (two, four and 11 months) and close to that recommended in Québec was tested in a study that included a four-dose schedule for the same vaccine (trial 002). Unfortunately, we do not have a study comparing the immune responses of PCV-7 and PCV-10 in a two-dose schedule at a young age for the primary vaccination and a booster shot at the first birthday, as recommended in Québec, and including repeated measurements of opsonophagocytic activity after the two first doses and after the booster shot.

In randomized and non-randomized phase-III trials, PCV-10 demonstrated its non-inferiority to PCV-7 in terms of common antigens, reaching the reference threshold (0.20 µg/mL) in more than 90% of vaccinated subjects for the three additional serotypes (measured after three primary doses), the induction of functional antibodies, and immune memory. It should be noted that the maximum concentrations of antibodies obtained after three primary doses were generally less with PCV-10 than PCV-7 (trials 001, 003 and 011). In terms of average OPA titres (GMT) after three doses of the primary vaccination, the advantage of PCV-7 over PCV-10 shows in terms of serotypes 6B and 14 in particular.

Antibodies directed against relative serotypes 6A and 19A were detected after administering PCV-10, with a comparable functional activity to that observed with PCV-7 for 6A and a higher functional activity for 19A (trials 001, 003 and 011). Immune response was also detected for protein D with PCV-10, but to date no reference threshold has been proposed for this parameter.

In one trial (002), a schedule of three doses of PCV-10 (two, four, 11 months) was compared to a schedule of four doses (two, three, four, 11 months). Generally, the titres measured after the primary series were weaker with two doses than three. The proportion of subjects that reached the reference threshold (0.20 µg/mL) was at least 93% with two doses compared to 96% with three doses for nine of the 10 serotypes. A more significant difference was observed for serotype 6B (56% with two doses compared to 63% with three doses). In terms of opsonophagocytic activity, titres of OPA $\geq$8 were obtained in at least 83% of vaccinated subjects with two doses and at least 91% with three doses for eight of the 10 serotypes

included in the vaccine. Lesser responses were observed for serotype 1 (61% with two doses compared to 63% with three doses) and 6B (75% with two doses compared to 89% with three doses). The persistence of antibodies was measured at the age of 11 months, prior to the booster shot. Generally, a decrease in antibody titre was observed in the two groups, and the proportion of subjects who maintained titres above the reference value was lower in those receiving two doses than those receiving three for the primary vaccination. After the booster shot, a strong response was observed for all antigens, and the differences between the groups tend to diminish in terms of reaching thresholds, although differences persist in the average concentrations of antibodies (GMC-ELISA) and average titres in the functional test (GMT-OPA). Schedule 3+1 proves more effective than schedule 2+1 for cross-reactive antibodies against serotypes 6A and 19A, as well as for antibodies directed against protein D. For immune memory, weaker immune responses after two doses than after three for the primary vaccination and less difference after the booster shot were observed with PCV-7 (Lockhart et al., 2006).

In another trial (011), the antibody titres were measured two months (age of six months) after the administration of two doses (at age two and four months) of PCV-7 and PCV-10. Generally, responses were similar with the two vaccines for common antigens, with slightly more significant responses in favour of PCV-10 for OPA (serotypes 6B, 19F 23F), while fewer subjects had a weak response against serotype 18C with PCV-7 than with PCV-10. The OPA response to serotype 1 was weak with two doses of PCV-10 in contrast to the response measured by ELISA. For serotypes 5 and 7F, the responses to two doses of PCV-10 were excellent for the two markers. The cross-reactive OPA response was better with PCV-10 than with PCV-7, against serotypes 6A and 19A, and for the latter practically no activity was measured with PCV-7, while only 5% of subjects responded to two doses of PCV-10 (considerably better cross-reactions against 19A were, however, observed with PCV-10 in trial 002).

An open trial measured immune response after a booster shot of PCV-10 administered at age 12-18 months in children who received three doses of PCV-7 for their primary vaccination (trial 007). For the seven serotypes included in PCV-7, the PCV-10 booster shot induced antibodies of ELISA $\geq$0.2 ug/mL in at least 97% of subjects, and titres of OPA $\geq$8 in 95% of subjects. In terms of additional serotypes, responses that surpassed the threshold were observed in at least 85% of subjects for the ELISA measurement and 31% to 99% for the additional serotypes.

There are no immunogenicity studies of a simultaneous vaccination with PCV-10 and Pentacel® from Sanofi-Pasteur. However, the results presented for a simultaneous vaccination with Infanrix-hexa and Infanrix-penta from GSK were reassuring. This was also the case for the simultaneous administration of PCV-10 and an anti-meningococcal conjugate vaccine C-CRM_{197} and with Priorix-Tetra (RROV).

3.3. CLINICAL EFFICACY

To date, we have no information on the clinical protection provided by PCV-10. Trials are underway but the results will not be available for some time. We do have the results of a four-dose otitis trial with an 11-valent vaccine using protein D (serotype 3 was included in this vaccine, but the immune response was weak and clinical efficacy nil for this serotype in particular) (Prymula et al., 2006). In this trial, protection was 34% (IC95%: 21% to 44%) against episodes of otitis media, 53% (IC95%: 35% to 66%) against otitis caused by strains of pneumococcus included in the vaccine, 35% (IC95%: 2% to 57%) against otitis caused by non-encapsulated strains of Hi, and 60% (IC95%: -27% to 88%) for preventing the placement of a ventilation tube. Cross-protection was observed against strains related to those in the vaccine (66% on average; IC95%: 22% to 85%). At the age of 15-18 months, after the booster shot, a reduction of the prevalence of nasopharyngeal carriage of streptococcal strains in the vaccine and of *Haemophilus* was observed. These results were better than those observed with PCV-7, in another trial with a relatively similar methodology: protection of 6% (IC95%: -4% to 16%) against episodes of otitis media, 57% (IC95%: 45% to 67%) against otitis caused by pneumococcal serotype strains in the vaccine, and 39% (IC95%: 4% to 61%) for preventing the placement of a ventilation tube during the follow-up until four to five years (Eskola et al., 2001; Fletcher et al., 2007). A detailed analysis of the differences between the FinOM and POET studies showed that the main reason explaining the advantage of the 11-valent vaccine in preventing episodes of all types of otitis was the absence of any replacement by otopathogens not covered by the vaccine in subjects, while a replacement was observed with PCV-7 (De Wals et al., 2009). We do not know why a bacterial replacement was observed with PCV-7 and not PCV-11. Several hypotheses may be offered: a different environmental context that affected the transmission, different prevalence of otopathogens that may cause the replacement, or chance. The second reason explaining the advantage of PCV-10 over PCV-7 was the additional efficacy associated with protein D to prevent otitis caused by non-typeable strains of Hi. Extrapolation of these results must be done with caution, but it may be considered that the new vaccine modified to improve immune response to certain serotypes is not inferior to its precursor. Since it is accepted that a lower level of antibodies is sufficient to prevent invasive infections than for mucous and respiratory tract infections (Jokinen et al., 2004), it can reasonably be assumed that the 11-valent vaccine and its successor PCV-10 will be effective against invasive infections, given the performance of PCV-11 in preventing otitis and diminishing carriage.

