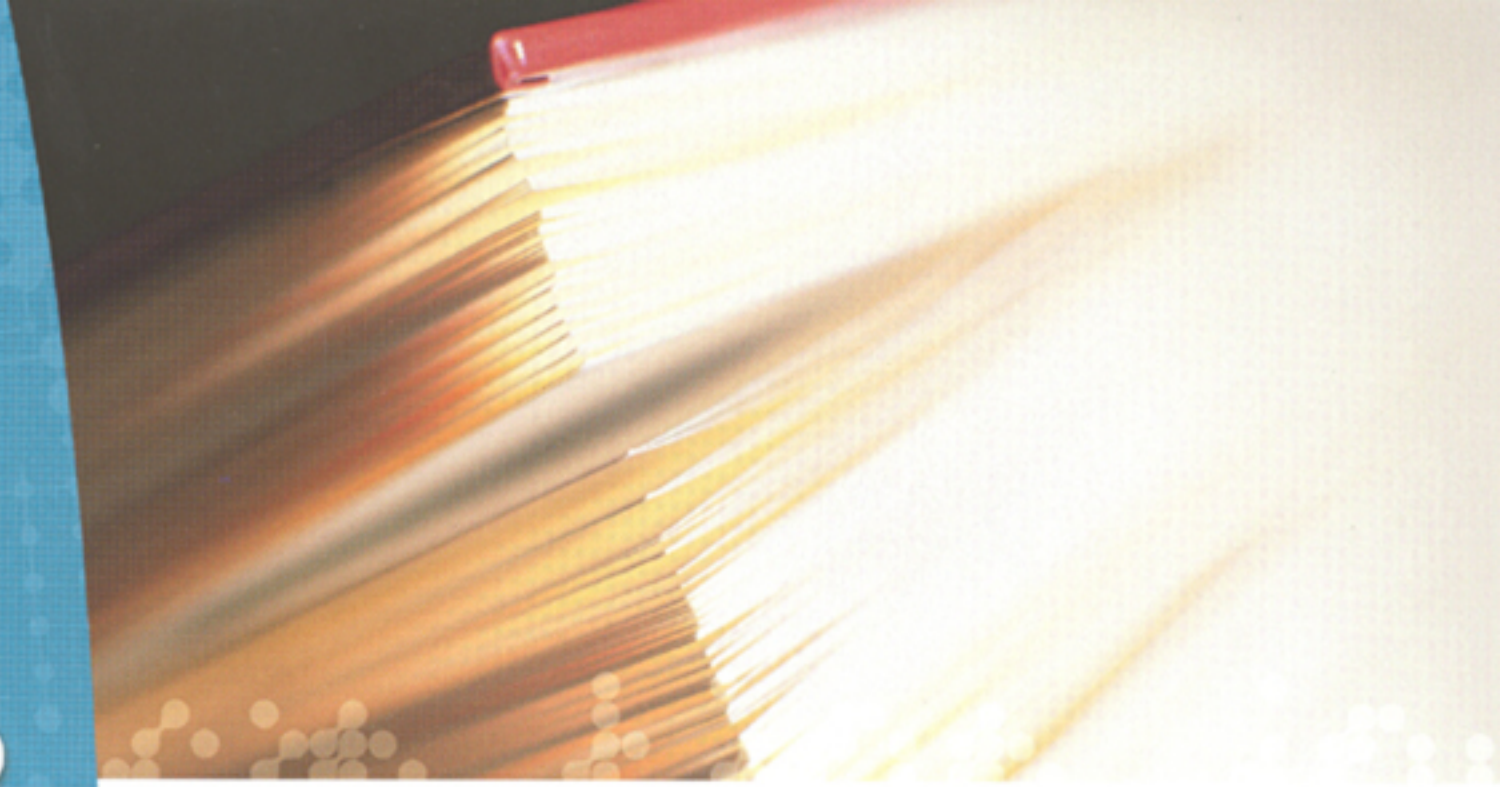

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ASSESSMENT OF THE APPROPRIATENESS OF AN IMMUNIZATION PROGRAM FOR PNEUMOCOCCAL INFECTIONS IN CHILDREN USING A REDUCED NUMBER OF DOSES OF CONJUGATE VACCINE

INSTITUT NATIONAL DE SANTÉ PUBLIQUE DU QUÉBEC

Québec

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ABSTRACT

At the request of the Quebec Department of Health and Social Services, this opinion has been prepared in order to assess the appropriateness of an immunization program for pneumococcal infections in children using a reduced number of doses of 7-valent pneumococcal conjugate vaccine (PVC-7). This opinion is further to a first opinion issued in 2002, and takes account of the results of new studies. The routine vaccination strategy consisting of 4 doses of PCV-7 (at 2, 4, 6, and 12 months) is the one used as a reference. The strategies which are compared with it consist of three doses administered at the ages of 2, 4 and 6 months or at the ages of 2, 4 and 12 months, or else a further strategy consisting of 2 doses administered at 2 and 4 months. A simulation model was developed to estimate the marginal benefits and costs of different schedules, and preliminary results are presented. As no data exist on the effectiveness of a reduced number of doses of vaccines to prevent non-invasive pneumococcal infections, chiefly otitis and pneumonia without bacteremia, the analysis is restricted to invasive infections.

We can estimate that, without a vaccination program, just over 200 cases of invasive infection could occur annually in Quebec in the population under 10 years of age. Supposing a fatality rate of 2%, we could expect about 4 deaths per year in this group. We observe an increase in the prevalence of strains showing reduced sensitivity to the usual antibiotics. The majority of the strains resistant to at least one antibiotic, and those that are multiresistant, belong to the serotypes which appear in PCV-7.

A recent study in the United Kingdom compared the immunogenicity of a 3-dose schedule (at 2, 3, and 4 months) and a 2-dose schedule (at 2 and 4 months) for a 9-valent pneumococcal vaccine very similar to PCV-7: the antibody levels were similar in both groups when measured at the ages of 5 months and 12 months, as was the anamnestic response after a booster dose. In this study, the antibody levels measured after two doses (at 2 and 4 months) were similar to those observed after 3 doses (at 2, 4 and 6 months) in the Kaiser Permanente randomized test in the United States.

The CDC took advantage of the situation of shortage which prevailed in the United States after licencing of the vaccine, in 2000, to carry out a case-control study. The preliminary results indicate that the protection conferred by a single dose is less than that associated with two or more doses. Protection rates exceeding 90% are obtained with two-, three- or four-dose schedules, and there is no statistically significant difference between these different schedules. In a context of immunization with a variable number of doses, in the United States, group immunity has been noted, which translates into a greater-than-expected reduction in the frequency of invasive infections caused by the vaccine serotypes, the levels of vaccination coverage in the population being known. A reduction in the frequency of infections was also observed in most unvaccinated groups.

Very premature birth is associated with a high risk of infection, but the immune response to PCV-7 is equivalent to that observed in infants born at term, and no failure was noted among the premature infants vaccinated in the Kaiser Permanente randomized test. In Italy, where a three-dose schedule is used (at 3, 5 and 11 months), the immune response in a group of premature infants was equivalent to that observed in infants born at term.

To achieve maximum reduction in the costs of a new program, in Quebec, PCV-7 must be administered at the same time as other vaccinations that have already been scheduled at the ages of 2 months (1 injection), 4 months (1 injection), 6 months (1 injection) and 12 months (2 injections). It should be mentioned that immunization for varicella (one dose) should be offered as early as the age of 12 months, although this vaccine is not yet included in the regular schedule in Quebec. Moreover, immunization for influenza in the fall is now recommended for all infants between 6 and 23 months, with two doses to be administered in the first year and a single dose thereafter.

