COMITÉ SUR L'IMMUNISATION DU QUÉBEC

HPV Vaccination in Québec: Knowledge Update and Expert Panel Proposals

INSTITUT NATIONAL
DE SANTÉ PUBLIQUE
DU QUÉBEC

Québec

Advisory Report of the Comité sur l'immunisation du Québec and the HPV Ad Hoc Scientific Committee

HPV Vaccination in Québec: Knowledge Update and Expert Panel Proposals

Direction des risques biologiques
et de la santé au travail

July 2012

Institut national de santé publique Québec

AUTHORS

Comité sur l'immunisation du Québec

HPV ad hoc scientific committee

EDITORIAL COMMITTEE

Ève Dubé, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Vladimir Gilca, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Patricia Goggin, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Chantal Sauvageau, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

ACTIVE CIQ MEMBERS

François Boucher, Département de pédiatrie, Université Laval, Centre hospitalier universitaire de Québec, Pavillion CHUL (CHUQ-CHUL) and Centre de recherche du Centre hospitalier universitaire de Québec

Nicole Boulianne, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Alex Carignan, Département de microbiologie et d'infectiologie, Université de Sherbrooke

Gaston De Serres, Département de médecine sociale et préventive, Université Laval, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Philippe De Wals, Département de médecine sociale et préventive, Université Laval, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Charles Frenette, Department of Microbiology-Infectious Diseases and Infection Prevention, McGill University Health Centre

Vladimir Gilca, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Maryse Guay, Département des sciences de la santé communautaire, Université de Sherbrooke et Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Caroline Quach, Montréal Children's Hospital, Department of Pediatrics et McGill University

Chantal Sauvageau, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Bruce Tapiéro, Service des maladies infectieuses, Centre hospitalier universitaire Sainte-Justine

CIQ LIAISON MEMBERS

Lucie Bédard, Ordre des infirmières et infirmiers du Québec et Agence de la santé et des services sociaux de Montréal/Direction de santé publique

Dominique Biron, Fédération des médecins omnipraticiens du Québec, Clinique pédiatrique Sainte-Foy

Marjolaine Brideau, Association québécoise d'établissements de santé et de services sociaux, Centre de santé et de services sociaux de Thérèse-de-Blainville

Ngoc Yen Giang Bui, Comité consultatif québécois sur la santé des voyageurs, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Marc Lebel, Association des pédiatres du Québec et Centre hospitalier universitaire Sainte-Justine

Céline Rousseau, Association des médecins microbiologistes infectiologues du Québec et Hôpital Sainte-Justine

Dominique Tessier, Collège québécois des médecins de famille et Clinique médicale du Quartier Latin

Louise Valiquette, Representative of the Table de concertation nationale en maladies infectieuses et Agence de la santé et des services sociaux de Montréal/Direction de santé publique

LEGAL DEPOSIT – 3rd QUARTER 2013
BIBLIOTHÈQUE ET ARCHIVES NATIONALES DU QUÉBEC
LIBRARY AND ARCHIVES CANADA
ISBN: 978-2-550-65702-6 (FRENCH PDF)
ISBN: 978-2-550-68757-3 (PDF)

CIQ EX-OFFICIO MEMBERS

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

Marc Dionne, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Monique Landry, Direction de la protection de la santé publique, Ministère de la Santé et des Services sociaux

Bruno Turmel, Direction de la protection de la santé publique, Ministère de la Santé et des Services sociaux

MEMBERS OF THE INSPQ HPV AD HOC SCIENTIFIC COMMITTEE

Paul Brassard, Royal Victoria Hospital et McGill University

Marc Brisson, Centre de recherche FRSQ, Centre hospitalier *affilié* universitaire de Québec, Département de médecine sociale et préventive, Université Laval

Michel Couillard, Laboratoire de santé publique du Québec, Institut national de santé publique du Québec

François Coutlée, Hôpital Notre-Dame du Centre hospitalier de l'Université de Montréal (CHUM)

Ève Dubé, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Eduardo Franco, McGill University, Department of Oncology, Epidemiology and Biostatistics

Patricia Goggin, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Anne-Marie Grenier, Agence de la santé et des services sociaux de la Mauricie et du Centre-du-Québec et Ministère de la Santé et des Services sociaux

Bruno Leclerc, Université du Québec à Rimouski

Marie-Hélène Mayrand, Institut national de santé publique du Québec et Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM)

Lina Noël, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Zeev Rosberger, Jewish General Hospital et McGill University

Michel Roy, Hôtel-Dieu de Québec, Centre hospitalier universitaire de Québec (CHUQ)

Philippe Sauthier, Hôpital Notre-Dame, Centre hospitalier de l'Université de Montréal (CHUM)

Jocelyne Sauvé, Agence de la santé et des services sociaux de la Montérégie

PERSONS CONSULTED

Horacio Arruda, Ministère de la Santé et des Services sociaux

Marc Steben, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Sylvie Venne, Ministère de la Santé et des Services sociaux

PROFESSIONALS WHO SUPPORTED THE DEVELOPMENT OF THIS ADVISORY REPORT

Marie-Claude Boily, Centre de recherche FRSQ, Centre hospitalier *affilié* universitaire de Québec
Department of Infectious Disease Epidemiology, Imperial College, London, UK

Fannie Defay, Unité de recherche en santé publique, Centre hospitalier universitaire de Québec (CHUQ)

Mélanie Drolet, Centre de recherche FRSQ, Centre hospitalier *affilié* universitaire de Québec
Département de médecine sociale et préventive, Université Laval

Marie-Claude Gariepy, Unité de recherche en santé publique, Centre hospitalier universitaire de Québec (CHUQ)

Marilou Kiely, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Jean-François Laprise, Centre de recherche FRSQ, Centre hospitalier *affilié* universitaire de Québec

France Lavoie, Unité de recherche en santé publique, Centre hospitalier universitaire de Québec (CHUQ)

Talia Malagon, Centre de recherche FRSQ, Centre hospitalier *affilié* universitaire de Québec
Département de médecine sociale et préventive, Université Laval

Najwa Ouhoummane, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Andrea Trevisan, Laboratoire de santé publique du Québec (LSPQ), Institut national de santé publique du Québec

Nicolas Van de Velde, Centre de recherche FRSQ, Centre hospitalier *affilié* universitaire de Québec
Département de médecine sociale et préventive, Université Laval

LAYOUT

Marie-France Richard, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

ACKNOWLEDGEMENTS

With respect to the survey conducted during the development of this advisory report (see Section 9.5), we would like to thank all those who took the time to fill out the questionnaire, as well as the Fédération des médecins omnipraticiens du Québec (FMOQ), the Association des pédiatres du Québec (APQ) and the Association of Obstetricians and Gynecologists of Québec (AOGQ) for their support during the data collection process. We would also like to thank Josiane Rivard for her invaluable technical assistance. The expenses related to the survey and to the expert panel meetings were covered by the Québec Ministry of Health and Social Services (MSSS).

Note

This document is an English translation of the French advisory report entitled *La vaccination contre les VPH au Québec : mise à jour des connaissances et propositions du comité d'experts.* Institut national de santé publique du Québec. Juillet 2012. 148 p.

Section 14 is based on the following report: Laprise JF, Drolet M, Van de Velde N, Malagon T, Boily MC, Brisson M. *Efficacité populationnelle et coût-efficacité des programmes de vaccination contre les VPH au Québec* (Population-level effectiveness and cost-effectiveness of HPV vaccination programs in Québec). This French version of the report was submitted to the Institut national de santé publique du Québec (INSPQ) in April 2012. The English version of the section 14 has not been reviewed by the authors.

A translation key for all figures is provided at the end of this document.

The authors thank the Public Health Agency of Canada for the English translation.

BACKGROUND AND SUMMARY

BACKGROUND

In April 2008, the Québec Ministry of Health and Social Services (MSSS) announced the implementation of a human papilloma virus (HPV) vaccination program for the fall of 2008. This announcement followed the October 2007 publication of the report of the Comité sur l'immunisation du Québec (CIQ) entitled *Prevention by Vaccination of Diseases Attributable to the Human Papillomavirus in Québec*. At the time the report was written, only the quadrivalent vaccine was approved for use in Canada. The report did not make a direct comparison between the quadrivalent vaccine (Gardasil®) and the bivalent vaccine (Cervarix™). In February 2008, the CIQ wrote a second report entitled *Advice of the Institut national de santé publique du Québec on Human Papillomavirus Vaccines*, which gave an affirmative answer to the question: "Do the two HPV vaccines have an equivalent ability to achieve the stated goal of the immunization program, which is to reduce the incidence of and mortality associated with cervical cancer?"