The question that remains very difficult to answer is regarding the clinical protection provided by a three-dose schedule of PCV-10 compared to four doses of the same vaccine, knowing that the antibody titres measured after the second dose and booster shot are weaker than in a four-dose configuration. For the seven serotypes common to PCV-10 and PCV-7, it may be assumed that direct and indirect protection is similar for the two vaccines, and that there is additional protection with PCV-10 against serotypes 1, 5 and 7F to the same extent as that observed for the seven other serotypes with PCV-7. Cross-protection against serotype 6A should exist with PCV-10, but greater uncertainty surrounds serotype 19A and for all types of infection caused by non-typeable strains of Hi (especially with a three-dose schedule). The existence of protection against community-acquired pneumonia among children may be

assumed, but with much uncertainty regarding the level of protection, both for three and four doses, given the lack of precise information on the distribution of pathogens causing non-bacteremic pneumonia in children and the lack of data on protection thresholds for this pathology.

3.4. SAFETY

To date, all conjugate vaccines against capsulated bacteria have demonstrated excellent safety profiles after the administration of millions of doses. Data regarding PCV-10 are more limited and involve several thousand individuals who participated in immunogenicity trials. The product monograph reports that 12 879 doses of the vaccine were administered as a primary vaccination to 4 595 healthy children, and 3 870 children received a booster shot during the second year of their live (GSK, 2008). No serious side effect was observed. The data indicate that mild general and local side effects were not much more frequent with PCV-10 than with PCV-7.

PCV-10 contains 2.26 mg of aluminum phosphate per dose, or 0.500 mg of Al (GSK, 2008), which is slightly more than in PCV-7, which contains 0.50 mg of aluminum phosphate per dose, or 0.125 mg of Al (Wyeth, 2009). This pharmaceutical adjuvant, which increases immune response, is used in many vaccines, and to date has never been causally associated with serious side effects (Jefferson et al., 2004).

4. IMMUNIZATION STRATEGIES

The goal of Québec's national public health program is a 60% reduction by 2012 in the incidence of invasive pneumococcal infections among children aged six months to two years (MSSS, 2003). This goal was accomplished following implementation of a free routine vaccination program for young children, involving three doses of PCV-7 in 2004, and the catch-up that accompanied this measure (Boulianne et al., 2007; De Wals et al., 2008a). To improve the performance of this program, three strategies are possible: improve the rate of coverage of the current program; change from a three-dose to four-dose program of PCV-7, or use a more effective vaccine in a three-dose program. The first strategy is difficult to achieve because the current rate of coverage is already very high (Boulianne et al., 2007), and increasing it would not be simple since the reasons for resistance to the program are diverse. Avoiding delays in the administration of the recommended doses is another strategy, but would prevent only a small number of cases given the rarity of vaccine failure after two doses of PCV-7 or more (Boulianne et al., 2007). A United States case-control study found that a three-dose vaccination program with PCV-7 according to the schedule adopted in Québec (two, four and 12 months) was only marginally less effective than a four-dose program following the traditional schedule of two, four, six and 12-18 months (Whitney et al., 2006). Observations in Québec of a three-dose vaccination program (Boulianne et al., 2007; De Wals et al., 2008a) are not that different from those observed in the United States for four doses of the vaccine, and the vaccine coverage was fairly comparable for three doses and more (Black et al., 2005; Hicks et al., 2007). In Québec, vaccine failure is rare and exists mainly in children who received less than the recommended number of doses, who received them late, or who received only one dose and were waiting for a second dose at four months (Boulianne et al., 2007). Adopting a more effective vaccine based on current recommendations regarding the number of doses and schedule therefore seems the most relevant strategy in an epidemiological context of an increasing incidence of invasive infections caused by *streptococcus pneumoniae* serotypes not covered by PCV-7. We do not currently recommend the strategy that would consist of adopting a more effective vaccine and changing to a four-dose schedule, since the cost-effectiveness ratio would clearly not be worthwhile. This option should be considered only if it can be demonstrated that four doses of a new vaccine provides much greater efficacy than three doses for a majority of the pathogens covered, which does not appear to be the case with PCV-10 (subject to complementary data on cross-protection against serotype 19A). In the case of a price war between two very similar or only slightly dissimilar products, the best strategy would therefore be to choose the product that offers the best cost-effectiveness ratio.

5. COST-EFFECTIVENESS OF THE PROGRAM

Very thorough data on the epidemiology and cost of pneumococcal infections in Québec prior to the introduction of PCV-7 are available and were used in previous economic analyses (Jetté et al., 2001; De Wals et al., 2003; Petit et al., 2003; Morrow et al., 2007). Information has currently been collated on the epidemiological change associated with the introduction of the universal vaccination program for children in 2004 (Boulianne et al., 2007; De Wals et al., 2008a; Jetté et al., 2008 a and b). However, it is uncertain that equilibrium has been attained, particularly in terms of the replacement of strains included in the vaccine by other pathogens, and there is a lack of epidemiological data on pneumonia among adults and the placement of ventilation tubes by tympanocentesis among children following the introduction of PCV-7. It is therefore difficult today to do a valid simulation comparing the post-PCV-7 situation with what preceded in the case that a new vaccine is introduced to replace the former. To overcome this problem, we carried out a simulation study comparing the potential economic and epidemiological impact of PCV-7 and PCV-10 in terms of the situation that prevailed prior to the introduction of PCV-7 in Québec. Results of this analysis give an idea of the relative benefits of the two vaccines. The methodology is presented in appendix.