To compare the advantages and disadvantages of different schedules for the routine immunization of children, a simulation model was developed, based on the one created for assessing PCV-7 cost-effectiveness ratios in Canada. The perspective chosen is that of a child presenting no immune deficiency. The rates of protection against invasive infections caused by the serotypes contained in PCV-7 were determined by experts on the basis of the results of the randomized test in the United States and those of the CDC case-control study. The results of the simulations show that the reduction in morbidity is 71.6% for the 4- and 6-month schedule, 74.3% for the 2-, 4- and 6-month schedule, 77.8% for the 2-, 4- and 12-month schedule, and 78.1% for the 2-, 4-, 6- and 12-month schedule. With a vaccine purchased at a unit cost of $70 and an administration cost of about $8 per dose ($7 for the health-care system and $1 for families), immunization of one child costs over $300 for the 4-dose schedule and the costs are reduced proportionally with a reduced number of doses. After actualization of the costs and benefits at the rate of 3% per year, the incremental cost-benefit indices for the 4-dose schedule in relation to the other three schedules were calculated. Moving from a 2-dose program to a 4-dose program makes it possible to avoid some 16 new cases of invasive infection in a cohort of 100 000 infants, but the additional cost is $15.65 million for society, which gives an incremental cost of $964 000 per additional case avoided. Moving from the most effective 3-dose program (at 2, 4 and 12 months) to a 4-dose program, the incremental costs become astronomical: less than one additional case avoided for a difference of $7.83 million, which amounts to an investment on the order of $2 million for each quality-adjusted life-year gained.

At present, the accessibility of 7-valent pneumococcal conjugate vaccine is limited in Quebec, and that is a source of inequity. A public vaccination program aimed at all children should be implemented as quickly as possible. Considering all the immunogenicity and effectiveness data available, the Quebec Immunization Committee considers that a minimum of 2 doses of PCV-7 at an early age is necessary in order to ensure a satisfactory level of short-term protection. The benefit provided by a third dose of vaccine at the age of 6 months seems modest. A booster dose given at the age of one year results in a good anamnestic response which can significantly prolong protection time and amplify a program's impact on transmission of the strains of *S. pneumoniae* belonging to the serotypes which appear in PCV-7. Moreover, the experience acquired with other conjugate polysaccharide vaccines must be taken into account in the decision. In the United Kingdom, a program of immunization against *Haemophilus influenzae* Type b began in 1992. Three doses of conjugate vaccine were offered at the ages of 2, 3 and 4 months respectively, with no booster shots. After a few years of complete success, the number of cases increased among vaccine recipients and a catch-up campaign with a fourth dose was implemented in 2003. This phenomenon has not been observed in countries where offer a booster dose is offered in the second year. Again in the United Kingdom, a loss of protection was observed in children who had received three doses of conjugate meningococcal vaccine on the regular schedule (at 2, 3 and 4 months), whereas a high degree of protection still remained as much as 4 years after a dose of vaccine received after the age of 12 months. It is not impossible for an immunization schedule

based on four doses of PCV-7 to be slightly more effective than a three-dose schedule, but the difference in terms of cases prevented is certainly very small while the additional cost in large, which translates into incremental cost-effectiveness indices that are difficult to accept. The savings generated by a three-dose schedule could be used to fund other prevention programs offering much greater health benefits than those associated with the fourth dose of PCV-7. For all these reasons, the majority of the members of the QIC consider that the 2-, 4- and 12- month schedule is the most worthwhile option for a universal program of vaccination for pneumococcal infections in children in Quebec, although at the same time they recognize the difficulties associated with multiple injections in a single visit.

It will therefore be necessary to provide adequate information for parents, mentioning the safety of simultaneous multiple injections compared to deferred injections, the risk of disease associated with delayed administration of a vaccine, and the inconvenience of making another appointment. It is also crucial to provide information and training programs for the vaccinators who will have to manage the administration of three or four vaccines in a single visit.

For children who have a medical condition possibly associated with altered immune response and are liable to respond less well to PCV-7, maintenance of a four-dose schedule is recommended. In the northern regions, otitis is a particular problem and access to care is limited for the treatment of infections that require hospitalization. For operational reasons, the schedule implemented in Nunavik includes four doses of PCV-7 offered at the ages of 2, 4, 6 and 18 months respectively. In such a context, maintenance of the present schedule is preferable.

Assessment of any new health program is a duty to the public and the taxpayer, especially as there is uncertainty about the program’s actual impact. Even before implementation of a PCV-7 immunization program, assessment of the program must be planned for, with the main question being the populational effectiveness of a schedule based on a reduced number of doses of PCV-7, should such an option be chosen.

RÉSUMÉ

À la demande du ministère de la Santé et des Services sociaux du Québec, le présent avis a été préparé afin d'évaluer la pertinence d'un programme d'immunisation contre les infections pneumococciques de l'enfant comportant un nombre réduit de doses de vaccin pneumococcqiue conjugué 7-valent (VPC-7). Cet avis fait suite à un premier avis émis en 2002 et tient compte des résultats de nouvelles études. La stratégie de vaccination de routine qui comporte 4 doses de VPC-7 (2, 4, 6 et 12 mois) est celle qui sert de référence. Les stratégies qui lui sont comparées comportent trois doses administrées à l'âge de 2, 4 et 6 mois, ou à l'âge de 2, 4 et 12 mois, ou encore une stratégie comportant 2 doses administrées à 2 et 4 mois. Un modèle de simulation a été développé pour estimer les bénéfices et coûts marginaux de différents calendriers et des résultats préliminaires sont présentés. Comme il n'existe aucune donnée sur l'efficacité d'un nombre réduit de doses de vaccins pour prévenir les infections pneumococciques non invasives, principalement les pneumonies non accompagnées d'une bactériémie et les otites, l'analyse est restreinte aux infections invasives.

On peut estimer que, sans programme de vaccination, un peu plus de 200 cas d'infection invasive pourraient survenir annuellement au Québec dans la population âgée de moins de 10 ans. En supposant un taux de létalité de 2 %, on pourrait s'attendre à environ 4 décès par an, dans ce groupe. On observe une augmentation de la prévalence des souches ayant une sensibilité réduite aux antibiotiques usuels. Les souches résistantes à au moins un antibiotique ou multirésistantes appartiennent en majorité aux sérotypes qui figurent dans le VPC-7.

Une étude récente au Royaume-Uni a comparé l'immunogénicité d'un calendrier à 3 doses (2, 3, 4 mois) et à 2 doses (2, 4 mois) pour un vaccin pneumococcique 9-valent très semblable au VPC-7 : les niveaux d'anticorps étaient similaires dans les deux groupes lors de mesures à l'âge de 5 mois et de 12 mois, ainsi que la réponse anamnestique après une dose de rappel. Dans cette étude, les niveaux d'anticorps mesurés après deux doses (2 et 4 mois) étaient semblables à ceux observés après 3 doses (2, 4 et 6 mois) dans l'essai randomisé de la Kaiser Permanente aux Etats-Unis.

La situation de pénurie qui a prévalu aux États-Unis depuis l'homologation du vaccin en 2000 a été mise à profit par le CDC pour entreprendre une étude cas-témoin. Les résultats préliminaires indiquent que la protection conférée par une seule dose est inférieure à celle associée à deux doses ou plus. Des taux de protection supérieurs à 90 % sont obtenus par des calendriers à deux, trois ou quatre doses, et il n'y a pas de différence statistiquement significative entre ces différents calendriers. Dans un contexte d'immunisation avec un nombre variable de doses, aux Etats-Unis, on a constaté une immunité de groupe qui se traduit par une réduction de la fréquence des infections invasives causées par les sérotypes vaccinaux supérieure à ce qui était attendu, connaissant les taux de couverture vaccinale dans la population visée. Une réduction de la fréquence des infections a également été observée dans la plupart des groupes non vaccinés.