Since the publication of these two documents, approval of the quadrivalent vaccine has been extended to boys and men aged 9-26 and to women aged 27-45, and the bivalent vaccine has been approved for girls and women aged 10-25. Consequently, in a letter dated June 30, 2010, the MSSS asked the Institut national de santé publique du Québec (INSPQ for advice on three questions:

1) Should the objective of the human papillomavirus (HPV) vaccination program as recommended by the CIQ, namely to reduce the morbidity and mortality associated with cervical cancer, be maintained (or expanded)?
2) Depending on the answer to the previous question, can the quadrivalent and bivalent vaccines be considered equivalent in their ability to achieve the health objective?
3) As a corollary, what does the INSPQ recommend concerning the inclusion of boys in the HPV vaccination program?

The issue of the prevention of diseases attributable to HPV extends beyond the scope of infectious diseases traditionally covered by vaccination. This is why the CIQ again worked with an expanded expert panel from the fields of gynecology, cancer control and sexually transmitted infections.

Method and phases of the process

First, a committee drafted a synthesis of the knowledge that has become available since August 15, 2007, the date when the literature review for the detailed report of October 2007 was completed; this synthesis was presented using the model developed by Erickson and colleagues.[1] A review of the published and unpublished literature and its references (for example, the proceedings of the main conferences about HPV) was carried out by individuals considered experts in each subject area. The literature was analyzed and summarized by the person responsible for that subject area, and only the documents relevant to the questions

[1] Erickson LJ, De Wals P, Farand L. An analytic framework for immunization programs in Canada. *Vaccine* 2005;23:2470-6.

considered in this advisory report were included. For example, several articles on the acceptability of HPV vaccination in Asia and Africa have been published in recent years but have not been included here. In addition, special attention was paid to the methodology of the studies that were reviewed, and the editorial team endeavoured to make any necessary distinctions among them when appropriate.

In addition to reviewing what has been published elsewhere, specific data for Québec were compiled on the acceptability of vaccination among health care professionals, on population impact and on cost-effectiveness. Presentations and a working document were produced to support discussions at meetings of the CIQ (December 2010 and December 2011) and of the expanded committee (May 2011 and January 2012), which brought together more than 30 experts in diseases attributable to HPV. At these two meetings, presentations were made and specific issues were discussed. A round table was held in order to solicit the opinions of each committee member on the key issues. After the second meeting, an initial set of proposals (recommendations) was prepared by the editorial team. The wording of the proposals reflected the fact that consensus was not reached on certain issues. In those cases, the majority viewpoint was expressed. Following an e-mail consultation, the proposals that appear on pages IX-XI were approved by all the members of the expanded committee.

In addition, the INSPQ asked the members of its Ad Hoc Scientific Committee on HPV Vaccination, which includes the members of the CIQ, to declare any situations that might constitute a conflict of interest with respect to the subject of study. The Committee members were therefore required to complete a declaration of interest form in order to disclose any direct or indirect ties with private companies or public institutions whose products or activities are related to the field of HPV vaccination.

Contents of this advisory report

Following this Background and Summary section, the report updates the knowledge base, regrouped into four main areas: the burden of HPV-related diseases (sections 1 to 4); the characteristics of the available vaccines (sections 5 to 8); the acceptability, feasibility and ethical issues associated with HPV vaccination (sections 9 to 13); and the related economic analyses (section 14). Lastly, proposals/recommendations are presented and research avenues are suggested. The document concludes with appendices that summarize the interests declared by the committee members and provide a description of the studies on the acceptability of HPV vaccination.

SUMMARY

Burden of disease

The human papillomavirus (HPV) belongs to the *Papillomaviridae* family, which includes at least 100 genotypes affecting the skin and mucous membranes. Of these, about 40 affect the anogenital area in particular, and approximately 15 are oncogenic. Genotypes 16 and 18 are responsible for 70-76% of cervical cancer cases worldwide. Genotypes 6 and 11 are non-oncogenic but are responsible for most cases of condyloma (anogenital warts [AGW]).

HPV prevalence and incidence data are estimated on the basis of epidemiological studies and are better documented in women than men. HPV prevalence varies widely by geographic region, age, the selected subpopulation and HPV detection method. In women, the overall age-adjusted prevalence of genital infections worldwide is estimated at 11.7%. It peaks in young women aged 20-24 and declines subsequently with age. The risk of acquiring HPV infection is particularly high in the first few years after sexual activity begins. According to some estimates, more than 70% of sexually active women will contract an HPV infection at some time in their lives. Among men, the prevalence of genital infection is just as high, if not higher, but varies less with age.

HPV is usually transmitted sexually, and the risk of contracting the infection is largely determined by sexual behaviour, including the number of sexual partners. While the infection is common in the population, the majority of infections will clear spontaneously. A persistent infection increases the risk of progression to cancer, but this process takes many years, which explains why cervical cancer is rare before the age of 30 and practically non-existent before the age of 20. The precursor stages of cervical cancer can be detected by cytological screening (Pap test), and there are effective treatments for halting the progression to cancer. However, over half of cervical cancer cases are currently associated with inadequate screening.

A number of cancers are caused by HPV. In Québec, from 2004 to 2007, there were an average of 281 new cervical cancer cases and 69 deaths per year. HPV is also associated with a certain proportion of cancers of the anogenital area, including cancers of the anus (83%), vulva (66%), vagina (70%) and penis (49%). It is also found in cases of oropharyngeal cancer (47%) and, to a lesser extent, in cancers of the oral cavity (16%) and larynx (14%). HPV 16 is the genotype most frequently associated with these types of cancer.

When the proportion of cancers attributable to HPV and especially to genotypes 16 and 18 (as estimated from the data in the literature) is applied to those cancers associated with HPV[2] that were reported during the 2004-2007 period, the number of potentially vaccine-preventable cancer cases is 356 per year in women and 179 in men. Excluding cancers of the oral cavity and larynx (whose causal link with HPV infection is still under study), the number of potentially preventable cancers is 339 in women and 129 in men.

In estimating this clinical burden, one must also include the substantial resources allocated to cervical cancer screening. Over 1 million cervical cancer screening tests are performed every year in Québec, not to mention the resources devoted to the assessment of abnormal results and the treatment of precursor stages.

The non-oncogenic HPV types also contribute to the burden of disease. AGW, usually associated with genotypes 6 and 11, affect both men and women with peak incidence observed before the age of 30. In Canada, only Manitoba and British Columbia currently have population-based data on the incidence and prevalence of this disease, estimated from the number of medical visits for the condition. In Manitoba, women aged 20-24

[2] The term “cancers associated with HPV” refers here to a whole category, even though not all the cancer cases in this category are caused by HPV.

(5.7/1,000 person-years) and men aged 25-29 (4.6/1,000 person-years) had the highest rates. In British Columbia, between 1998 and 2006 the standardized incidence rate was 1.3/1,000 person-years among men and 1.2/1,000 person-years among women. Applying these data to the Québec population yields an estimated 14,000 cases of AGW diagnosed annually in Québec men and women.

Recurrent respiratory papillomatosis (RRP), which is also associated with genotypes 6 and 11, can affect both adults and young children. In Canada, the incidence of the juvenile form is estimated at 0.24 per 100,000 child-years among children under the age of 14 (there are approximately two new cases per year in Québec). While rare, the disease can lead to a high level of morbidity and repeated surgery in some individuals.

Vaccines

Immunogenicity

The two HPV vaccines approved for use in Canada have proven to be immunogenic in the short and medium term. Both vaccines are more immunogenic and better tolerated when administered in preadolescence and adolescence. Two doses of the bivalent or quadrivalent vaccine administered at 6-month intervals to individuals aged 9-14 induce antibody titres similar to or higher than those observed after three doses of vaccine administered to individuals aged 15-26 in whom clinical efficacy has been demonstrated. There are no important differences in vaccine immunogenicity between males and females of the same age. Most of the data from clinical studies conducted by the vaccine manufacturers are difficult to compare. Only one study directly compares the immunogenicity of the two vaccines, and it shows that the bivalent vaccine is more immunogenic for HPV 16, HPV 18 and certain other HPV types (HPV 31, HPV 33, HPV 45) closely related genetically to the two included in both vaccines. However, the quadrivalent vaccine induces additional immunity against HPV 6 and HPV 11, which are responsible for non-cancerous lesions associated with HPV (primarily AGW and RRP).

Efficacy

Vaccine efficacy data are limited to individuals aged 15 and over. In women, both vaccines have proven efficacious in preventing:

- cervical, vulvar and vaginal cancers and their precursors caused by HPV 16 and HPV 18, and
- cervical adenocarcinoma *in situ*.

In both males and females the quadrivalent vaccine is also efficacious in preventing AGW caused by HPV types 6 and 11 as well as anal cancers and their precursors caused by HPV 16 and HPV 18.

Approval of the vaccines for individuals under the age of 15 has been based exclusively on bridging immunogenicity studies.

Vaccine efficacy appears to decline with age at administration. There are two possible explanations for the decline in efficacy with age: 1) a weaker immune response and 2) a higher percentage of individuals who are infected before receiving the vaccine.