The residual epidemiological and economic burden of the pathologies associated with pneumococcal infections is presented in Table 3, according to different scenarios. In the vaccine-free scenario, invasive pneumococcal infections are 50 times less frequent than pneumonia and otitis, which are particularly numerous at nearly 360 000 cases per year. Deaths are mostly caused by non-bacteremic pneumonia in adults. In the vaccine-free scenario, there are 30 deaths per invasive pneumococcal infection or per community-acquired pneumonia of all causes among children under five years of age. The number of survivors with sequela is low, due to the low incidence of pneumococcal meningitis in the population.

Table 3: Residual burden of the disease in the Québec population and the costs associated with different three-dose vaccination scenarios

Residual burden of the disease	No vaccine	PCV-7	PCV-10
Number of cases			
All outcomes	412 328	377 336	351 508
Invasive infections	1 021	612	612
Pneumonia (hospitalized or not)	52 168	51 274	51 081
Otitis media (episodes)	359 138	325 450	299 815
Placement of ventilation tubes	14 410	10 834	8 113
Deaths (invasive infections and pneumonia)	4 138	4 088	4 086

Table 3: Residual burden of the disease in the Québec population and the costs associated with different three-dose vaccination scenarios (cont'd)

Residual burden of the disease	No vaccine	PCV-7	PCV-10
Number of cases			
Survivors with after-effects (meningitis)	13	8	8
Lost life-years (discounted by 3%)	40 719	39 861	39 800
QALYs lost (discounted by 3%)	41 094	37 989	37 788
Associated costs			
Direct program costs for the health system	$0	$18 960 173	$18 960 173
Direct program costs for families	$0	$453 322	$453 322
Direct program costs for society	$0	$19 413 494	$19 413 494
Direct costs of the disease for the health system	$176 613 262	$167 582 886	$163 577 175
Direct costs of the disease for families	$33 205 852	$30 866 155	$29 345 591
Direct costs of the disease for society	$209 819 114	$198 449 041	$192 922 766
Total direct costs for the health system (program and disease)	$176 613 262	$186 543 059	$182 537 348
Total direct costs for families (program and disease)	$33 205 852	$31 319 476	$29 798 913
Total indirect costs (loss of productivity)	$410 875 381	$388 762 013	$381 606 142
Total costs for society (program, disease and loss of productivity)	$620 694 495	$606 624 548	$593 942 403

(QALYs = Quality-adjusted life-years)

The data indicate that use of both vaccines reduces the burden of the disease, and the reduction is greater with PCV-10 than PCV-7. At a purchase price of $73 per dose for each of the vaccines, the annual cost of the vaccination program is about $20 million, and most of that cost is borne by the health system. Without vaccination, the societal cost of considered pathologies is in the order of $620 million, including indirect costs of about $410 million. For both vaccines, a reduction in the burden of the disease is forecast, which from a societal perspective is greater than the cost of the program. From a societal perspective, the two programs are therefore beneficial economically. However, for the health system, both programs cost more than the reduction in the direct costs of the disease.

Marginal cost-effectiveness indices of various scenarios are presented in Table 4. The use of PCV-7 results in a roughly 40% reduction to invasive pneumococcal infections throughout the population, a consequence of the direct protection of children and group immunity. The efficacy of PCV-10 is not superior to PCV-7 for invasive pneumococcal infections, due to the rarity of the three new serotypes included in PCV-10 in the pre-PCV-7 context, which served as the reference for the basic model. However, PCV-10 may have a superior effect than PCV-7 in preventing pneumonia and otitis media, which would potentially mean a marginal improvement of 60 life-years and 200 healthy life-years. Neither of the programs is profitable

for the health system, but the economic indices are appealing. It is generally agreed that indices below $50 000 or $20 000 per life-year gained or per healthy life-year gained are favourable to the adoption of a program, and this is the case for the two vaccines (Laupacis et al., 1992). From a societal perspective, both programs offer greater gains than costs, an aspect that justifies the existence of a pneumococcal vaccination program for children in Québec. Both for the health system and for society in general, PCV-10 is preferable if its sale price is equal to that of PCV-7.

We calculated the price differential between the two vaccines, which gives equivalent cost-effectiveness indices for the health system. In the basic model, the purchase price of each vaccine is estimated at $73 per dose. PCV-7 would have to be sold at $54 per dose to produce a $/QALY ratio equivalent to that of PCV-10. Therefore, a $19 price differential would be justified from a strictly economic perspective for the health system.

Table 4: Marginal cost-effectiveness indices for various scenarios

Marginal cost-effectiveness indices	PCV-7 vs. no vaccine	PCV-10 vs. no vaccine	PCV-10 vs. $PCV\text{-}7_7$
Case differences			
All outcomes	-34 992	-60 820	-25 827
Invasive infections	-410	-410	<1
Pneumonia (hospitalized or not)	-894	-1 087	-193
Otitis media	-33 688	-59 323	-25 634
Death	-50	-52	-2
Survival with after-effects	-6	-6	<1
Lost life-years (discounted by 3%)	-859	-920	-61
Lost QALY (discounted by 3%)	-3 106	-3 306	-201
Marginal costs			
Δ Total direct costs for the health system (program and disease)	$9 929 797	$5 924 086	$-4 005 711
Δ Total direct costs for families (program and disease)	$-1 886 375	$-3 406 939	$-1 520 564
Δ Total indirect costs (disease)	$-22 113 368	$-29 269 239	$-7 155 871
Δ Total costs for society (program and disease)	$-14 069 947	$-26 752 092	$-12 682 146
Health system perspective			
$/outcome prevented	$284	$97	Dominant*
$/life-year gained (discounted by 3%)	$11 561	$6 440	Dominant*
$/QALY gained (discounted by 3%)	$3 197	$1 792	Dominant*
Societal perspective			
$/outcome prevented	Dominant*	Dominant*	Dominant*
$/life-year gained (discounted by 3%)	Dominant*	Dominant*	Dominant*
$/QALY gained (discounted by 3%)	Dominant*	Dominant*	Dominant*

* The first strategy provides greater health benefits at a lower cost than the second.