La grande prématurité est associée à un risque élevé d'infection, mais la réponse immunitaire au PCV-7 est équivalente à celle observée chez les enfants nés à terme et aucun échec n'a été constaté parmi les prématurés vaccinés dans l'essai randomisé de la Kaiser Permanente. En Italie, où un calendrier à trois doses est utilisé (3, 5 et 11 mois), la réponse immunitaire chez un groupe d'enfants prématurés a été équivalente à celle observée chez des enfants nés à terme.

Afin de réduire au maximum les coûts d'un nouveau programme, au Québec, l'administration du VPC-7 doit se faire à l'occasion d'autres vaccinations déjà prévues à l'âge de 2 mois (1 injection), de 4 mois (1 injection), de 6 mois (1 injection)et 12 mois (2 injections). Il faut mentionner que l'immunisation contre la varicelle (une dose) doit être offerte dès l'âge de 12 mois, bien que ce vaccin ne soit pas encore inclus dans le calendrier régulier au Québec. Par ailleurs, l'immunisation contre l'influenza au cours de l'automne est maintenant recommandée pour tous les enfants âgés entre 6 mois et 23 mois, deux doses devant être administrées la première année et une seule dose par la suite.

Afin de comparer les avantages et inconvénients de différents calendriers pour l'immunisation de routine des enfants, un modèle de simulation a été développé, à partir de celui élaboré pour évaluer les rapports coût-efficacité du VPC-7 au Canada. La perspective choisie est celle d'un enfant qui ne présente pas de déficience immunitaire. Les taux de protection contre les infections invasives causées par les sérotypes contenus dans le VPC-7 ont été déterminés par des experts à partir des résultats de l'essai randomisé aux États-Unis et de ceux de l'étude cas-témoin du CDC. Les résultats des simulations montrent que la réduction de la morbidité est de 71,6 % pour le calendrier 4-6 mois, de 74,3 % pour le calendrier 2-4-6 mois, de 77,8 % pour le calendrier 2-4-12 mois et de 78,1 % pour le calendrier 2-4-6-12 mois. Avec un vaccin acheté au prix unitaire de 70 $ et un coût d'administration d'environ 8 $ par dose (7 $ pour le système de santé et 1 $ pour les familles), l'immunisation d'un enfant revient à plus de 300 $ pour le calendrier comportant 4 doses et les coûts sont réduits de façon proportionnelle avec un nombre réduit de doses. Après actualisation des coûts et bénéfices au taux de 3 % par an, les indices coût-bénéfice incrémentaux du calendrier à 4 doses, par rapport aux trois autres calendriers, ont été calculés. Ainsi, passer d'un programme à 2 doses à un programme à 4 doses permet d'éviter environ 16 nouveaux cas d'infection invasive dans une cohorte de 100 000 enfants, mais le coût supplémentaire est de 15,65 millions pour la société, ce qui donne un coût incrémental de 964 000 $ par cas évité supplémentaire. En passant du programme à 3 doses le plus efficace (2, 4 et 12 mois) à un programme à 4 doses, les coûts incrémentaux deviennent faramineux : moins d'un cas évité supplémentaire pour une différence de 7,83 millions $, ce qui revient à un investissement de l'ordre de 2 millions $ pour chaque année de vie gagnée ajustée pour la qualité.

À l'heure actuelle, l'accessibilité au vaccin pneumococcique conjugué 7-valent est limité au Québec, et cela est source d'inéquité. Un programme public de vaccination visant l'ensemble des enfants devrait être implanté le plus rapidement possible. En considérant l'ensemble des données d'immunogénicité et d'efficacité disponibles, le Comité sur l'immunisation du Québec estime qu'un mininum de 2 doses de VPC-7 en bas âge est nécessaire pour assurer un niveau satisfaisant de protection à court terme. Le bénéfice procuré par une troisième dose de vaccin donnée à 6 mois semble modeste. Une dose de rappel donnée à l'âge d'un an entraîne une bonne réponse anamnestique qui peut allonger significativement la durée de la protection et amplifier l'impact d'un programme sur la transmission des souches de *S. pneumoniae* appartenant aux sérotypes qui figurent dans le VPC-7. Par ailleurs, l'expérience acquise avec d'autres vaccins polysaccharidiques conjugués doit être prise en compte dans la décision. Au Royaume-Uni, un programme d'immunisation contre l'*Haemophilus influenzae* de type b a débuté en 1992. Trois doses de vaccin conjugué étaient offertes, respectivement, à l'âge de 2, 3 et 4 mois, et aucun rappel n'était fait. Après quelques années de plein succès, le nombre de cas a augmenté chez les vaccinés et une campagne de rattrapage avec une quatrième dose a été mise en œuvre en 2003. Ce phénomène n'a pas été observé dans les pays qui offrent une dose de rappel dans la seconde année. Toujours au Royaume-Uni, une perte de protection a été observée chez les enfants qui avaient reçu trois doses de vaccin méningococcique conjugué suivant le calendrier régulier

(2, 3 et 4 mois), alors qu'un haut degré de protection subsistait jusque 4 ans après une dose de vaccin reçue après l'âge de 12 mois. Il n'est pas impossible qu'un calendrier d'immunisation comportant quatre doses de VPC-7 soit légèrement plus efficace qu'un calendrier comportant 3 doses mais la différence en termes de cas prévenus est certainement très faible, alors que le coût supplémentaire est important, ce qui se traduit par des indices coût-efficacité incrémentaux difficilement acceptables. Les économies générées par un calendrier à trois doses pourraient servir au financement d'un autre programme de prévention procurant beaucoup plus de bénéfices sanitaires que ceux associés à la quatrième dose de VPC-7. Pour toutes ces raisons, la majorité des membres du CIQ considère que le calendrier 2, 4 et 12 mois est l'option la plus intéressante pour un programme de vaccination universelle contre les infections pneumococciques de l'enfant au Québec, tout en reconnaissant les difficultés liées aux injections multiples lors d'une même visite.

Il faudra donc prévoir une information adéquate aux parents, mentionnant l'innocuité des injections multiples simultanées par rapport aux injections différées, le risque de maladie associé au retard dans l'administration d'un vaccin, et les inconvénients liés à la prise d'un nouveau rendez-vous. Il est également crucial de prévoir des programmes d'information et de formation pour les vaccinateurs qui devront gérer l'administration de trois ou quatre vaccins lors d'une même visite.

Pour les enfants qui ont une condition médicale possiblement associée à une altération de la fonction immunitaire et qui risquent de répondre moins bien au PCV-7, le maintien d'un calendrier à quatre doses est recommandé. Dans les régions nordiques, les otites constituent un problème particulier et l'accès aux soins est réduit pour le traitement des infections qui requièrent une hospitalisation. Pour des raisons opérationnelles, le calendrier implanté au Nunavik comporte quatre doses de PCV-7 offertes respectivement à l'âge de 2, 4, 6 et 18 mois. Dans un tel contexte, le maintien du calendrier actuel est préférable.

L'évaluation de tout nouveau programme de santé est un devoir envers la population et le contribuable, d'autant plus qu'il existe des incertitudes quant à l'impact réel du programme. Dès avant la mise en œuvre d'un programme d'immunisation avec le VPV-7, il faudra planifier son évaluation, la principale question étant l'efficacité populationnelle d'un calendrier comportant un nombre réduit de doses de VPC-7, advenant le choix de cette option.