The duration of clinical vaccine efficacy as currently known is at least nine years in females and at least three years in males.

There are no head-to-head comparisons of the efficacy of the two vaccines. The study eligibility criteria, the point at which infections and lesions are counted, and the way in which the results are analyzed and presented are different for the two vaccines. In the medium term, some fairly similar cohort analyses show excellent efficacy of both vaccines against persistent infections and lesions due to the HPV types included in the vaccine. Both vaccines have also shown some degree of cross-protection. The existing data seem to show greater cross-protection after administration of the bivalent vaccine. The duration of protection against the vaccine HPV types and the duration of cross-protection are still unknown.

The population-level impact of immunization two to four years after implementation of a program with the quadrivalent vaccine has been reported for AGW. Ecological data from some sexually transmitted disease clinics in Australia show a decrease of up to 90% in the percentage of individuals with a diagnosis of AGW. While it is difficult to extrapolate these data to the general population, they do indicate the possibility that implementing a vaccination program with the quadrivalent vaccine will result in a considerable decrease in AGW within a relatively short period of time.

There have been relatively few studies on the efficacy of a reduced number of doses. However, the limited available data on the immunogenicity and efficacy of schedules that include only two doses are encouraging.

The efficacy of both HPV vaccines in reducing the number of cytological abnormalities and subsequent procedures has also been demonstrated and ranges from 20% to 33%.

It is plausible that both HPV vaccines protect against certain non-anogenital cancers associated with HPV 16 and HPV 18 and that the quadrivalent vaccine protects against RRP as well. However, there are currently no clinical data on the impact of vaccination on these diseases.

On the basis of the existing data, the two HPV vaccines approved for use in Canada are efficacious in the short and medium term, and both could be used in the publicly funded vaccination program. However, only the quadrivalent vaccine protects against AGW.

Safety

Both vaccines are well tolerated. Mild and moderate injection site reactions are apparently more frequent following administration of the bivalent vaccine. There is no increase in adverse reactions with the number of vaccine doses administered.

Acceptability, feasibility and ethical issues

Acceptability

Recent data show that the majority of both the general public and health care professionals favour the vaccination of girls aged 9-17. They also approve of vaccinating boys, as well as women aged 18-26. The cost of the vaccine is the greatest barrier, and a physician's recommendation is the most decisive factor in the acceptability of vaccination.

In Québec, in 2010-2011, HPV vaccine coverage rates in elementary grade 4 and Secondary III (grade 9) exceeded 75%, indicating high acceptability of vaccination among parents for their daughters and among teenaged girls.

The results of the survey of Québec health care professionals, while requiring cautious interpretation because of the low response rate, indicate significant interest in the vaccination of boys, although women aged 18-26 were selected as the first priority if the publicly funded vaccination program were expanded.

Feasibility

Organizing the delivery of vaccination services is a major challenge for any vaccination program aimed at women in the 18-26 age group, who generally cannot be reached through school-based programs. However, the vaccination of school-aged boys appears to be easier to achieve. Indeed, expanding HPV vaccination to the entire school population rather than targeting just girls could be done fairly easily. In both cases, it would be essential to devote more effort to informing and educating the public and health care professionals about the important role of vaccines in preventing diseases caused by HPV, and it can be assumed that vaccine coverage in boys would be comparable to that in girls.

Ethical issues

Several ethical issues have already been raised in connection with HPV vaccination. More issues will arise with approval of the bivalent vaccine for girls and women aged 10-25 and of the quadrivalent vaccine both for women over the age of 26 and for boys and young men aged 9-26.

First, the lack of a publicly funded HPV vaccination program aimed at women over the age of 18 and at young men raises ethical issues of social justice. As well, there are risks of stigmatization if, for epidemiological or logistical reasons, HPV vaccines were offered free of charge only to certain subgroups of the population (men who have sex with men [MSM] and HIV-positive individuals). Lastly, choosing the objective of the publicly funded vaccination program could raise the issue of whether it adheres to the principle of utility (cost/benefit).

Economic analyses

School vaccination for girls with the bivalent or quadrivalent vaccine is highly cost-effective, and the cost-effectiveness ratio of the quadrivalent vaccine continues to be lower than that of the bivalent vaccine in almost all the scenarios that have been analyzed, assuming that vaccine costs are equal.

In all the scenarios analyzed, the cost-effectiveness ratio of vaccinating only girls with the bivalent or quadrivalent vaccine is below the generally accepted Québec cost-effectiveness threshold. The existing vaccination program for girls is therefore considered cost-effective. In almost all these scenarios, the estimated cost-effectiveness ratio for the bivalent vaccine is higher than for the quadrivalent vaccine, assuming that vaccine costs are equal. The difference is mainly attributable to the burden of AGW prevented with the quadrivalent vaccine. The bivalent vaccine would therefore have to cost less than the quadrivalent vaccine in order for it to represent an economically worthwhile alternative to the quadrivalent vaccine.

Adding the vaccination of boys to the existing vaccination program for girls would likely not be cost-effective and would provide very few additional benefits to women and heterosexual men; most of the benefits would go to MSM.

The analyses predict that in heterosexual men, there will be a significant reduction in the burden related to diseases caused by HPV through the indirect protection (herd immunity) conferred on them by the vaccination of girls with the quadrivalent vaccine. Most of the benefits of the vaccination of boys would go to MSM, who presumably are unprotected by the vaccination of girls but who represent a small percentage of the male population. For all the scenarios considered, the economic analyses predict that adding the vaccination of boys to that of girls would result in cost-effectiveness ratios far higher than the generally accepted Québec threshold.

Proposals

The objective that most of the participants in the Ad Hoc Scientific Committee agreed on is the following:

Reduce the incidence, morbidity and mortality of cancers, precancerous lesions and other diseases associated with HPV.

The Committee believes that the available information on the immunogenicity and clinical efficacy of the quadrivalent HPV vaccine and the preliminary results of Phase IV studies in other countries demonstrate that the Québec program, consisting of routine vaccination of girls in grade 4 and a catch-up program up to the age of 18 with a quadrivalent vaccine, will be effective in reducing the burden of precancerous lesions and cancers attributable to HPV, as well as AGW, in the target population. The vaccine coverage currently achieved (± 80%) in girls is also expected to have a considerable indirect impact on the male heterosexual population, with respect to both AGW and certain cancers. Modelling results also indicate that the program will be cost-effective (< $20,000/quality-adjusted life-year [QALY]) on the basis of the standards generally accepted in Québec.

Replacing the quadrivalent vaccine (Gardasil®) with the bivalent vaccine (Cervarix™) would mean abandoning the goal of preventing diseases caused by HPV types 6 and 11, such as AGW and potentially laryngeal papillomatosis. However, the prevention of cancers would be slightly improved should the bivalent vaccine confer greater cross-protection against certain oncogenic types. Economic analyses conducted in Québec show that to be as cost-effective as the quadrivalent vaccine, the bivalent vaccine would have to cost considerably less. The

majority of the members of the Ad Hoc Scientific Committee expressed reservations about the possibility of abandoning protection against AGW (both in girls through direct protection and in boys through herd immunity). Abandoning such protection could also trigger negative reactions from health care professionals and the public. On the other hand, replacing the quadrivalent vaccine with the bivalent vaccine could minimize program costs should the bivalent vaccine prove to cost significantly less than the quadrivalent vaccine.

The efficacy of the quadrivalent vaccine in men has been well demonstrated. However, adding universal vaccination of preadolescents would have only a marginal impact on the male heterosexual population, as long as vaccine coverage in the female population is maintained. The major benefit of a free vaccination program for boys would be to reduce the burden of AGW and certain cancers in men who will later have sexual relations with men, because they will have been vaccinated at the time when vaccine efficacy is highest (i.e. before the start of sexual relations). However, at the current cost of the quadrivalent vaccine, extending the program to all preadolescent boys in order to provide more protection to a minority of them would not be cost-effective (> $180,000/QALY) according to generally accepted standards. A free vaccination program for all boys could be justified by political and equity considerations, primarily with respect to MSM, but not by arguments of significant epidemiological impact or efficiency of the program. In the event of a substantial reduction in the cost of the quadrivalent vaccine, such conclusions could change.

Extending the existing program in order to provide free vaccination to women aged 18 and over would probably have a limited impact on the burden of diseases caused by HPV in this population. The magnitude of the reduction is difficult to determine for each age group. Vaccine efficacy declines when vaccination takes place after the start of sexual activity. Approximately 50% of women aged 18-20 are already vaccinated, since they have been targeted by the catch-up program since 2008. Extending the existing program would be quite expensive, because three doses of the vaccine would have to be administered outside the school environment. The cost-effectiveness ratios of such an extension would definitely be less favourable than those achieved by the existing school-based program aimed at girls under the age of 18. There is also considerable uncertainty about the feasibility of such an addition to the program and the level of vaccine uptake that could be achieved.