(QALY = Quality-adjusted life-years)

Since significant uncertainty exists regarding the efficacy of PCV-10 at preventing pneumonia and reducing the frequency of tympanic ventilation tubes, we carried out a sensitivity analysis by assuming that PCV-10 was equivalent to PCV-7 for preventing these two conditions. In this scenario, the residual economic burden of the disease following introduction of PCV-10 is $164 155 039 for the health system and $29 404 183 for families, while indirect costs are $382 593 547. For the health system, the cost per life-year gained is $7 570 and $2 002 for a healthy life-year gained. PCV-10 maintains an advantage over PCV-7 due to the former's better performance in preventing otitis media. In this latter scenario, the price differential that generates similar cost/QALY indices for the health system is $13 per dose. If a schedule of three doses of PCV-10 were less effective in preventing otitis, this differential would be less.
In the model, we compared routine vaccination scenarios for young children with three doses of PCV-7 or PCV-10, following the schedule recommended in Québec (two, four and 12 months). Scenarios with four doses were the subject of another analysis, and the results were very close to those presented here (De Wals et al., 2008b). In an analysis prior to the introduction of PCV-7, scenarios with three doses of the vaccine were compared to scenarios with four doses, and it appeared the marginal benefit of the fourth dose was low, generating unattractive cost-effectiveness indices (CIQ, 2005). Data presented by GSK show that for serotypes common to the two vaccines, the immune response after two, three and four doses are not generally different than those obtained with PCV-7 (trials 001 and 011). It would therefore be reasonable to assume that the same conclusions as those observed in the economic analysis of three versus four doses of PCV-7 apply to three versus four doses of PCV-10.

The study results show there is practically no difference in the effectiveness of the two vaccines in preventing invasive pneumococcal infections in the various scenarios considered and the epidemiological situation that prevailed in Québec prior to the introduction of PCV-7. However, since PCV-7 was introduced in Québec, an increase in the incidence of certain serotypes not included in the vaccine have been observed among children under five years of age (Jetté et al., 2008 a and b). This phenomenon is caused in part by ecological replacement. The highest increase of incidence was observed for serotype 19A. The increase in incidence of the other serotypes was much more modest. From 2000-2003, three cases of serotype 1 were identified compared to four cases from 2006-2008. Serotype 5 did not appear during these two periods among children under five years of age in Québec. However, an increase in the incidence of serotype 7F was observed, with eight cases recorded from 2000-2004 compared to 18 from 2006-2008 (provisional number). In all, there was an average of 6.6 cases per year of invasive infections caused by the three additional serotypes included in PCV-10. Assuming nine-tenths of these cases could be prevented by adopting PCV-10 over PCV-7, a marginal benefit of six cases of invasive infection per year among the group of children under five years of age can be expected. This benefit would increase if there was a sustained increase in the incidence of serotypes 1 and 7F among children.

In the basic model, we assumed the effectiveness of the two vaccines was equal for serotype 19A. The results of comparative trial 001 by GSK show that the proportion of subjects that attain an antibody titre of $\geq$0.2 µg/mL (ELISA dosage one month after three doses of the

vaccines administered at two, three, and four months) is not different for PCV-7 (28.7%; IC95%: 19.9% to 39.0%) or PCV-10 (22.6%; IC95%: 17.8% to 27.9%), while measurement of opsonophagocytic activity shows a significant advantage for PCV-10 (19.5% of subjects with an OPA titre ≥8; IC95%: 15.0% to 25.0%) compared to PCV-7 (3.4% of subjects with an OPA titre of ≥8; IC95%: 0.7% to 9.5%). The advantage of PCV-10 over PCV-7 in terms of the functional activity of antibodies against serotype 19A was also observed in GSK study 011 with a schedule of three doses administered at two, four and six months. If this difference in antibody functional activity measured *in vitro* translates into greater clinical protection against invasive infections caused by serotype 19A in a three-dose schedule, the advantage of PCV-10 over PCV-7 therefore becomes considerable in the current Québec context.

We know the current sale price of PCV-7 in Québec, but we do not know what prices will be offered by the two producers in a competitive market. In the basic model, we assumed the same price for both products, and price differentials that generate equivalent cost-effectiveness indices were estimated. The conclusion from these analyses is that at equal price, PCV-10 is more attractive economically than PCV-7. An estimate of the price differential that would be justified between the two vaccines depends on several considerations, including the uncertainty that exists in terms of the residual burden of pneumococcal infections in Québec in the context of PCV-7 use and the marginal impact PCV-10 may have.

5.1. PROGRAM FEASIBILITY

Acceptance of PCV-7 by the public and health professionals is very good, which brings high vaccination coverage rates (Boulianne et al., 2007). Changing to a potentially more effective and equally safe new vaccine with the same schedule should not be a problem for parents or professionals. A replacement should not be complex in terms of product management in the field, and there would be no problems in the use of PCV-10 by children who already received one or more doses of PCV-7. A product change means training activities for vaccinators and preparation of new information documents for parents. A schedule change at the same time as a product change would be much more complex.

5.2. PROGRAM EVALUATION

In Québec, a comprehensive assessment plan for the PCV-7 program was implemented, including the monitoring of vaccine coverage and surveillance of invasive infections, community-acquired pneumonia and otitis (Boulianne et al., 2007). This monitoring system must be maintained and improved through adequate funding. It would thus become possible to extend the surveillance of invasive infections among adults by laboratories, something which is now carried out in a non-comprehensive manner by the Laboratoire de santé publique du Québec. Another proposal would be to improve the validity of sources by supplying the mandatory disease declaration file directly from the referring laboratory. A case-control study is currently underway to assess the efficacy of PCV-7 in a three-dose schedule. It is essential that recruitment be reinforced for this study if a new vaccine is adopted for which we have no data on clinical efficacy.

The current monitoring of side effects associated with PCV-7 is done passively (ESPRI file). It would be particularly important to implement an active and stronger surveillance system for side effects if a new, little-studied vaccine is adopted.

5.3. RESEARCH QUESTIONS

Studies are planned or underway in other countries to evaluate the clinical efficiency of PCV-10. In Canada, studies demonstrating the absence of interference when PCV-10 is administered at the same time as other vaccines on provincial and territorial lists will be required. Québec can contribute in a useful way to the evaluation of any new pneumococcal vaccine in phase-IV studies on immune interference during the simultaneous administration of various vaccines, the field efficacy of the product, and indirect effects.

5.4. OTHER CONSIDERATIONS

In the United States, an increase in invasive infections caused by resistant serotype 19A strains was observed in the years following introduction of PCV-7, especially among children (Hicks et al., 2007). The same phenomenon was observed for otitis (Pichichero et al., 2007). In Québec, the increase of incidence of invasive infections caused by serotype 19A affected children under five years of age especially: an average of five cases per year was determined in the period 2000-2003 compared to 47 cases in 2008 (provisional number). Currently, 19A has become the most frequent serotype among children under five years of age, representing half of invasive infections in this age group. Given the weak performance of PCV-7 against this serotype, both in terms of immunogenicity (trial 011) and clinical efficacy (Whitney et al., 2006), and the uncertainty of cross-protection provided by PCV-10, especially in a schedule of three doses (trial 002), the usefulness of any vaccine that includes this serotype in its composition must be evaluated rapidly. A 13-valent vaccine using protein CRM_{197} for conjugation is currently being developed, and it contains the polysaccharide 19A (Scott et al., 2007). This new vaccine is destined to replace PCV-7, and may be licensed in the near future in Canada. Our plan is to carry out an economic analysis of the relative usefulness of this 13-valent vaccine compared to PCV-10 in the current Québec context of PCV-7 use, and including scenarios with three and four doses of the new vaccines. Funding for this study is recommended.