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1 INTRODUCTION

In Canada, the first 7-valent pneumococcal conjugate vaccine (PCV-7) was licenced in 2001. The manufacturer's recommendation is to administer three doses at an early age for primary immunization and a booster dose during the second year (Wyeth-Ayerst Canada Inc. 2001). The recommendation of the National Advisory Committee on Immunization (NAIC) is to give 3 doses of vaccines at the same time as the other vaccines provided in the schedule at the ages of 2, 4 and 6 months, and the booster dose between 12 and 15 months (NAIC 2002). An economic analysis done for Canada indicated that such a program would significantly reduce the burden of disease in children, but that the cost-effectiveness indices, established for a purchase price of $58 per dose, were not favorable compared to other immunization programs (De Wals et al. 2003). In 2002, in response to the report of the Working Group on Conjugate Antipneumococcal Vaccine (INSPQ 2003), the Quebec Immunization Committee (QIC) issued an opinion recommending introduction of this vaccine into the regular immunization program, indicating that the vaccine should be offered as a matter of priority to very premature infants, children under 5 years old suffering from chronic medical conditions associated with a high risk of infection, and children in Nunavik, where the incidence of pneumococcal disease is particularly high. This order of priorities has been followed and, at the present time, PCV-7 vaccine is being offered free of charge to children in the northern regions, premature infants and children who have a medical condition associated with a high risk of infection. Moreover, the vaccine is offered by the federal government to First Nations children living on reserves. A decision on the universality of this program must be taken soon in the context of a monopoly over marketing of the vaccine and a PCV-7 selling price on the order of $70 per dose. During the year 2004, the results of immunogenicity and clinical studies comparing schedules using a variable number of doses of conjugate pneumococcal vaccine were revealed; they permit assessment of immunization schedules using a smaller number of doses than had been advocated previously (INSPQ 2003).

2 REPORT OBJECTIVES

At the request of the Quebec Department of Health and Social Services, this opinion has been prepared in order to assess the appropriateness of an immunization program for pneumococcal infections in children using a reduced number of doses of conjugate vaccine. The reference strategy is one consisting of 4 doses of PCV-7 (at 2, 4, 6 and 12 months) and the strategies which are compared consist of three doses administered at the ages of 2, 4 and 6 months or at the ages of 2, 4 and 12 months, or else a further strategy consisting of 2 doses administered at 2 and 4 months. The advantages and disadvantages of the different strategies are compared, taking account of the published and unpublished data on the immunogenicity and effectiveness of different immunization schedules as well as the opinions of experts. A simulation model was developed to estimate the marginal benefits and costs of different schedules, and preliminary results are presented. For reasons that are explained below, a reduced number of doses is not envisioned for children in the northern regions or those having a medical condition associated with a high risk of infection. As no data exist on the effectiveness of a reduced number of doses of vaccines to prevent non-invasive pneumococcal infections, chiefly otitis and pneumonia without bacteremia, the analysis is restricted to invasive infections, i.e. meningitis, septicemia and pneumonia accompanied by bacteremia. Invasive infections are responsible for most deaths and for the most serious sequelae. This opinion is structured around the decision-making criteria proposed for public immunization programs in Canada (Erickson 2004).

3 BURDEN OF DISEASE

A study was carried out using several surveillance populational databases in Canada in order to estimate the incidence of invasive streptococcal infections in the years 1997-1998 (Petit et al. 2003). The results presented in Table I show that the risk of invasive infection is maximal before the age of one year and decreases subsequently. The risk of meningitis is concentrated in the first year. From these data, we can estimate that, without a vaccination program, just over 200 cases of invasive infection could occur annually in Quebec in the population under 10 years of age. Supposing a fatality rate of 2% (Scheifele et al. 2000), we could expect about 4 deaths per year in this group.

Table I: Rate of incidence (per 100 000 person-years) of invasive pneumococcal infections as a function of age

Age group	Meningitis rate	Bacteremia Rate*	Rate for all invasive infections	Quebec population 2003	Estimated number of cases annually
<1 year	19.37	94.81	114.18	71 826	82.0
1 year	4.58	78.32	82.90	73 243	60.7
2 years	0.99	32.62	33.61	73 223	24.6
3 years	0.73	18.53	19.26	74 983	14.4
4 years	0.47	12.82	13.29	75 646	10.1
5 years	0.46	4.65	5.11	79 015	4.0
6 years	0.46	4.65	5.11	83 867	4.3
7 years	0.46	4.65	5.11	87 742	4.5
8 years	0.46	4.65	5.11	89 867	4.6
9 years	0.46	4.65	5.11	91 834	4.7
Total					213.9

* Including septicemia, isolated bacteremia and those associated with a site of infection such as pneumonia.

Source: Petit et al., 2003

In Quebec, invasive pneumococcal infections are reportable diseases and nosological definitions are advocated. The results presented in Table II show a rise in incidence between 1999 and 2003, and the total number reported gradually approaches that estimated previously (Table I). The reportable disease record (Fichier MADO) has not been validated to ensure the sensitivity and specificity of the reporting. That there was an improvement in the reporting of cases between 1999 and 2003 is not to be excluded.

Table II : Rate of incidence (per 100 000 person-years) of invasive pneumococcal infections as a function of age reported in Quebec

Age group	1999	2000	2001	2002	2003
< 1 year	73.1	82.3	97.6	98.0	100.8
1-4 years	47.9	45.4	62.7	58.8	61.8
5-9 years	4.4	6.1	8.0	5.6	6.0
Cumulative incidence	125.4	133.8	168.3	162.4	168.6

Source: Fichier MADO 2004

The strains of *S. pneumoniae* isolated from sterile sites or liquids in the laboratories of 24 sentinel hospitals are systematically transmitted to the Quebec Public Health Laboratory (LSPQ) (INSPQ 2004). The four pediatric tertiary care centers in Quebec appear on the list of sentinel hospitals. Between 1996 and 2002, the number of strains isolated in persons under 10 years of age varied between a minimum of 116 and a maximum of 197, with an average of 149 cases per year. During this period, the proportion of strains belonging to one of the serotypes contained in PCV-7 was 86.2% in children under 2 years of age (563/653), 82.8% in children between 2 and 4 years of age (232/280) and 77.0% in those between 5 and 9 years of age (87/113). In general, we observe an increase in the prevalence of strains showing reduced sensitivity to the usual antibiotics. The majority of the strains resistant to at least one antibiotic, and those which are multiresistant, belong to the serotypes which appear in PCV-7.

4 VACCINE CHARACTERISTICS

4.1 IMMUNOGENICITY

Like all conjugate polysaccharide vaccines, PCV-7 induces a thymus-dependent immune response which is manifested at the earliest age and is characterized by the production of serum antibodies having a great affinity for bacterial epitopes and persistence of a memory (Stein 1992). For pneumococcal infections, the relation between clinical protection and serum concentration of the antibodies directed against different type and subtype specific polysaccharides is poorly defined, and it is difficult to predict the short- and medium-term level of effectiveness from a distribution of the levels of serum antibodies in a group, one month after immunization (Eskola et al. 2004). There are few studies comparing different vaccination schemes. One study in Gambia compared the titers of antibodies, at the age of 5 months, in two groups of 30 infants, the first having received 3 doses of 5-valent pneumococcal conjugate vaccine (at 2, 3 and 4 months) and the second 2 doses (at 2 and 4 months): the titers were appreciably higher in the first group than in the second, especially for serotype 14 (Leach et al. 1996). A recent study in the United Kingdom compared the immunogenicity of a 3-dose schedule (at 2, 3 and 4 months) and a 2-dose schedule (at 2 and 4 months) for a 9-valent pneumococcal conjugate vaccine very similar to PCV-7: the antibody levels were similar in both groups when measured at the ages of 5 months and 12 months, as was the anamnestic response after a booster dose with the 9-valent conjugate vaccine (Goldblatt et al. 2004). In this study, the antibody levels measured after two doses (at 2 and 4 months) were similar to those observed after 3 doses (at 2, 4 and 6 months) in the Kaiser Permanente randomized test (Black et al. 2000). For all serotypes, serum antibody levels measured after a booster dose between 12 and 23 months are much higher than after a primovaccination with three or two doses between 2 and 6 months (Black et al. 2000; Goldblatt et al. 2004).