The implementation of pilot projects for targeted vaccination of MSM could be explored, since free vaccination of all preadolescents is not an efficient strategy with the current cost of the vaccines. The scientific evidence suggests that the effectiveness of such a strategy, whereby the vaccine would in most cases be administered after the start of sexual relations, may be limited. Furthermore, the feasibility, acceptability and cost of such a program have not been carefully evaluated. Studies would have to be conducted to examine these aspects.

The vaccination of certain other population subgroups deemed at greater risk of acquiring HPV-associated diseases (e.g. Aboriginal people) or of experiencing complications (e.g. people with certain chronic diseases) could also be explored. A careful and specific analysis of this issue, which was not possible within the framework of this advisory report, should be understaken.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AGW	Anogenital warts
AIN	Anal intraepithelial neoplasia
AIS	Adenocarcinoma *in situ*
APC	Annual percent change
95% CI	95% confidence interval
CIN	Cervical intraepithelial neoplasia
CIQ	Comité sur l'immunisation du Québec (Québec immunization committee)
cLIA	Competitive Luminex based immunoassay
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FiTQ	*Fichier des tumeurs du Québec* (Québec cancer registry)
GMT	Geometric mean titres
HC2	Hybrid Capture 2
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
IARC	International Agency for Research on Cancer
INSPQ	Institut national de santé publique du Québec
KAP	Knowledge, attitudes and practices
LSIL	Low-grade squamous intraepithelial lesion
MSSS	Ministère de la Santé et des Services sociaux (Québec Ministry of Health and Social Services)
NACI	National Advisory Committee on Immunization
NHANES	National Health and Nutrition Examination Survey
PCR	Polymerase chain reaction

PIN	Penile intraepithelial neoplasia
QALY	Quality-adjusted life-year
RAMQ	Régie de l'assurance maladie du Québec (Québec health insurance plan)
RMITT-2	Restricted Modified Intention to Treat-2
RRP	Recurrent respiratory papillomatosis
TVC	Total vaccinated cohort
VaIN	Vaginal intraepithelial neoplasia
VE	Vaccine efficacy
VIN	Vulval intraepithelial neoplasia
VLPs	Virus-like particles

1 EPIDEMIOLOGY AND NATURAL HISTORY OF HPV INFECTION

The purpose of this section is to describe the epidemiology of the infection and its main clinical manifestations in order that the potential impact of HPV vaccines can be better understood. The data available for Québec will be presented in section 2.

1.1 HUMAN PAPILLOMAVIRUS

The human papillomavirus (HPV) belongs to the *Papillomaviridae* family, which includes at least 100 genotypes affecting the skin and mucous membranes. Of these, about 40 affect the anogenital area in particular.

In the 1990s, clinical, biological and epidemiological studies confirmed the causal relationship between HPV and cervical cancer[1, 2] and highlighted the strong association of certain genotypes with cervical cancer.[3] In 2003, of the 40 or so types of HPV that affect the anogenital area, approximately 15 were considered “high oncogenic risk,” three potentially oncogenic and 15 “low oncogenic risk” (Table 1). The oncogenic types 16 and 18 are responsible for 70-76% of cervical cancer cases worldwide.[4] Since the first studies, it has been determined that HPV is also associated with several other cancer sites, while the low-risk genotypes are associated with anogenital warts (AGW), mainly types 6 and 11, and recurrent respiratory papillomatosis (RRP).

Table 1 2003 classification of HPV genotypes by degree of risk for cervical cancer[3]

Group	Genotypes	Clinical manifestations
Established high risk	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82	Cervical cancer Low-grade and high-grade cervical lesions Other anogenital and oropharyngeal cancers
Probably high risk	26, 53, 66	
Established low risk	6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108	Condyloma acuminata (AGW) RRPCertain cervical lesions (mainly low-grade)

A more recent classification established by a working group of the International Agency for Research on Cancer (IARC)[5] defines HPV 16 as the most serious because of its link with several cancer sites (group 1 in Table 1). Types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 are also part of group 1, since there is sufficient evidence linking them to cervical cancer. Category 2 includes types 68, 26, 53, 66, 67, 70, 73, 82, 30, 34, 69, 85 and 97, for which the evidence of a link to cervical cancer is more limited. Types 6 and 11 are part of category 3, considered non-carcinogenic.

1.2 PREVALENCE OF HPV INFECTION

HPV infections are very common throughout the world. Since most infections are transitory and asymptomatic, HPV is not a notifiable disease in Canada. Prevalence and incidence data are estimated on the basis of epidemiological studies and are currently better documented in women than men.

Anogenital area

Among women, HPV prevalence in the genital area varies by geographic region, age, the selected subpopulation and the HPV detection method used. It peaks in young women aged 20-24 and declines subsequently with age. A second peak of lower magnitude is sometimes observed in certain countries in women over 55 years of age. In a recent meta-analysis of HPV prevalence, which included 194 studies involving more than 1 million women with normal cytological findings, the overall prevalence of HPV was 11.7% (95% confidence interval [CI]: 11.6-11.7%), after adjustment for the region, average age of the group tested, study year, detection method and proportion of high-risk HPV types tested.[6] Prevalence ranged from 4.7% (95% CI: 4.6-4.7%) in North America to 33.6% (95% CI: 30.2-37.1%) in Sub-Saharan Africa. The two oncogenic HPV types targeted by vaccination, namely types 16 and 18, were the most frequent in all the studies, with an adjusted prevalence of 3.2% and 1.4% respectively. In addition, all 12 high-risk oncogenic HPV types (group 1 of the IARC classification) accounted for 70% of HPV infections in the female population worldwide.[6]

Another systematic review, with meta-analysis limited to Canadian studies, confirms the higher prevalence of HPV infections among young women under the age of 20 followed by a gradual decline with age.[7] In the studies carried out in a screening context, i.e. in asymptomatic women, types 16 and 18 were the two most frequent types, with a respective prevalence (non-age-adjusted) of 8.6% (95% CI: 6.5-10.7%) and 3.3% (95% CI: 1.5-5.1%). However, several populations covered by these studies were female students or high-risk populations, such as Aboriginal peoples, which might explain the higher prevalence of genotypes 16 and 18 than in the aforementioned meta-analysis.

HPV infections are also frequent in men, but their prevalence varies considerably depending on the subjects' geographic region, the anatomical site from which the sample was collected (penile shaft, coronal sulcus, urethra, sperm, scrotum or anus), the sampling technique and the HPV detection method. In addition, the choice of the study population (heterosexuals, men who have sex with men [MSM] or men seropositive for the human immunodeficiency virus [HIV]) has a major impact on the results. Generally, among heterosexuals, HPV is detected more frequently in the penile shaft/coronal sulcus/glans penis than in the other sites,[8, 9] whereas among MSM, the highest rate of HPV infections is found at the anal site. Multiple infections are particularly frequent in MSM.

Unlike the case in women, HPV prevalence among men varies much less by age and remains relatively constant into old age.[10, 11] It has also been observed that the risk of infection in men varies depending on whether they have sexual relations with women only, men only or both (the latter have the highest prevalence of HPV infection).[3]

According to the most recent systematic review of 62 studies published between 1989 and 2009 and involving 14,800 sexually active men, the prevalence observed in the low-risk populations ranged from 2% to 84%, whereas it could be as high as 93% in certain high-risk groups, such as HIV-infected MSM.[10] Because of the heterogeneity of the data, an overall prevalence rate could not be calculated. However, in North American studies in the general population, overall prevalence ranged from 26% to 65%, which suggests that the infection is at least as frequent, if not more so, in men than in women. In another systematic review published earlier, the results were similar, with an overall prevalence in the general population estimated at more than 20% in 56% of the studies.[12]

Most Québec studies on the prevalence of HPV infections are limited to the female population and are usually based on convenience samples. Only one study deals specifically with (high-risk) men and heterosexual couples. The following table summarizes the findings of these studies.

[3] According to data from the Québec population health survey, the *Enquête québécoise sur la santé de la population*, conducted by the Institut de la statistique du Québec in 2008, the proportion of men 15 years of age and older who reported having had sexual partners of the same sex during the previous 12 months was 2.1% and the proportion of those who reported having had partners of both sexes was 0.4%. Lifelong proportions for partner sex were not evaluated in this survey.