6. CONCLUSIONS AND RECOMMENDATIONS

PCV-7 was licensed on the basis of randomized clinical trials, and much information is available on the direct and indirect effects associated with its introduction in immunization programs for children in North America (Grijalva et al., 2008). PCV-10 is a new vaccine that presents two interesting characteristics: the presence of three additional pneumococcal polysaccharides (1, 5 and 7F) and the use of protein D from Hi for conjugation. PCV-10 was licensed in Canada on the basis of immunogenicity data, but we do not yet have information on the clinical efficacy of the vaccine apart from a randomized study of a precursor with a slightly different composition. The uncertainty regarding PCV-10 involves field efficacy, indirect effects in a three-dose schedule, and safety in terms of rare effects.

In terms of the invasive pneumococcal infections caused by the seven serotypes in PCV-7, the direct protection provided by PCV-10 should be the same. The presence of three additional serotypes in PCV-10 brings relatively modest complementary protection in the current Québec context: about six cases of invasive infections prevented per year among children under five years of age, which represents about 10% of the total of residual cases. The indirect protection that may be generated by PCV-10 requires evaluation, since the antibody levels induced by the new product are generally lower than in the old. The protection provided by PCV-10 against invasive infections caused by pneumococcus serotype 19A is uncertain, which is also the case for rare invasive infections caused by non-encapsulated Hi strains.

The contribution of PCV-10 in preventing community-acquired pneumonia among children should be at least equal to that observed with PCV-7, and the existence of additional protection (extending eventually to empyema and infections in patients with chronic pulmonary disease) associated with the presence of type 1 pneumococcal polysaccharide and protein D from Hi may be cited.

Non-encapsulated Hi strains probably play a significant role in the etiology of acute bacterial otitis in Québec as elsewhere. The fact that PCV-10 induces antibodies directed against Hi represents a definite advantage for preventing otitis, but it is difficult to precisely quantify the scope of this benefit due to the numerous uncertainties regarding the distribution of otopathogenic bacteria in Canada, the protection provided by three doses of PCV-10 compared to four doses, and the replacement phenomenon that can occur with any vaccine.

The available data allow us to predict a very good level of safety of PCV-10. This vaccine may be administered at the same time as other vaccines offered in Québec during visits at the age of two, four and 12 months, and it can also be offered to children who already received one or more doses of PCV-7. Complementary studies will nonetheless be required to confirm the safety of PCV-10 and the absence of significant interference when it is administered at the same time as Pentacel® from Sanofi Pasteur.

At the same price, PCV-10 appears preferable over PCV-7 for the regular immunization program for children in Québec. We tried to put a number on the price differential between

the two vaccines that would tip the balance in favour of one vaccine or the other in an economic perspective for the health system, but the estimates should be considered with much caution given the numerous uncertainties in the model parameters.

The advantage of PCV-10 is especially evident for populations that live in Québec's two most northerly regions and that receive four doses of a pneumococcal conjugate vaccine. Otitis is very frequent in these populations, and pneumococcal serotypes 1 and 5 can cause outbreaks. PCV-10 should be offered as soon as possible to these populations.

The use of PCV-10 among children who have received one and three doses of PCV-7 should not be a problem.

A new 13-valent vaccine is currently being developed and contains serotypes 19A and 7F, which are increasing in Québec. If the vaccine is licensed, a study comparing its usefulness to that of PCV-7 and PCV-10 should be carried out rapidly, giving a maximum of flexibility in the choice of product used in Québec.

7. REFERENCES

Black S, Shinefield H, Baxter R et coll. (2006). Impact of the use of heptavalent pneumococcal conjugate vaccine on disease epidemiology in children and adults. Vaccine 24 Suppl. 2: S2-79-80.

Black S, Shinefield H, Fireman B et coll. (2000). Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 19: 187-95.

Black S, Shinefield H, Ling S et coll. (2002). Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. Pediatr Infect Dis J 21: 810-15.

Boulianne N, De Wals P, Deceuninck G et coll. (2007). Impact du programme d'immunisation par le vaccin pneumococcique conjugué heptavalent (VPC-7), au Québec, Canada. Québec : Institut national de santé publique du Québec, 48 p.

(CIQ) Comité sur l'immunisation du Québec (2005). Évaluation de la pertinence d'un programme d'immunisation contre les infections pneumococciques chez l'enfant comportant un nombre réduit de doses de vaccin conjugué-Édition révisée. Québec : Institut national de santé publique du Québec, 40 p.

De Wals P, Carbon M, Sévin É et coll. (unpublished manuscript). Physician claims for otitis media after implementation of pneumococcal conjugate vaccine program in the province of Quebec, Canada.

De Wals P, Erickson L, Poirier B et coll. (2009). How to compare the efficacy of conjugate vaccines to prevent acute otitis media? Vaccine, accepted for publication.

De Wals P, Jetté L, Sévin É et coll. (2008a). Changes in the epidemiology of invasive pneumococcal disease (IPD) following implementation of a 7-valent pneumococcal conjugate vaccine (PCVPC-7) program in Quebec, Canada. Poster: 48th Annual ICAAC/IDSA 46th Annual Meeting, Washington DC.

De Wals P, Petit G, Erickson LJ et coll. (2003). Benefits and costs of immunization of children with pneumococcal conjugate vaccine in Canada. Vaccine 21: 3757-3764.

De Wals P, Poirier B, Petit G et coll. (2008b). Simulation model for comparing the costs and effectiveness of different pneumococcal conjugate vaccines. Poster: Vaccine 2nd Global Congress, Boston Mass.

De Wals P, Robin É, Fortin É et coll. (2008c). Pneumonia after implementation of the pneumococcal conjugate vaccine in the province of Québec, Canada. Pediatr Infect Dis J 27: 963-8.

Erickson LJ, De Wals P, Farand L. (2005). An analytical framework for immunization programs in Canada. Vaccine 23: 2468-74.