4.2 CLINICAL EFFECTIVENESS

The clinical effectiveness of PCV-7 was assessed in the context of a randomized test in the United States (Black et al. 2000). In the experimental group with follow-up to the age of 3 years, with reference to the control group, a reduction of 94% (confidence interval: 80% to 99%) was observed in the incidence of bacteremia caused by a pneumococcus strain of one of the serotypes contained in the vaccine. The reduction in incidence was 97% (confidence interval: 83% to 100%) in the subgroup that had received four doses according to the protocol. Another study, using the cluster randomization technique, was carried out in Apache and Navajo communities in the United States, and the protection against invasive infections caused by the pneumococcus serotypes included in PCV-7 was 77% (confidence interval: -10% to 95%) with the regular 4-dose schedule (O'Brien et al. 2003a). This same vaccine administered in 3 doses at the age of 6, 10 and 14 weeks in an underprivileged population in South Africa showed 83% effectiveness (confidence interval: 39% to 97%) against invasive infections caused by the serotypes included in the vaccine (Klugman et al. 2003).

In the United States, PCV-7 was licenced in February 2000 and its utilization was immediately recommended by the public health authorities (CDC 2000). As early as the following year, supply problems appeared and grew gradually worse, with the result that administration of 3 doses or even 2 doses was advocated for immunizing young children (CDC 2001; CDC 2004a). The supply seems to have improved in mid-2004 and utilization of the regular schedule was re-established (CDC 2004

b). The situation of shortage that prevailed in the United States after licencing of the vaccine in 2000 affords a good opportunity for studying the effect of a reduced number of doses. The National Immunization Survey, covering a sample of children between the ages of 19 and 35 months, in 2003, indicates that 14.0% of children did not receive PCV-7, 6.6% received a single dose, 13.0% received 2 doses, 31.5% received three doses and only 34.9% respected the full 4-dose schedule (CDC, unpublished data). Given the high proportion of children who received a smaller number of doses than in the optimum schedule, a case-control study was undertaken in the regions participating in the Active Bacterial Core Surveillance program (CDC 2004a). This surveillance system covers a population of nearly 16 million persons. The cases of invasive infection identified in children under the age of 6 years were matched with three controls selected at random in the birth records, and a survey was carried out to verify the case diagnosis and the vaccination status of both cases and controls, along with certain potential confusion factors, including race, socioeconomic level, passive smoking and daycare attendance. The preliminary results, relating to 654 cases and 2088 controls, indicate that the protection conferred by a single dose is less than that associated with two or more doses (Table III). Protection rates exceeding 90% are obtained with two-, three- or four-dose schedules, and there is no statistically significant difference between these different schedules. The effectiveness levels observed in this case-control study with 2, 3 or 4 doses do not differ from the level measured in children who received 4 doses in the Kaiser Permanente randomized test in the United States (Black et al. 2000). In that test, the participants had been followed up until the age of 36 months, on the average, but the duration of the follow-up was very variable and generally shorter in the case-control study (Cynthia Whitney, personal communication). Analysis of the case-control study data as a function of time elapsed since administration of the different doses of vaccine was not done.

Table III: Effectiveness of PCV-7 for preventing invasive pneumococcal infections caused by the serotypes contained in the vaccine as a function of vaccination schedule

Schedule	Number of cases	Number of controls	Effectiveness (CI 95 %)
3 doses ≤ 6 months and 1 dose 12-18 months	0	25	100% (-12% to 100%)
3 doses ≤ 6 months	15	95	92% (83 % to 97%)
2 doses ≤ 6 months and 1 dose 12-18 months	1	6	95% (33% to 100%)
2 doses ≤ 6 months	9	76	96% (88% to 99%)
1 dose ≤ 6 months	ND	ND	67% (28% to 85%)

ND = Data not available
CI 95% = 95% confidence interval

Source: CDC, unpublished data

4.3 POPULATIONAL EFFECTIVENESS

PCV-7 has an effect on the transmission of strains of *S. pneumoniae* (O'Brien et al. 2003b; Eskola et al. 2004). The specific IgG type antibodies induced by the vaccine are diffused in the mucous membranes and secretions and may inhibit colonization of the rhinopharynx by homologous strains (Ghaffar et al. 2004). In the United States, in a context of immunization with a variable number of doses, group immunity has been noted, which translates into a greater-than-expected reduction in the frequency of invasive infections caused by the vaccine serotypes, the levels of vaccination coverage in the population being known. A reduction in the frequency of infections was also observed in most unvaccinated groups (Black et al. 2001; Whitney et al. 2003). The most recent data from the Active Bacterial Core Surveillance program show a reduction in the incidence of invasive infections caused by the serotypes contained in PCV-7 in practically all segments of the population (Table IV). The incidence of infections caused by the other serotypes increased slightly in certain groups, but at the moment the replacement of the vaccination strains is far from complete (Cynthia Whitney, personal communication).

Table IV: Decrease in incidence of invasive pneumococcal infections caused by the serotypes contained in PCV-7, between 1998-1999 and 2003

Age group	Decrease %	CI 95%
<2 months	-50%	-81% to +16%
2 months to 23 months	-96%	-97% to -94%
5 years to 17 years	-54%	-68% to -33%
20 years to 39 years	-68%	-74% to -60%
65 years and over	-65%	-69% to -59%

CI 95% = 95% confidence interval

Source: CDC, unpublished data

The prevalence of antibiotic-resistant strains is particularly high among the serotypes contained in PCV-7 and, in the United States, the frequency of invasive infections caused by strains not sensitive to penicillin decreased by 35% between 1999 and 2001 (Whitney et al. 2003). However, recent data suggest an increase in the circulation of antibiotic-resistant clones belonging to serotypes which do not appear in PCV-7 (Messina et al. 2004)

4.4 GROUPS AT HIGH RISK OF INFECTION

The medical conditions associated with a high risk of pneumococcal infection which currently justify the free provision of PCV-7, in Quebec, are: sickle-cell anemia, congenital or acquired asplenia, splenic dysfunction, congenital immunodeficiencies, diseases associated with immunosuppressive treatment or radiotherapy, chronic renal insufficiency, chronic cardiac and pulmonary diseases, diabetes mellitus, meningeal fistula, the presence of a cochlear implant and

certain congenital metabolic diseases. Most of these conditions are associated with immunological anomalies which may result in a less good response to PCV-7 (NACI 2002). Premature birth is also associated with a high risk of infection, but the immune response to PCV-7 is equivalent to that observed in infants born at term, and no failure was noted among the premature infants vaccinated in the Kaiser Permanente randomized test (Shinefield et al. 2002). In Italy, where a three-dose schedule is used (at 3, 5 and 11 months), the immune response in a group of premature infants was equivalent to that observed in infants born at term (Esposito et al. 2004). No published studies on the immunogenicity or effectiveness of PCV-7 in native populations in Canada exist.

4.5 SAFETY

The results of the post-marketing surveillance studies and randomized tests in the United States demonstrate that PCV-7 is very safe and that the side effects resulting from a third or fourth dose of vaccine are generally minor (Wyeth-Ayerst Canada Inc. 2001; Eskola et al. 2004; Wise et al. 2004). This argument will therefore be of little importance in the decision that must be made.

5 IMMUNIZATION STRATEGIES

To achieve maximum reduction in the costs of a new program, PCV-7 must be administered at the same time as other vaccinations that have already been scheduled. Knowing that the protection conferred by a single dose of PCV-7 is insufficient for this option to be followed, the four schedules that can be envisioned are presented in Table V.