Table 2 Prevalence of anogenital HPV infections in Québec

Reference	Context and sample size	Overall prevalence	Specific prevalence
Richardson et al., 2000[13]	Cross-sectional study conducted in Montréal, female students visiting a university health centre in Montréal, 1992-1993 Mainly 18-24 years old (3% > 30 years old) n = 375 Detection using MY09/MY11 primer set and dot blot hybridization	All HPV types: 22.7% High-risk HPV types: 11.8% Low-risk HPV types: 6.2% Non-identified HPV types: 7.1% Mixed infection with at least one high-risk type: 2.7%	The most frequent: High-risk HPV types: HPV 16: 4,7% HPV 51: 2.2% Low-risk HPV types: HPV 66: 1.6% HPV 6: 1.1% HPV 11: 1.1%
Richardson et al., 2003[14]	Baseline data from a prospective study conducted in Montréal, women visiting a university health centre (McGill-Concordia cohort), 1996-1998 17-42 years of age, average 23 and median 21 n = 621 Detection using MY09/MY11 primer set and line blot assay for genotyping	All HPV types: 29% High-risk HPV types: 21.8% Low-risk HPV types: 14.8%	The most frequent: High-risk HPV types: HPV 16: 7% HPV 18: 3.1% HPV 51: 2.9% HPV 31: 2.6% Low-risk HPV types: HPV 53: 4.3% HPV 84: 3.8% HPV 6: 2.7% HPV 11: not available
Mayrand et al., 2006[15]	Women recruited as part of a controlled clinical trial, visiting a screening centre in Montréal, 2002-2004 30-69 years of age, n = 4,184 Detection using the Hybrid Capture 2 (HC2) test (pool of 13 high-risk HPV types)	7.7% for the high-risk HPV types included in the HC2 test, specifically by age group: • 30-39 years of age: 12.7% • 40-49 years of age: 5.9% • 50-59 years of age: 4.8% • 60-69 years of age: 3.8%	Not available
Hamlin-Douglas et al., 2008[16]	Baseline data from a prospective study conducted in Nunavik, primary care context Inuit women, 2002-2007 15-69 years of age, n = 554 Detection using PGMY primer and line blot assay for genotyping	Overall prevalence at the beginning of the study: All HPV types: 28.9% < 20 years of age: 58% High-risk HPV types: 20.4% Multiple infections in 40% of the positive cases	HPV 16 the most frequent

Table 2 Prevalence of anogenital HPV infections in Québec (cont'd)

Reference	Context and sample size	Overall prevalence	Specific prevalence
Burchell et al., 2010[17]	Cross-sectional study conducted in Montréal, female university students 18-24 years of age and their new partner (six months or less), 2005, n = 263 couples Detection using polymerase chain reaction (PCR) (LA-HPV)	Overall prevalence: 64% in at least one partner and 47% in both partners, 87% of which match for at least one type	HPV 16: 22% of the couples
de Pokomandy et al., 2009[18]	HIV-seropositive MSM recruited for the longitudinal study Human Immunodeficiency and Papillomavirus Research Group in Montréal 20-69 years of age, n = 247	HPV in the anal canal: 97.9% Median number of HPV types: 5	HPV 16: 38.2% HPV 6: 35.5% HPV 42: 28.6% HPV 18: 24.5% HPV 11: 23.2%

Oral region

Because of HPV's association with certain cancers of the head and neck (oropharyngeal cancers), a number of researchers have turned their attention to determining whether there is evidence of HPV infection in the oral region. Among both men and women, the prevalence of HPV in the oral region is lower than in the genital area. In a meta-analysis of 18 studies involving more than 4,000 asymptomatic subjects, the overall prevalence of all genotypes was estimated at 4.5% (95% CI: 3.9-5.1%), of all high-risk genotypes at 3.5% (95% CI: 3.0-4.1%) and of genotype 16 at 1.3% (95% CI: 1.0-1.7%).[19]

In another study of nearly 1,700 asymptomatic men, the prevalence of oral HPV infection was 4% (95% CI: 3.1-5.0%). HPV 16 was the most frequent type, with a prevalence of 0.6% (95% CI: 0.2-1.1%).[20]

In a large population-based survey conducted recently in the United States (National Health and Nutrition Examination Survey [NHANES]), the overall prevalence of HPV in the oral region was 6.9% (95% CI: 5.7-8.3%); this was higher among men, at 10.1% (95% CI: 8.3-12.3%), than women, at 3.6% (95% CI: 2.6-5.0%).[21] Two peaks were observed, the first at 30-34 years (7.3%) and a second, higher, peak at 60-64 years (11.4%). This bimodal pattern was particularly evident in men (not significant in women).

The only available Québec data on the prevalence of oral HPV infections come from a case-control study conducted in Montréal, in which the prevalence of HPV infections in the controls was estimated at 5% (6/129), compared with 19% (14/72) in all cases of oral cancer and 43% (9/21) in patients with cancer of the tonsils and the base of the tongue.[22]

Seroprevalence

Although they can reflect exposure to HPV regardless of the anatomical site sampled, serological tests that can estimate the prevalence of HPV infections have been used to a lesser extent than viral DNA assays, since immune response is inconsistent and the results are more difficult to compare in the absence of standardized technology.[23] In two recent studies conducted with large populations, serological titres were systematically higher in women than men.[24, 25] According to the authors, these results may be explained by a longer duration of infection in women and a stronger immune response when the affected site is a mucosal surface rather than a keratinized surface.

1.3 INFECTION ACQUISITION, TRANSMISSION AND NATURAL HISTORY OF THE DISEASE

The modes of acquisition, transmission and progression of HPV infections have been amply described, particularly in women and in relation to cervical cancer.[26-28] HPV is usually transmitted sexually, and the risk of contracting the infection is largely determined by sexual behaviour, including the number of sexual partners, the sex of these partners, age at the onset of sexual activity and the frequency of sexual relations. Other modes of transmission (nosocomial or from inanimate objects) remain possible but are considered relatively unlikely. HPV is thought to be transmitted more easily than other sexually transmitted infections.[29] Using condoms offers limited protection, since HPV can be transmitted through contact with the genital regions not covered by the condom.[30] More recently, oral-genital sexual relations have been identified as a risk factor for oropharyngeal cancers.[31-33]

The risk of acquiring HPV infection is particularly high in the first few years after sexual activity begins. In a study of female university students in Montréal followed for 24 months, the cumulative incidence of cervical infections for all HPV types was 18% after one year and 36% after two years.[14] According to some estimates, more than 70% of sexually active women will contract an HPV infection at some time in their lives.[34, 35] However, even if the risk of acquiring HPV infection is almost ubiquitous in the population, in most infected individuals the infection will spontaneously clear in less than 24 months. Persistent infection by an oncogenic type increases the risk of progression to invasive cervical cancer, but this process usually takes many years, even decades. Because of this slow progression, the precursor stages (intraepithelial neoplasia grade 2 or 3, or cervical intraepithelial neoplasia [CIN] 2/3) can be detected by cytological screening (Pap test) and treated, in order to prevent invasive cancer. Until the advent of HPV vaccines, cervical cancer screening was practically the only way to prevent the disease.

1.4 PATHOGENICITY

1.4.1 HPV-associated cancers

Oncogenic HPV infections play a role in the genesis of several types of cancer, but their contribution as an etiological agent (attributable risk fraction) varies by cancer site.

In this document, the term “HPV-associated cancer” will be used to refer to the category for which this association is recognized, regardless of whether or not HPV has been detected in each case. The term “HPV-positive” will be reserved for cancers in which the detection of

HPV in histopathological specimens or exfoliated cells has been confirmed. According to experts at the Centers for Disease Control and Prevention (CDC), the proportion of cancers in which HPV has been detected currently constitutes the best available estimate for determining the attributable risk fraction.[36] However, calculating an attributable risk fraction by genotype is complicated by the fact that multiple infections are common.[37]

1.4.1.1 Cervical cancer

Cervical cancer is the third-leading cause of cancer in the female population worldwide (after breast cancer and colorectal cancer) and accounts for nearly 9% of female cancers.[38] There are large disparities among countries, since the standardized annual incidence rate (for the worldwide population) ranges from 30/100,000 in developing countries, where there is little or no screening, to 9/100,000 in developed countries. The annual mortality rate varies from 9/100,000 (in developing countries) to 3.2/100,000 (in developed countries).

HPV is currently recognized as a necessary cause of cervical cancer, and HPV DNA has been detected in 90% to 99.7% of cases.[1, 4, 39] However, the risk varies depending on the genotype concerned.

Worldwide, types 16 and 18 are responsible for approximately 70% of cases of squamous cell cervical cancer and 75% to 85% of cervical adenocarcinomas, a less frequent form of cervical cancer (approximately 15%). These two genotypes are also present in the majority of high-grade lesions. Infections by other types (including low-risk types) are more frequent in low-grade lesions or in cases that have no lesions. The following table summarizes the distribution of the main high-risk genotypes by degree of severity of cervical lesions, worldwide, estimated in meta-analyses.