Erickson P, Wilson RW, Shannon I et coll. (1995). Years of healthy life. Statistical Note No.7. National Center for Health Statistics, Hyattsville MD, USA.

Eskola J, Kilpi T, Palmu A et coll. (2001). Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 344: 403-9.

Finley C, Clifton J, Fitzgerald JM et coll. (2008). Empyema: An increasing concern in Canada. Can Respir J 15: 85-9.

Fletcher MA, Fritzell B. (2007). Brief review of the clinical effectiveness of PREVENAR® against otitis media. Vaccine 25: 2507-12.

Forsgren A, Riesbeck K, Janson H. (2008). Protein D of *Haemophilus influenza*: A protective nontypeable *H. influenza* antigen and a carrier for pneumococcal conjugate vaccines. Clin Infect Dis 46: 726-31.

Grijalva CG, Griffin MR. (2008). Population-based impact of routine infant immunization with pneumococcal conjugate vaccine in the USA. Expert Rev Vaccines 7: 83-95.

GSK (2008). Synflorix. Product monograph. Mississauga ON: GlaxoSmithKine Inc.

Guay M, De Wals P, Jetté L et coll. (2003). Utilisation du vaccin antipneumococcique conjugué au Québec. Québec : Institut national de santé publique du Québec.

Hansen J, Black S, Shinefield H et coll. (2006). Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than 5 years of age for prevention of pneumonia. Pediatr Infect Dis J 25: 779-81.

Hausdorff WP, Feikin DR, Klugman KP. (2005). Epidemiological differences among pneumococcal serotypes. Lancet Infect Dis 5: 83-93.

Hicks LA, Harrison LH, Flannery B et coll. (2007). Incidence of pneumococcal disease due to non-pneumococcal conjugate vaccine (PCVPC-7) serotypes in the United States during the era of widespread PCVPC-7 vaccination, 1998-2004. J Infect Dis 196: 1346-54.

Jefferson T, Rudin M, Di Pietrantoni C. (2004). Adverse events after immunisation with aluminium-containing DPT vaccines: systematic review of evidence. Lancet Infect Dis 4: 84-90.

Jetté L, Bourgault A-M, De Wals P. (2008 a). Programme de surveillance du pneumocoque. Québec : Institut national de santé publique du Québec, 53 p.

Jetté LP, Delage G, Ringuette L et coll. (2001). Surveillance of invasive *Streptococcus pneumoniae* infection in Quebec, Canada, from 1996 to 1998: Serotype distribution, antimicrobial susceptibility, and clinical characteristics. J Clin Microbiol 39: 733-7.

Jetté L, Bourgault A-M, Raynal L et coll. (2008 b). Impact of 7-valent pneumococcal conjugate (PCVPC-7) on serotype distribution and susceptibility profiles of invasive *S. pneumonia* (I*Sp*) isolates in Quebec. Poster: 48th Annual ICAAC/IDSA 46th Annual Meeting, Washington DC.

Jódar L, Butler J, Carlone G et coll. (2003). Serological criteria for evaluation and licensure of new pneumococcal conjugate vaccine formulations for use in infants. Vaccine 21: 3265-72.

Jokinen JT, Ahman H, Kilpi TM, Kâythy MH. (2004). Concentration of antipneumococcal antibodies as a serological correlate of protection: An application to acute otitis media. J Infect Dis 190: 545-60.

Laupacis A, Feeny D, Detsky AS et coll. (1992). How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. Can Med Assoc J 146: 473-81.

Lee LH, Frasch CE, Falk LA et coll. (2003). Correlates of immunity for pneumococcal conjugate vaccines. Vaccine 21: 2190-6.

Leibovitz E, Jacobs MR, Dagan R (2004). Haemophilus influenza. A significant pathogen in acute otitis media. Pediatr Infect Dis J 23: 1142-55.

Lockhart SP, Hackell JG, Fritzell B. (2006). Pneumococcal conjugate vaccines: emerging clinical information and its implications. Expert Rev Vaccines 5: 553-64.

(MSSS) Ministère de la Santé et des Services sociaux (2003). Programme national de santé publique 2003-2011. Québec : Direction de la communication du ministère de la Santé et des Services sociaux.

Melegaro A, Edmunds WJ. (2004). Cost-effectiveness analysis of pneumococcal conjugate vaccination in England and Wales. Vaccine 22: 4203-4214.

Morrow A, De Wals P, Petit G et coll. (2007). The burden of pneumococcal disease in the Canadian population prior to routine use of the 7-valent pneumococcal conjugate vaccine. Can J Infect Dis Med Microbiol 18: 121-7.

Murphy TF. (2003). Respiratory infections caused by non-typeable Haemophilus influenza. Curr Opin Infect Dis 16: 129-34.

Murphy TF, Faden H, Bakaletz LO et coll. (2009). Nontypeable Haemophilus influenza as a pathogen in children. Pediatr Infect Dis J 28: 43-8.

(NACI) National Advisory Committee on Immunization. (2002). An Advisory Committee Statement (ACS) on recommended use of pneumococcal conjugate vaccine. Can Commun Dis Rep 28 (ACS-2): 1-32.

Petit G, De Wals P, Law B et coll. (2003). Epidemiological and economic burden of pneumococcal disease in Canadian children. Can J Infect Dis 14: 215-20.

Pichichero ME, Casey JR. (2007). Emergence of a multiresistant serotype 19A pneumococcal strain not included in the 7-valent conjugate vaccine as an otopathogen in children. JAMA 298: 1772-8.

Proulx JF, Déry S, Jetté LP et coll. (2002). Pneumonia epidemic caused by a virulent strain of *Streptococcus pneumonia* serotype 1 in Nunavik, Quebec. Can Commun Dis Rep 28-16: 129-31.

Prymula R, Peeters P, Chrobok V et coll. (2006). Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both *Streptococcus pneumonia* and non-typable *Haemophilus influenzae*: a randomized double-blind efficacy study. Lancet 367: 740-48.

Romney MG, Hull MW, Gustafson R et coll. (2008). Large community outbreak of Streptococcus pneumonia serotype 5 invasive infection in an impoverished, urban population. Clin Infect Dis 47: 768-74.

Scott DA, Komjathy SF, Hu BT, et coll. (2007). Phase 1 trial of a 13-valent pneumococcal conjugate vaccine in healthy adults. Vaccine 25: 6164-6.