Table V: Possible schedules for administration of PCV-7 in Quebec

Schedules	2 months	4 months	6 months	12 months	18 months
Regular vaccines	DTaP-IPV-Hib	DTaP-IPV-Hib	DTaP-IPV-Hib	MMR MenC-Con	DTaP-IPV-Hib MMR
PCV-7 4 doses	PCV-7	PCV-7	PCV-7	PCV-7	
PCV-7 3 doses	PCV-7	PCV-7	PCV-7		
PCV-7 3 doses bis	PCV-7	PCV-7		PCV-7	
PCV-7 2 doses	PCV-7	PCV-7			

It should be mentioned that immunization for varicella (one dose) should be offered as early as the age of 12 months, although this vaccine is not yet included in the regular schedule in Quebec. Moreover, immunization for influenza in the fall is now recommended for all infants between 6 and 23 months, with two doses to be administered in the first year and a single dose thereafter.

6 PROGRAM COSTS AND BENEFITS

To compare the advantages and disadvantages of different schedules for the routine immunization of children, a simulation model was developed, based on the one created for assessing PCV-7 cost-effectiveness ratios in Canada (De Wals et al. 2003). The perspective chosen is that of a child presenting no immune deficiency who is offered 2, 3 or 4 doses of PCV-7 following the schedules indicated in Table V. Only invasive infections were considered and the specific incidence rates by age are those estimated for Canada (Petit et al. 2003). It was assumed that the incidence rate at the age of 4 and 5 months was equal to two-thirds the rate between 6 and 11 months and that the incidence rate at the age of 2 and 3 months was equal to one-third the rate between 6 and 11 months. The rates of protection against invasive infections caused by the serotypes contained in PCV-7 were determined by experts on the basis of the results of the randomized test in the United States (Black et al. 2000) and those of the CDC case-control study (CDC, unpublished data). The effectiveness rates measured in the case-control study were adjusted in a manner proportional to that measured in the randomized test, which is the reference. It was considered necessary to wait for 2 weeks for a dose of vaccine to become effective. On the basis of the results of the immunogenicity study in the United Kingdom (Goldblatt et al. 2004), the same protection was conferred with a booster dose given after 2 or 3 doses at the time of the primary vaccination. On the basis of the preliminary data on the evolution of the protection conferred by serogroup C conjugate meningococcal vaccine in Quebec, it was assumed that the effectiveness of PCV-7 decreased by 3% each year, with the decrease commencing earlier if the number of doses was smaller and no booster dose was given. Thus the decrease in effectiveness starts at the third birthday in two scenarios, at the second birthday in the third scenario and at the first birthday in the last scenario. The effectiveness rates used in the model are indicated in Table VI.

Table VI: Rates (%) of protection against invasive infections caused by the serotypes of *S. pneumoniae* included in PCV-7, as a function of different vaccination strategies, in the simulation model

Vaccination strategy	Age category											
	2-3mo	4-5mo	6-11mo	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr	8 yr	9 yr
2-4-6-12 months	50.25	85.23	92.50	97.40	97.40	94.40	91.40	88.40	85.40	82.40	79.40	78.40
2-4-6 months	50.25	85.23	92.50	92.50	89.50	86.50	83.50	80.50	77.50	74.50	71.50	68.50
2-4-12 months	50.25	85.23	91.30	97.40	97.40	94.40	91.40	88.40	85.40	82.40	79.40	76.40
2-4 months	50.25	85.23	91.30	88.30	85.30	82.30	79.30	76.30	73.30	70.30	67.30	64.30

Without vaccination, the risk of invasive infection for all serotypes combined, for a healthy child between the age of 2 months and his tenth birthday, is approximately 250 per 100 000, or 1 case per 400 children (Table VII). The probability of death through invasive infection is 1 in 25 000. To calculate the effect of vaccination, the protection rate conferred by PCV-7 for each age category and the proportion of invasive strains belonging to the serotypes included in the vaccine were taken into account (INSPQ 2004). The residual morbidity and mortality for each schedule are related to morbidity and mortality in the absence of any vaccination to calculate the effectiveness rate. The most effective schedule is the one involving 4 doses of vaccine, but the differences with the two- or three-dose schedules are small.

Table VII: Residual morbidity and mortality by invasive pneumococcal infection, as a function of different vaccination strategies

Risk of invasive pneumococcal infection†	No vaccine	2-4-6-12 months	2-4-6 months	2-4-12 months	2-4 months
Meningitis	21.9	5.1	5.6	5.3	6.0
Bacteremia with hospitalization	141.0	30.7	36.2	31.1	40.1
Bacteremia without hospitalization	86.4	18.8	22.2	19.0	24.6
All invasive infections	249.2	54.7	64.1	55.4	70.8
Death	4.2	0.9	1.1	1.0	1.2
Program effectiveness					
Reduction in morbidity and mortality		78.1%	74.3%	77.8%	71.6%

† Cumulative risk between the ages of 2 months and 9 years, per 100 000.

For analysis of the direct and indirect costs of vaccination, a breakdown was done between those covered by the public health-care system and those borne by families. With a vaccine purchased at a unit cost of $70 and an administration cost of about $8 per dose ($7 for the health-care system and $1 for families), immunization of one child costs over $300 for the 4-dose schedule and the costs are reduced proportionally with a reduced number of doses (Table VIII).

Table VIII: Cost per individual immunized for the different vaccination strategies

Cost	2-4-6-12 months	2-4-6 months	2-4-12 months	2-4 months
for families	$5	$4	$4	$2
for the health-care system	$308	$231	$231	$154
for society	$313	$235	$235	$157

After actualization of the costs and benefits at the rate of 3% per year, each case of invasive infection which is avoided costs $75 000 in the most efficient scenario and nearly $150 000 in the least profitable one (Table IX). In 1992, Laupacis et al. proposed a threshold of $100 000 per quality-adjusted life-year to distinguish socially acceptable interventions (Recommendation C) from those which are difficult to justify (Recommendation D). After adjustment for inflation, the threshold today is $125 000. The 2-dose schedule meets this condition and the others exceed this threshold. However, taking account of a reduction in the cost of otitis treatment would significantly improve the profitability of the programs. In the study carried out for a 4-dose program in Canada, the societal cost, including gains in productivity and the benefits associated with prevention of non-invasive infections, was $116 000 per quality-adjusted life-year, with variability of between $8 000 and $174 000 (De Wals et al. 2003). By way of comparison, a varicella vaccination program, with a vaccine purchase price of $35 per dose, is economically beneficial for society and neutral for the health-care system (Brisson et al. 2002; Getsios et al. 2002). For an immunization program using one dose of serogroup C conjugate meningococcal vaccine given at the age of 12 months and purchased for $50, the cost-utility ratio would be $42 000 per quality-adjusted life-year, in the basic scenario (De Wals et al. 2004). At present, the cost of this vaccine is only half that figure.

Table IX: Cost-effectiveness indices of the different vaccination strategies

Cost-effectiveness index §	2-4-6-12 months	2-4-6 months	2-4-12 months	2-4 months
Cost per case* prevented	$149 122	$114 916	$109 324	$ 75 755
Cost per death prevented	$8 812 070	$6 753 585	$6 465 417	$4 438 882
Cost per year of life gained	$288 057	$220 311	$211 363	$144 669
Cost per quality-adjusted life-year	$260 235	$198 410	$191 041	$130 066

§ Net cost for society, with an actualization rate of 3% per year.
* Invasive pneumococcal infection.