Table 3 Frequency (%) and relative contribution of the main high-risk HPV genotypes by degree of severity of cervical lesions, worldwide

	Normal cytology[6, 40]	**Low-grade lesion**[41]	**High-grade lesion**[42]	**Invasive cancer (squamous cell)**[4, 39, 43]	**Invasive cancer (adenocarcinoma)**[4, 39, 43]
HPV 16	1.8-5.8	27	45	59-62	36-52
HPV 18	0.7-2.3	9	10	8-18	39
HPV 45	0.5-1	5	3	4-7	5-12
HPV 31	0.7-1	12	9	4	1-2
HPV 33	0.5	8	5	4-5	1-2

More particularly in Canada, the HPV types most commonly encountered in cases of invasive cervical cancer are, in decreasing order, types 16, 18, and 45. The following table indicates the exact prevalences of the main high-risk genotypes reported in the Canadian meta-analysis mentioned earlier.[7]

Table 4 Prevalence of high-risk HPV types in invasive cervical cancer cases in Canada, according to the meta-analysis conducted by Tricco et al.

Genotype	Sample size	Prevalence (%)	95% CI
HPV 16	172	48.8	34.0-63.6
HPV 18	219	17.1	6.4-27.9
HPV 45	96	7.7	2.4-13.0
HPV 33	172	2.1	0.0-4.2
HPV 31	172	1.2	0.0-2.7

In another Canadian study, the prevalence of HPV detected in exfoliated cervical cells was 88.5% in invasive cancer cases, and the two oncogenic genotypes 16 and 18 were present in 52.1% and 18.1% of the cases respectively.[44]

These results concerning the severity of cervical infections by genotype in cervical cancer cases agree with those of prospective studies showing that in women who had normal cytological results at the beginning of the study but who were infected by type 16 and to a lesser extent by types 18, 31 and 33, there was a higher risk of high-grade cervical lesions developing in the short term than in women infected by other genotypes.[45, 46]

1.4.1.2 Other cancers

HPV is also associated with other cancers of the anogenital area, particularly cancers of the anus (men and women), vulva, vagina and penis, and with oropharyngeal cancers. However, although the etiological role of HPV has been confirmed by numerous molecular studies demonstrating viral integration of HPV in the host and the expression of oncogenic proteins for at least some of these cancer sites, the proportion of these cancers actually caused by HPV remains lower than that estimated for cervical cancer, which is close to 100%.

For each HPV-associated cancer site, the following table presents the estimated proportion of cancers that are HPV-positive, as well as the estimated specific prevalence of the main high-risk genotypes, namely types 16, 18, 31, 33 and 45. For these estimates, preference was given to North American data when available.[37, 39, 47-51]

Although a statistically significant prevalence of HPV infections has been observed in cancers of the larynx and of the oral cavity, the etiological role of HPV in these cancers has not yet been confirmed.[36]

Table 5 Proportion of cancers in which HPV is detected (HPV-positive) and specific prevalence of the main high-risk HPV genotypes, by cancer site

	Overall prevalence	Specific prevalence				
		HPV 16	HPV 18	HPV 31	HPV 33	HPV 45
Cancer site	**%**	**%**	**%**	**%**	**%**	**%**
Cervix	≈ 100	60	19	4	4	5
Vulva	66	52	4	1	8	2
Vagina	70	60	10	0	0	0
Anus*	83	71	7	3	4	0
Penis	49	45	2	2	1	1
Oropharynx	47	42	1	0	2	0
Oral cavity	16	10	3	0	1	0
Larynx	14	10	3	2	0	0

* For this cancer site, only the squamous cell morphology is included.

Research is continuing, and other cancer sites could eventually be added to this list (lungs, esophagus, prostate and bladder, for example). At present, the data are too preliminary or contradictory to be included in this overview.

The following section briefly describes the main HPV-associated cancer sites.

a) Other anogenital cancers

Cancers of the vulva and vagina are relatively rare in the population, and a high proportion of these cancers occur in elderly women. The majority of cases are squamous cell carcinomas and, for cancers of the vulva, HPV is associated more particularly with the subset of carcinomas of the basaloid type but rarely or never with the keratinizing type. Their natural history is less well understood than that of cervical cancer, but precursor states are often described using terminology similar to that of the cervix (VIN and VaIN for vulval or vaginal intraepithelial neoplasia grade 1, 2 or 3, depending on the severity). This classification is controversial,[4] and a number of experts recommend using only the more advanced grades to describe the precursors, as is the case for cervical cancer, in which grade 1 (CIN1) is no longer considered a cancer precursor state.

Although the incidence rate of these two cancers has remained relatively stable in the last few decades, an increase in the vulvar cancer precursors (VIN3) has been observed in certain sectors of the population over the past decade (cited in the general review by Giuliano et al.[52]). HPV 16 is the most frequently encountered type in vulvar cancers and also in VIN3. In the case of vaginal cancer, most North American studies have reported the presence of only the two oncogenic HPV types 16 and 18.

[4] We have provided this classification for information purposes, since this is the nomenclature used in vaccine studies.

Anal cancer shares several common features with cervical cancer, such as a cell transformation zone that is particularly vulnerable to the effect of HPV infection and a fairly similar natural history of the disease. Most anal cancers are squamous cell carcinomas, but adenocarcinomas are also seen. HPV 16 is the most commonly encountered genotype in this type of cancer.

The incidence of anal cancer is generally higher among women than men. Over the past few decades, an increase in this type of cancer has been reported in both the male and female populations but more specifically in MSM. HIV-seropositive MSM have the highest incidence rate of this cancer. For example, in the United States the annual incidence of anal cancer in the HIV-infected population (male and female population, but largely dominated by men at 76%) in 2000-2003 was estimated at 78/100,000, 60 times higher than in the general population (1.3/100,000) and seven times higher than the incidence of cervical cancer among women in general (11.4/100,000).[53]

These data can be explained, in part, by the increased life expectancy of seropositive individuals receiving highly active antiretroviral therapy, but, paradoxically, this therapy has had little apparent effect on the natural history of anal intraepithelial neoplasias (AIN).

Cancer of the penis is fairly rare in industrialized countries and affects mainly elderly men. Most penile cancers are squamous cell carcinomas, but, as is the case with vulvar cancers, HPV is mainly associated with the basaloid type and not with the keratinizing type. HPV is detected in approximately half of cancers of the penis, and HPV 16 is the most frequently identified genotype.[51]

Finally, it should be pointed out that for all anogenital cancers, cancer can occur at more than one site in the same individual, either synchronously or consecutively (for example, cervical cancer followed by anal cancer).[54, 55] There is also a geographic correlation between the incidence of cancer of the penis and that of cervical cancer, as well as a concordance of these two cancers in married couples, suggesting a common HPV etiology.[56]

b) Oropharyngeal cancers

Most oropharyngeal cancers are squamous cell carcinomas and are more frequent in men than women. Smoking and alcohol consumption have long been recognized as important risk factors for these diseases. More recently, HPV was recognized as having an etiological role in a certain proportion of them. A high prevalence of HPV is found particularly in cancers of the oropharynx (including the tonsils and the base of the tongue), with an average estimated proportion of 47% in North America, and to a lesser extent in cancers of the oral cavity and larynx, at approximately 15%.[47, 57-61]

The natural history of these cancers is still poorly understood. However, it has been observed that individuals with HPV-positive oropharyngeal cancer are on average younger, do not necessarily have high alcohol or tobacco consumption levels and are more likely to engage in risky sexual behaviours, such as having a larger number of sexual partners.[62] It has also been observed that patients with HPV-positive cancer often responded better to treatment and had a better prognosis than patients whose cancers were not HPV related.[63, 64]

A significant increase in oropharyngeal cancers, more specifically cancers of the tonsils and the base of the tongue, has been observed recently in a number of countries, including the United States, Sweden, Denmark, Australia and Canada (British Columbia).[65-73] This increase has occurred despite a general downward trend in the other cancers of the oral cavity, particularly in men, in parallel with the reduction in smoking rates. In Sweden, the proportion of HPV-positive cancers of the tonsils increased from 23% in the 1970s to 93% in 2006-2007,[65] and in the United States the proportion of HPV-positive oropharyngeal cancers increased from 16.3% during the 1984-1989 period to 71.7% during the 2000-2004 period.[71] The authors of this last study predict that if this upward trend continues, the number of HPV-positive oropharyngeal cancers could soon exceed the number of cervical cancers.

In a study conducted in France, the proportion of HPV-positive cancer was significantly higher among men than women: 63.5% versus 42.2% ($p = 0.002$) for cancers of the oropharynx and 17.2% versus 8.0% ($p = 0.049$) for cancers of the oral cavity.[74] This is the only study reporting a difference in the proportion of HPV-positive cancers by sex.