Schuerman L, Prymula R, Henckaerts I et coll. (2007). ELISA IgG concentrations and opsonophagocytic activity following pneumococcal protein D conjugate vaccination and relationship to efficacy against acute otitis media. Vaccine 25: 1962-8.

Tsang RSW, Mubareka S, Sill ML et coll. (2006). Surveillance de l'infection invasive à *Haemophilus influenzae* au Manitoba à l'ère de la post-vaccination : mise en lumière d'un changement épidémiologique. Can Commun Dis Rep 32: 125-130.

Whitney CG, Pilishvili T, Farley MM et coll. (2006). Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. Lancet 368: 1495-502.

(WHO) World Health Organization (2005). Recommendations for the production and control of pneumococcal conjugate vaccines. Annex 2. World Health Organ Tech Rep Ser 927: 64-98.

Wyeth Pharmaceuticals. Prevnar. Product monograph. Montreal: Wyeth Canada, 2008.

APPENDIX 1:

METHODOLOGY OF THE COST-EFFECTIVENESS ANALYSIS

Model structure

A static and deterministic compartmental model was developed from previous models using Microsoft's Excel software (De Wals et al., 2003; CIQ, 2005). In this model, a stationary population of all ages is observed during a year, and the frequency of disease in the absence of any vaccination is compared to the forecast frequency for the routine vaccination of young children. This approach is preferable to a cohort study when a phenomenon of group immunity exists and the model must be calibrated according to empirical observations (Melegaro et al., 2004). Five mutually exclusive pathologies were considered: pneumococcal meningitis; pneumococcal bacteremia (with or without pneumonia); all causes of community-acquired pneumonia, hospitalized or not (without bacteremia); and otitis media. Added to this is the placement of ventilation tubes in the case of serous otitis. Vaccination of young children provides direct protection up to the age of nine, and indirect protection for the population in general. This latter notion of group immunity means fewer incidences of the pathologies in all age groups, as well as an ecological change in the distribution of streptococcus serotypes circulating in the population. Vaccination induces a replacement phenomenon of the streptococcus serotypes that are included in vaccines by other pathogens, which leads to an increase in incidences of pathologies in the general population. Group immunity and replacement are represented by two parameters of the model, the first modifying the incidence of invasive infections and the second the overall effectiveness of the vaccine against the invasive infections (which diminishes when the circulation of vaccine strains decreases). In the basic model, we assumed there was neither group immunity nor replacement by pneumonia or otitis media.

Demographic parameters

The population is that of the 2006 census in Québec, and is divided into 129 age categories (24 categories by month between birth and 23 months old and 105 categories of one year between two and 106 years old). Life expectancy at each age was calculated according to 1990-1992 Canadian survival tables, adjusted for the increase in life expectancy up to 2004. Quality-adjusted life expectancy was calculated using usefulness indices specific to each age category from the United States National Health Survey (Erickson et al., 1995). Life work income expectancy for each age was calculated using Canadian statistics on the proportion of people who have employment income (2006) and on the average income of people who are employed (2000).

Epidemiological parameters

Specific base incidence rates per age for the various outcomes considered in the analysis come from the study carried out prior to the introduction of PCV-7 in Canada (Morrow et al., 2007). The decrease in quality of life associated with each outcome and survivors of meningitis who have permanent physical after-effects are those used in an economic study in the United Kingdom (Melegaro et al., 2004). For children under five years of age, the distribution of serotypes among the invasive pneumococcal infections is that observed in Québec in the network of surveillance hospitals prior to the introduction of PCV-7 (Jetté et al., 2008 a and b). Given the absence of Canadian data on the distribution of bacterial pathogens in cases of acute otitis media, the proportions observed in the control group in a

vaccine trial in Finland were used (Eskola et al., 2001). The distributions of pathogens used in the basic model are presented in Table A1.

Table A1: Distribution (%) of pathogen agents covered by the two vaccines in the basic model

Pathogen	Invasive infections	Otitis media
Streptococcus pneumoniae		
4	6.0	0.3
6B	18.0	4.2
9V	3.0	0.8
14	31.0	1.9
18C	8.0	1.3
19F	11.0	4.3
23F	6.0	6.1
6A	4.0	3.3
19A	4.0	1.9
1	0.3	0.0
5	0.0	0.0
7F	1.3	0.0
Haemophilus influenzae		
Non-typeable	0.0	21.3

Vaccine parameters

In terms of the effectiveness of PCV-7 for preventing invasive infections, we used the specific rates per serotype reported in the United States CDC case-control study (Whitney et al., 2006). The efficacies observed for one dose or more for each serotype were adjusted proportionally according to the average values observed for all seven serotypes for one, two, three and four doses, to generate specific protection rates according to the serotype and the number of doses received. An average individual protection rate according to the number of vaccine doses received was calculated by accounting for the distribution of serotypes observed in Québec among children under five years of age prior to the introduction of PCV-7 (Jetté et al., 2008 a and b). For each age category, we calculated an average population protection rate according to these values and the distribution of vaccine coverage observed in Québec in the target population (Boulianne et al., 2007). We assumed the vaccine efficacy was at its maximum after the booster shot given at age 12 months and would then diminish at a rate of 10% per year between the age of two and nine years, which is the upper limit of the vaccine's direct effectiveness. For PCV-10, we used the same approach by modulating the effectiveness of this vaccine against each serotype according to the PCV-10/PCV-7 ratios in the proportion of subjects with OPA titres $\geq$8 after three doses (trial 001). For serotype 19A, however, we considered that the two vaccines had the same efficacy as estimated in the CDC case-control study (26%). Maximum efficacies at age one according to the number of doses received are presented in Table A2.

Table A2: Maximum efficacy (%) of the two vaccines in the basic model

Outcome	PCV-7				PCV-10			
	1 dose	2 doses	3 doses	4 doses	1 dose	2 doses	3 doses	4 doses
Invasive pneumococcal infections	62.3	81.9	86.3	85.0	61.1	80.4	82.0	83.6
Hospitalized pneumonia	15.0	19.8	20.2	20.5	21.2	27.9	28.4	29.0
Non-hospitalized pneumonia	3.2	4.1	4.3	4.3	3.1	4.1	4.2	4.3
Otitis media	10.3	13.5	13.7	14.0	18.0	23.7	24.2	24.7
Placement of tympanic ventilation tube	39.7	39.1	39.9	40.6	52.3	68.8	70.2	71.6

The combined effect of group immunity, replacement and ecological change induced by PCV-7 was calibrated according to observations regarding the incidence of invasive infections in different age categories before and after the introduction of universal vaccination in Québec in 2004 (De Wals et al., 2008a). We therefore assumed that the PCV-7 program would lead to an overall decrease of 30% in the incidence of invasive infections in the overall population, but that among children under five years of age the total decrease resulting from the direct and indirect effects of the vaccine could not surpass 72%. We also assumed that the indirect effects of PCV-10 would not be different from those observed with PCV-7.