On the basis of the above data, it is possible to calculate the incremental costs and benefits of the 4-dose schedule in relation to the other three schedules. Thus moving from a 2-dose program to a 4-dose program makes it possible to avoid some 16 new cases of invasive infection in a cohort of 100 000 infants, but the additional cost is $15.65 million for society, which gives an incremental cost of $964 000 per additional case avoided (Table X). Moving from the most effective 3-dose program (at 2, 4 and 12 months) to a 4-dose program, the incremental costs become astronomical: less than one additional case avoided for a difference of $7.83 million, which amounts to an investment on the order of $12 million for each additional invasive infection prevented, or $563 million per death avoided.

Table X: Incremental cost-effectiveness indices of the reference strategy using 4 doses of vaccine, in relation to the strategies using a reduced number of doses

Cost-effectiveness indices§	2-4-6-12 months vs 2-4-6 months	2-4-6-12 months vs 2-4-12 months	2-4-6-12 months vs 2-4 months
Cost per additional case* prevented	$823 361	$11 723 553	$964 145
Cost per additional death prevented	$54 568 400	$562 737 690	$62 904 815
Cost per year of life gained	$1 869 893	$18 065 906	$2 135 324
Cost per quality-adjusted life-year	$1 822 733	$14 679 345	$2 057 615

§ Net cost for society, with an actualization rate of 3 % per year.
* Invasive pneumococcal infection

The results of these economic results are still tentative, for the working hypotheses must still be validated by experts outside Quebec. Sensitivity calculations will also be carried out in order to test the soundness of the model. Finally, it is expected that analyses from a populational perspective will be done, taking into account the vaccination coverage which can be predicted with different schedules, group immunity and, possibly, cross protection against the serotypes related to those appearing in PCV-7 and a certain level of replacement by strains not appearing in the vaccine. In any event, inclusion of group immunity in the model will have the effect of reducing the differences in populational effectiveness between the different schedules.

Scenarios including catch-up measures for children over 2 months and under 5 years of age were not assessed. That had been done for a 4-dose program and a catch-up following the recommendations of the NACI (2002). The cost-effectiveness indices of catch-up in different segments of the target population were less favorable than those of the basic program (De Wals et al. 2003). The same would be true for catch-up programs modified on the basis of a reduced number of doses in the basic schedule.

7 PROGRAM ACCEPTABILITY

A universal vaccination program against infant pneumococcal infections is demanded by numerous health-care professionals who are often helpless spectators in the face of the damage caused by the most serious infections, namely septicemia and meningitis. The seriousness of the disease is not perceived by everyone, certain vaccinators in particular. A survey carried out on a sample of students and adults in the Sherbrooke area, in 2001, indicated very strong support for introducing a meningitis vaccine, but much less enthusiasm for a pneumonia vaccine (De Wals et al. 2002). This observation will have to taken into account in the information campaign which must accompany the start-up of the new program, as well as in the information communicated to parents when the vaccination is given.

The problem of multiple injections deserves special attention. As indicated in Table V, introduction of PCV-7 into the regular schedule will translate into an increased number of visits involving administration of two doses, or even three or four doses of vaccine, when the varicella vaccine is administered at 12 months. The availability of a combined measles-rubella-mumps-varicella vaccine would certainly reduce the scope of the problem. In Quebec there is reluctance about administering several vaccines per injection in the same visit, although the practice is routine in the United States. It will therefore be necessary to provide adequate information for parents, mentioning the safety of simultaneous multiple injections compared to deferred injections, the risk of disease associated with delayed administration of a vaccine, and the inconvenience of making another appointment. It is also crucial to provide information and training programs for the vaccinators who will have to manage the administration of three or four vaccines in a single visit.

The reservations which parents and vaccinators have about multiple injections can lead to two harmful consequences: delaying of certain vaccinations to a later age, and a vaccination coverage rate lower than what is generally observed for basic vaccinations of children, which is over 90% (Nounawon et al. 2001; Guay et al. 2004). A priori, the vaccination rates with the recommended number of doses will be higher with 2-dose schedules (at 2 and 4 months) and 3-dose schedules (at 2, 4 and 6 months) than with 3-doses schedules (at 2, 4 and 12 months) and 4-dose schedules (at 2, 4, 6 and 12 months), as the 12-month vaccination visit is more often omitted than the visits between 2 and 6 months. However, partially vaccinated children should contribute to and benefit from group immunity.

8 PROGRAM FEASIBILITY

The main obstacle to implementing an immunization program using PCV-7 is its cost. We estimated the annual costs of utilization of the resources (and not the additional expenditures) of different schedules for the public sector, assuming a cohort of 72 500 births in Quebec, 5% of them being individuals at a high risk of infection who must receive 4 doses of vaccine. On the basis of the vaccination coverage data available in Quebec (Nounawon et al. 2001; Guay et al. 2004), coverage is estimated at 95% for vaccinations at 2 and 4 months, 93% for vaccination at 6 months and 90% for vaccination at 12 months. The probable price of the vaccine is on the order of $70 per dose and we assume that 5% of the doses purchased will not be used. The cost of administering the vaccine and managing the program, at all levels, is estimated at $7.05 per dose on the average, for the public sector. The results in Table XI indicate a total cost of approximately $22 million per year for a 4-dose program. A 3-dose program will cost approximately $17 million and a 2-dose program approximately $12 million. When implementing the program, it is necessary to add the cost of the public promotion campaign, information for health-care professionals and training for vaccinators. If an active catch-up campaign is organized during the first year for infants over 2 months old, an additional cost will have to be provided for. If catch-up is provided only on demand, an additional cost must also be anticipated, but the amount in that case is more difficult to estimate. Finally, a stronger surveillance system and evaluative studies will also have to be funded.

Table XI: Number of doses to be purchased and administered and annual cost of the program for the public sector, by vaccination schedule selected

Schedule	Doses 2 months	Doses 4 months	Doses 6 months	Doses 12 months	Doses to be administered	Doses to be purchased	Purchase cost ($)	Cost of administration ($)	Total cost ($)
2, 4, 6, 12 months	68 875	68 875	67 425	65 250	270 425	283 946	19 876 238	1 906 496	21 782 734
2, 4, 6 months	68 875	68 875	67 425	3 263	208 438	218 859	15 320 156	1 469 484	16 789 641
2, 4, 12 months	68 875	68 875	3 371	65 250	206 371	216 690	15 168 287	1 454 917	16 623 204
2, 4 months	68 875	68 875	3 371	3 263	144 384	151 603	10 612 206	1 017 905	11 630 111

We are of the view that most general practitioners and pediatricians will be favorable to a new program of universal vaccination against pneumococcus. However, some physicians might be tempted to follow the schedule recommended by the manufacturer should a program using a reduced number of doses be set up. This practice could be documented by monitoring the ratio of PCV-7 orders to MMR or DTaP-IPV-Hib. In the CLSCs, reluctance about implementing a new vaccination program is to be expected in the current organizational and budgetary context. Allocation of additional resources for setting up and carrying out this new program would certainly be a useful measure.

When a routine immunization program for nursing infants is implemented, the question of catch-up arises. If we wish to carry out active catch-up initiatives for a short period, it will be necessary to conduct a particularly intense promotional campaign. Additional visits will be necessary, which will translate into great organizational difficulties and high costs, but without any guarantee that the coverage rate will be satisfactory. Moreover, denying the vaccine to children who might benefit from it would be difficult for some parents to accept, and passive catch-up measures, on demand, could be a compromise solution.

9 CAPACITY TO ASSESS PROGRAM IMPACT

Assessment of any new health program is a duty to the public and the taxpayer, especially as there is uncertainty about the program's actual impact. Even before implementation of a PCV-7 immunization program, assessment of the program must be planned for. The components of such an assessment are discussed below.

Close monitoring of stock management and vaccine utilization must be set up in all regions in order to minimize waste and maximize rational utilization of the vaccines on the basis of the indications. The high-risk groups that are to receive four doses must be clearly defined.