1.4.2 Diseases associated with low-risk HPV types

Condyloma acuminata (or external anogenital warts)

Condylomas take the form of small, usually multiple, wart-like lesions in the anogenital area. These AGW are often asymptomatic but can sometimes cause itching or bleeding. They affect both men and women and are associated in most cases (approximately 85%) with HPV 6 and 11 infection.[75, 76] Although they are generally self-limited and respond to topical treatments, they can become a significant source of psychological distress, particularly because of the impact on body image and relations with partners.[77] The most serious cases sometimes require excision in a hospital. Because their incidence is fairly high in the population, they have a substantial clinical and economic burden. In Canada, AGW are not on the list of notifiable diseases, which complicates their surveillance.

In the United Kingdom, which has surveillance data on AGW, an eight-fold increase in the prevalence of these infections among men and an 11-fold increase among women were reported between 1971 and 2004.[78] In the United States, a large population-based survey of men and women aged 18-59 revealed that, during the 1999-2004 period, 5.6% of them already had a clinical history of AGW and that the proportion was higher among women (7.2%; 95% CI: 6.2-8.4%) than men (4%; 95% CI: 3.2-5.0%). The peak of prevalence was also detected earlier in women (25-34 years old) than in men (35-44 years old).[79]

In Canada, only Manitoba and British Columbia currently have population-based data on the incidence and prevalence of AGW, estimated by matching administrative records on medical procedures and hospital admissions.

In Manitoba, it is estimated that, on average, nearly 1,250 AGW cases were diagnosed annually between 1985 and 2004 (1.84% of the population); of these cases, 17% of men and 11% of women had more than one episode.[80] The standardized incidence rate peaked in 1992 for women (170/100,000 person-years) and for men (149/100,000 person-years). Since 1999, the incidence rate among men has increased, whereas the rate among women has

remained stable. Consequently, the male:female incidence rate ratio increased from 0.76 in 1985 to 1.25 in 2004.

During the 2000-2004 period, the highest rates were found among women aged 20-24 (466/100,000) and men aged 25-29 (392/100,000) (Figure 1).

In British Columbia, 43,586 episodes of anogenital warts occurred between 1998 and 2006 in 39,500 individuals, with an average of three consultations per episode.[81] The standardized incidence rate was 1.3/1,000 among men and 1.2/1,000 among women.

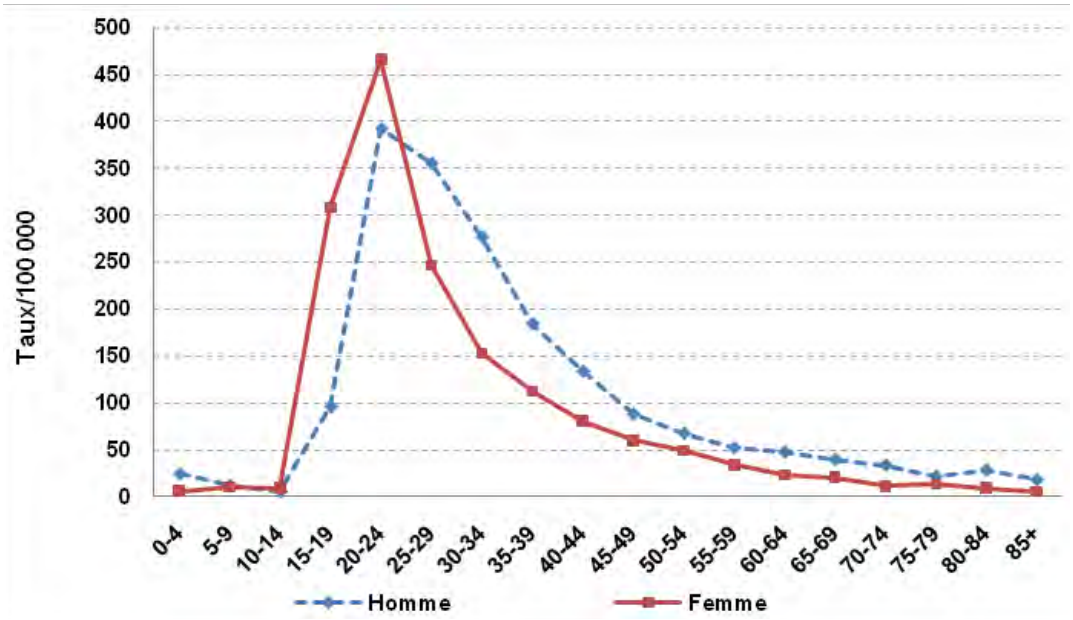


Figure 1 Incidence rate of AGW by sex and age, Manitoba, 2000-2004

Source: Erich Kliewer (personal communication).
Taux/100 000: Rate/100 000; *Homme*: Male; *Femme*: Female.

Recurrent respiratory papillomatosis

RRP is another condition related to low-risk HPV types. This disease, which exists in an adult form and a juvenile form, is characterized by warty growths along the mucous membranes of the respiratory tract and can cause airway obstruction and voice changes. There is also a small risk of spread deeper into the lower respiratory tract with malignant transformation in the bronchial area.[82]

The juvenile form, which is better documented, appears to be transmitted vertically at the time of birth. Although uncommon and histologically benign, the juvenile form can become particularly incapacitating for affected children because of its tendency to recur and the risk of serious, sometimes fatal, obstruction, requiring repeated surgical procedures. Genotypes 6 and 11 are the types most commonly involved.

The factors that predispose to this condition are poorly understood since HPV infections are relatively common in young women, whereas papillomatosis remains rare. Children born to mothers infected with AGW are at significantly increased risk of having RRP.[83]

The adult form, less severe, typically affects individuals aged 20-30 and may be transmitted by sexual contact. However, few data are available concerning its prevalence in the population.

2 QUÉBEC EPIDEMIOLOGICAL DATA ON HPV-ASSOCIATED CANCERS

The incidence and mortality data for HPV-associated cancers in Québec are derived from the Québec cancer registry, the *Fichier des tumeurs du Québec* (FiTQ) and the provincial death registry for the 1984-2007 period.[5]

2.1 CERVICAL CANCER

In Québec, when different types of cancer are ranked by incidence, cervical cancer is in 13th place of all cancers among women, with an estimated annual average of 281 cases and 69 deaths for the 2004-2007 period and standardized incidence and mortality rates (Québec population in 2001) of 7.0/100,000 and 1.6/100,000 person-years respectively (Table 6 below).

Compared with other anogenital cancers, cervical cancer develops at a younger age (71% of cases diagnosed before the age of 60). In 2007, the average age at diagnosis was 51, and the median age was 49. The annual incidence rate among female Quebecers under 30 years of age is still less than 1/100,000 (11 cases in 2007). This rate then increases with age, peaking at 40-49 years with an incidence of 13.3/100,000, and subsequently declining with age. A second peak is observed in women ≥ 60 years of age, with an incidence of 11.7/100,000.

The following figure shows the distribution of cervical cancers by age group in Québec.

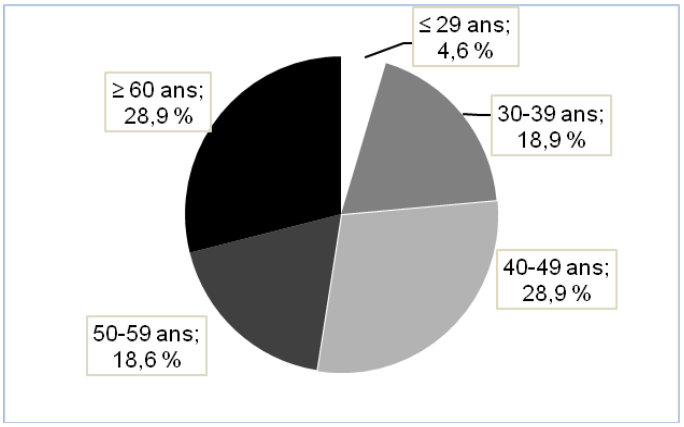


Figure 2 Distribution of cervical cancers by age group in Québec, 2004-2007

≤ 29 ans: ≤ 29 years old; *30-39 ans*: 30-39 years old; *40-49 ans*: 40-49 years old; *50-59 ans*: 50-59 years old; *≥ 60 ans*: ≥ 60 years old.

[5] The identification of cancer cases is based on the Third International Classification of Diseases for Oncology (ICD-O-3): cancer of the cervix (ICD-O-3 C53), cancer of the vagina (ICD-O-3 C529), cancer of the vulva (ICD-O-3 C51), cancer of the anus (ICD-O-3 C21), cancer of the penis (ICD-O-3 C60), cancer of the oropharynx (ICD-O-3 C019, C024, C051, C052, C090, C091, C098, C099, C142, C100, C102-104, C108, C109), cancer of the oral cavity (ICD-O-3 C020-023, C028, C029, C03, C04, C050, C058-062, C068, C069) and cancer of the larynx (ICD-O-3 C32).