The effectiveness of PCV-7 in preventing pneumonia was evaluated in a randomized trial in the United States, and the estimated level of protection depended on the definition chosen: the more specific the definition, the greater the protection (Black et al., 2002; Hansen et al., 2006). The choice of a maximum efficacy (four doses) of 20.5% for hospitalized pneumonia and 4.3% for non-hospitalized pneumonia in our model was made based on expert opinions. Efficacies for one, two and three doses were estimated according to relative efficacies observed for invasive infections (Whitney et al., 2006). Thus, the reduction in frequency predicted by the model for hospitalized pneumonia among children under five years of age (16.4%) is consistent with the results of the MedEcho file analysis comparing the frequency observed before and after implementation of the vaccination program in Québec (reduction of 13.2%), with the understanding that in this study the follow-up ended in March 2006 when the maximum effect of the program may not have been reached (De Wals et al., 2008a). Since there is no data on the effectiveness of PCV-10 in preventing pneumonia, the efficacy parameters were determined by experts who estimated that additional protection (29.0% versus 20.5%) for hospitalized pneumonia (but not for non-hospitalized pneumonia) was justified by the expanded coverage of the vaccine against pneumococcal serotypes frequently associated with pneumonia and against non-encapsulated strains of *haemophilus influenzae*. The relative efficacies of PCV-7 against invasive infections as a function of the number of doses were used to predict the relative efficacies against pneumonia as a function of the number of doses (Whitney et al., 2006), and the results are presented in Table A2. Data on vaccine coverage in Québec were used to generate average population efficacy

rates as a function of age (Boulianne et al., 2007). A linear decrease in protection from age two to three years was determined by expert opinion.

A study that has yet to be published used modelling to evaluate the relative performance of the different pneumococcal conjugate vaccines in preventing otitis (De Wals et al., 2009). It appears the superior performance of 11PN-PD, the precursor to PCV-10, compared to PCV-7 lay in its ability to prevent the replacement of bacteria otopathogens included in the vaccine by other otopathogens among vaccinated subjects and the expanded coverage against non-encapsulated strains of *haemophilus influenzae.* In the basic model, we hypothesized that the two vaccines would not induce replacement (or that the replacement would be offset by a collective immunity of the same magnitude). Results from the FinOM clinical trial were used to estimate specific protection rates per serotype (Eskola et al., 2001) and those from the POET study for PCV-10 (Prymula et al., 2006), by including cross-protection against strains related to the vaccine strains. Individual efficacy rates as a function of the number of doses and average population efficacy rates as a function of age were determined as with invasive infections by using the distribution of otopathogens observed in the control group of the randomized PCV-7 trial in Finland (Table A1) (Eskola et al., 2001). With these hypotheses, the decrease in the frequency of otitis media predicted by the model for PCV-7 among children under five years of age (9.4%) is relatively close to that estimated from an analysis of requests for the payment of medical fees to the Régie de l'assurance-maladie du Québec (13.2%) (De Wals et al., unpublished manuscript). Since otitis caused by pneumococcus is generally more severe than that caused by other otopathogens and resistance is more frequent, it follows that a reduction in the frequency of medical visits is greater than the reduction in the frequency of otitis media episodes as was observed in the United States clinical trial of PCV-7 (Black et al., 2000).

In terms of the placement of tympanic ventilation tubes, the efficacy of PCV-7 measured in randomized trials was between 24% and 39% (Fletcher et al., 2007). For PCV-10, we have a very imprecise estimate (60.3%; IC95%: -26.7% to 87.5%) observed in a randomized trial of a precursor to this vaccine (Prymula et al., 2006). In the United States clinical trial of PCV-7, the reduction in the frequency of tube placements was 2.9 times greater than the reduction in the frequency of otitis media episodes (Black et al., 2000), and we used this factor to estimate the specific population efficacies per age of the two vaccines for the placement of tympanic ventilation tubes as a function of the rates estimated for otitis episodes (Table A2).

To account for the uncertainty regarding PCV-10 efficacy parameters against pneumonia and the placement of tympanic ventilation tubes, we carried out a sensitivity analysis in which PCV-10 did not have greater efficacy than PCV-7 for the two outcomes.

Economic parameters

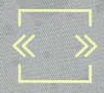
Costs are determined in 2007 Canadian dollars, and those from earlier years were adjusted according to the consumer price index in Canada. The cost of the vaccination program during the reference year was not subject to a discounting procedure since the direct and indirect effects of the vaccination occur during a short period. The same reasoning was applied to pathologies that occur in all age groups and that are principally influenced by the vaccination of young children during the reference year, and no discounting procedure was

applied to their treatment cost. However, a discounting procedure was applied for the long-term effects of pathologies that occur during the reference year, and all the future costs and benefits (financial and health) were calculated at their present value by using a negative annual rate of 3%.

In the basic model, we assumed that the purchase price of the two vaccines was $73 each per dose. The cost of administering the vaccine was determined according to a previous study (De Wals et al., 2003). Data on the annual cost of program management, monitoring and evaluation were provided by the ministère de la Santé et des Services sociaux du Québec and the Institut national de santé publique du Québec. Since pneumococcal conjugate vaccines are particularly safe, no costs were considered for the treatment of serious side effects. The unit costs of different pathologies come from estimates made in Canada (Petit et al., 2003; Morrow et al., 2007). The indirect costs of the disease were established using the human capital method, with deceased persons being no longer productive and survivors with sequela losing part of their production capacity. Production losses were established as a function of average income per age category.

In the event of a new vaccine for which we have no data on clinical efficacy, it is essential that the monitoring system be strengthened for pneumococcal infections and pathologies associated with pneumococcus in Québec, as well as case-control studies of vaccine efficacy against invasive pneumococcal infections.

N° de publication : 947



EXPERTISE
CONSEIL

INFORMATION

FORMATION

www.**inspq**.qc.ca

RECHERCHE
ÉVALUATION
ET INNOVATION

COLLABORATION
INTERNATIONALE

LABORATOIRES
ET DÉPISTAGE

Institut national de santé publique Québec