Studies must be undertaken in regions having vaccination records in order to study the evolution of the coverage rates for PCV-7 and the other vaccines in the regular schedule. The phenomenon of postponement of vaccinations to later visits and a later age must be tracked. In addition, surveys must be carried out periodically, using representative samples of the Quebec population to estimate the evolution of vaccination coverage rates.

Surveillance of the disease by laboratories must be strengthened and, ideally, any strain de *S. pneumoniae* isolated from a normally sterile sample from an child under 6 years of age should be sent to the Quebec Public Health Laboratory so that the evolution of serotype distribution and resistance to antibiotics can be monitored.

Any case of invasive pneumococcal infection must be reported to the appropriate Public Health Department. Any case in children under the age of 5 years must be investigated in order to confirm the bacteriological diagnosis, identify the clinical outcome, determine the person's vaccination status (complete history of vaccination against pneumococcus and influenza) and identify certain factors relating to the risk of disease and resistance to antibiotics. In addition, a survey of controls must be carried out in order to measure the effectiveness of PCV-7 as a function of the number of doses, age at administration of the first dose and time elapsed since administration of the last dose.

Finally, it will be necessary to carry out an epidemiological and economic impact study to ensure that the predictions generated by the simulation model have in fact been realized. Such a study can be based on surveillance data and exploitation of populational databases on death, hospitalization, medical visits and prescriptions of medications in Quebec.

10 RESEARCH QUESTIONS

The research questions in the field of prevention and control of infections caused by *S. pneumoniae* are numerous (Eskola et al. 2004). The main question relates to the identification of biological markers of immunity which permit licencing of new vaccines without having to carry out controlled clinical tests, which have been difficult to justify since an effective vaccine for young children has existed. The other question which absolutely must be dealt with is measurement of the populational effectiveness of a universal vaccination program using a reduced number of doses, should this option be selected, in Quebec.

11 PROGRAM EQUITY

At the present time, the accessibility of PCV-7 immunization is problematical. A survey done in Montérégie in 2004 indicates that PCV-7 is available in 96% of pharmacies, at prices ranging between $85 and $196 per dose (Cayer et al. 2004). Some CLSCs, meanwhile, administer the vaccine for a fee and the vaccine is available on the spot; others offer the service for a fee, but the vaccine must be purchased in a pharmacy (sometimes there is a strict requirement that the pharmacy ensure delivery of the vaccine); and, finally, some CLSCs offer no service. The distribution of private clinics which offer the vaccine is also very heterogeneous geographically, and in some areas there is no facility offering PCV-7 vaccination. At present the cost of PCV-7 and its administration must be borne by families, and economic status influences the decisions of parents. A free vaccination program would have the effect of reducing social inequalities in Quebec. In the United States, the introduction of PCV-7 into federal programs resulted in a reduction in the discrepancy in the incidence of invasive pneumococcal infections between Whites and Blacks (Flannery et al. 2004).

12 ETHICAL CONSIDERATIONS

Health professionals who have to propose a vaccine, although they know full well that some parents will not be able to purchase it, are confronted with an ethical problem which would be solved by a universal vaccination program in Quebec. From a social standpoint, adoption of a program using a reduced number of doses would save resources that could be allocated to another health program providing greater health benefits than those obtained through additional doses of PCV-7.

13 LEGAL CONSIDERATIONS

In Canada, companies that insure health professionals recommend to their members that they inform all parents about the vaccines recommended by the NACI, even if some of these are not included in the free vaccination programs offered by the provinces and territories. In the event that an immunization program using a reduced number of doses of PCV-7 is set up, we must ensure that it is considered to be a standard of practice. In Quebec, a recommendation of the Department of Health and Social Services, supported by an opinion from the Quebec Immunization Committee, and a schedule included in the Quebec Immunization Protocol, can be considered a standard of practice for vaccinators and guarantee them immunity from prosecution. A favorable opinion from the National Advisory Committee on Immunization would certainly strengthen the arguments of the defence.

14 PROGRAM CONFORMITY

As in the United States, routine immunization programs using 4 doses of PCV-7 have been, or soon will be, implemented in several Canadian provinces. Quebec is the only province to have begun considering the appropriateness of a program using a reduced number of doses. In Australia, a free and universal program based on 3 doses at the ages of 2, 4 and 6 months has been announced; it will start on 1 January 2005 (Australian Government 2004). In Italy, a schedule of three doses offered at the ages of 3, 5 and 11 months respectively is used (Esposito et al. 2004).

15 POLITICAL CONSIDERATIONS

From a political standpoint, the announcement of a new prevention program for children which could reduce certain social inequalities can only be beneficial. Public opinion should be generally favorable to the adoption of a program using a reduced number of doses, to the extent that the arguments justifying such a decision are clearly explained and there is a broad consensus in the scientific and professional communities on such a decision.

16 CONCLUSION

At present, the accessibility of 7-valent pneumococcal conjugate vaccine is limited in Quebec, and that is a source of inequity. A public vaccination program aimed at all children should be implemented as quickly as possible. Considering all the immunogenicity and effectiveness data available, the Quebec Immunization Committee considers that a minimum of 2 doses of PCV-7 at an early age is necessary in order to ensure a satisfactory level of short-term protection. The benefit provided by a third dose of vaccine at the age of 6 months seems modest. A booster dose given at the age of one year results in a good anamnestic response which can significantly prolong protection time and amplify a program's impact on transmission of the strains of *S. pneumoniae* belonging to the serotypes which appear in PCV-7. Moreover, the experience acquired with other conjugate polysaccharide vaccines must be taken into account in the decision. In the United Kingdom, a program of immunization against *Haemophilus influenzae* Type b began in 1992. Three doses of conjugate vaccine were offered at the ages of 2, 3 and 4 months respectively, with no booster shots. After a few years of complete success, the number of cases increased among vaccine recipients and a catch-up campaign with a fourth dose was implemented in 2003 (Trotter et al. 2003). This phenomenon has not been observed in countries which offer a booster dose in the second year. Again in the United Kingdom, a loss of protection was observed in children who had received three doses of conjugate meningococcal vaccine on the regular schedule (at 2, 3, and 4 months), whereas a high degree of protection still remained as much as 4 years after a dose of vaccine received after the age of 12 months (Trotter et al. 2004). It is not impossible for an immunization schedule based on four doses of PCV-7 to be slightly more effective than a three-dose schedule, but the difference in terms of cases prevented is certainly very small, while the additional cost in large, which translates into incremental cost-effectiveness indices which are difficult to accept. The savings generated by a three-dose schedule could be used to fund other prevention programs offering much greater health benefits than those associated with the fourth dose of PCV-7. For all these reasons, the majority of the members of the QIC consider that the 2-, 4- and 12- month schedule is the most worthwhile option for a universal program of vaccination for pneumococcal infections in children in Quebec, although at the same time they recognize the difficulties associated with multiple injections in a single visit.

For children who have a medical condition possibly associated with altered immune function and are liable to respond less well to PCV-7, maintenance of a four-dose schedule is recommended. In the northern regions, otitis is a particular problem and access to care is limited for the treatment of infections that require hospitalization. For operational reasons, the schedule implemented in Nunavik includes four doses of PCV-7 offered at the ages of 2, 4, 6 and 18 months respectively. In such a context, maintenance of the present schedule is preferable. Should other vaccines be introduced, revision of the schedule will probably be necessary.

In the event of adoption of a basic schedule including 3 doses, offered at the ages of 2, 4, 6, and 12 months respectively, the catch-up schedule could be as follows: 2 doses separated by an interval or 2 months or more and a booster between 12 and 18 months for infants 3 to 11 months of age and 2 doses separated by an interval of 2 months or more for infants 12 to 23 months of age. No data on the effectiveness of a single dose administered after the age of 2 years exist and, in addition, the incidence of invasive infections decreases rapidly after that age.

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