The majority of cases of cervical cancer are squamous cell carcinomas (67%) (Table 6). Adenocarcinomas are less common and account for 26% of cases in Québec. However, this proportion is higher than in other regions of the world where screening is less widespread (and where the proportion is usually around 15%). This could be explained by the fact that cytological screening is less effective in detecting adenocarcinoma and its precursors than in detecting squamous cell lesions.[84, 85] The other carcinomas (adenosquamous carcinoma, small-cell neuroendocrine carcinoma and other carcinomas) account for 7% of cases.

There was a clear decline in the incidence rate of cervical cancer in Québec between 1984 and 2007, with an annual percent change (APC)[6] of –2.4% (Figure 3 and Table 7). Over the same period, the mortality rate fell, on average, 3.1% a year. The decline in the incidence rate was greater during the 1980s (APC = –6.6%) and has slowed since 1988 (APC = –0.6%), whereas mortality has continued to fall since 1998 (APC = –4.6%).

Based on a matching of cancer registry and death registry data, the estimated five-year relative survival rate was 74% in a Québec study.[86] Survival remained stable between the 1984-1986 and 1993-1995 periods.

2.2 OTHER ANOGENITAL CANCERS

Other anogenital cancers are relatively rare compared with cervical cancer, with an annual incidence rate for each site often less than 2/100,000. These cancers mainly affect individuals over the age of 60.

In Québec, most other anogenital cancers are squamous cell carcinomas (76% to 96% of cases) (Table 6), and these are the cases most probably associated with HPV. Adenocarcinomas are less frequent and account for 6% of all cases. However, for anal cancer, adenocarcinomas constitute 24% of cases in women and 38% of cases in men. Most of the published surveillance data deal only with squamous cell cancers.

For the 2004-2007 period, the annual incidence rate for squamous cell carcinomas of the vulva was 1.4/100,000, with an average of 64 cases a year (Table 6). For all morphological types combined, the incidence rate was 1.8/100,000 (91 cases) and the mortality rate was 0.5/100,000 with 27 deaths a year. The incidence and mortality rates associated with cancer of the vulva remained stable in Québec over the observation period (Figure 3 and Table 7).

Squamous cell carcinoma of the vagina remains relatively rare in Québec, with an estimated 15 cases a year for 2004-2007 and an annual incidence rate of 0.3/100,000. For all morphological types combined, the incidence rate was 0.4/100,000 (19 cases) and the mortality rate was 0.3/100,000 (12 deaths). This type of carcinoma essentially affects elderly women (≈ 80% are 60 years of age or older at the time of diagnosis, no cases before age 40). This cancer is sometimes secondary to another HPV-associated cancer, in particular cervical cancer. However, certain metastatic cervical cancers may be misclassified as primary vaginal cancers. As is the case for cervical cancer, the incidence and mortality rates for vaginal cancer declined in Québec between 1984 and 2007. The APC was –3.7%

[6] APC is estimated by a Joinpoint regression model developed by the National Cancer Institute (Bethesda, USA).

and –2.0% respectively (Figure 3 and Table 7). Invasive cancer of the vagina is often diagnosed at an advanced stage, which explains its poor prognosis: a five-year relative survival of 45%, compared with 82% for cancer of the vulva.[86]

Anal squamous cell carcinomas affect both women and men. These uncommon carcinomas, in contrast to cervical cancer, affect an average of 35 Québec women and 24 Québec men a year and have an annual incidence of 0.8 and 0.6/100,000 respectively (Table 6). For all morphological types combined, the incidence rates were 0.9/100,000 among women (46 cases) and 0.7/100,000 among men (39 cases), and the mortality rate was 0.2/100,000 in both sexes (9 deaths among women and 8 deaths among men). The incidence of anal adenocarcinoma among men was 0.4/100,000, which is the highest incidence rate of all adenocarcinomas after adenocarcinoma of the cervix. The incidence of anal cancer has increased over the last two decades in Québec. The APC was 3.1% for women and 1.6% for men (Figure 3 and Table 7). The mortality rate remained stable in both sexes. In addition, although the five-year relative survival for anal cancer improved among Québec women (increasing from 56% in 1984-86 to 65% in 1993-95), it declined among men (from 56% to 46%).[86]

Squamous cell carcinoma of the penis is uncommon in Québec, with an average of 24 cases a year and an incidence rate of 0.7/100,000. For all morphological types combined, the incidence rate was 0.7/100,000 (26 cases) and the mortality rate was 0.1/100,000 (5 deaths). The incidence rate remained stable over time, but there was a year-over-year decline in the mortality rate of 3.4% (Figure 3 and Table 7). For cancer of the penis, the five-year relative survival decreased between 1984-86 and 1993-95 in Québec, from 75% to 59%.[86]

2.3 OROPHARYNGEAL CANCERS

The incidence and mortality rates of oropharyngeal cancers in Québec are shown in Table 6. For all morphological types combined, the incidence rate of cancers of the oropharynx was 5.4/100,000 among men (207 cases) and 1.7/100,000 among women (74 cases). The mortality rates were 1.2/100,000 among men (47 deaths) and 0.3/100,000 among women (16 deaths). The number of cases of cancer of the larynx and cancer of the oral cavity was particularly high in men (282 and 140 respectively). However, the contribution to the burden of HPV-associated diseases is more difficult to estimate for these two sites, since the proportion of HPV-positive cases is much lower.

Between 1984 and 2007, there was a steady decline in the incidence and mortality rates of cancer of the larynx and cancer of the oral cavity, particularly among men (Figure 3 and Table 7). This drop probably reflects the reduction in smoking, the main risk factor for these two cancers. By contrast, the incidence rate for cancer of the oropharynx increased by 2.6% a year among Québec women and 0.8% a year among Québec men.

No Québec data are available on the probability of survival following these cancers. For Canada (excluding Québec), the five-year relative survival for all cancers of the oral cavity is estimated at 61% (95% CI: 59-62%) for men and 66% (95% CI: 64-68%) for women. For cancer of the larynx, the five-year relative survival is estimated at 65% (95% CI: 62-67%) for men and 61% (95% CI: 56-66%) for women.[87]

Table 6 Average annual number[7] of cases and standardized incidence[8] and mortality rates of anogenital and oropharyngeal cancers by site, sex and morphology, Québec, 2004-2007

Site	Total	Squamous cell		Adenocarcinoma		Other[a]		Mortality	
	N	N (%)	Rate/100,000 (95% CI)	N (%)	Rate/100,000 (95% CI)	N (%)	Rate/100,000 (95% CI)	N (%)	Rate/100,000 (95% CI)
Female									
Cervix[b]	**281**	189 (67)	4.7 (4.4-5.0)	73 (26)	1.8 (1.6-2.0)	19 (7)	0.5 (0.4-0.6)	**69**	1.6 (1.4-1.8)
Vagina	**19**	15 (79)	0.3 (0.2-0.4)	3 (16)	0.1* (0.1-0.2)	1 (5)	0.03** (0.0-0.1)	**12**	0.3 (0.2-0.4)
Vulva	**81**	64 (79)	1.4 (1.2-1.6)	8 (10)	0.2* (0.1-0.3)	9 (11)	0.2* (0.1-0.3)	**27**	0.5 (0.5-0.7)
Anus	**46**	35 (76)	0.8 (0.7-1.0)	11 (24)	0.2 (0.2-0.3)	0	-	**9**	0.2* (0.1-0.3)
Oropharynx	**74**	68 (92)	1.6 (1.4-1.8)	3 (4)	0.1* (0.1-0.1)	3 (4)	0.1* (0.0-0.1)	**16**	0.3 (0.3-0.4)
Larynx	**62**	59 (95)	1.4 (1.2-1.6)	0	-	3 (5)	0.1** (0.0-0.1)	**28**	0.6 (0.5-0.7)
Oral cavity	**83**	69 (83)	1.6 (1.4-1.7)	11 (13)	0.3 (0.2-0.4)	3 (4)	0.1* (0.0-0.1)	**38**	0.8 (0.7-1.0)
Total	**646**	499 (77)	11.7 (11.2-12.3)	109 (17)	2.7 (2.5-3.0)	38 (6)	0.9 (0.8-1.1)	**199**	4,4 (4,1-4,7)
Total[c]	**501**	371 (74)	8.8 (8.4-9.3)	98 (20)	2.4 (2.2-2.7)	32 (6)	0.8 (0.7-1.0)	**133**	3.0 (2.7-3.2)
Male									
Anus	**39**	24 (61)	0.6 (0.5-0.8)	15 (38)	0.4 (0.3-0.5)	0	-	**8**	0.2* (0.2-0.3)
Penis	**26**	24 (92)	0.7 (0.5-0.8)	1 (4)	0.04** (0.0-0.1)	1 (4)	0.03** (0.0-0.1)	**5**	0.1* (0.1-0.2)
Oropharynx	**207**	198 (96)	5.1 (4,8-5.5)	2 (1)	0.1* (0.0-0.1)	7 (3)	0.2* (0.1-0.2)	**47**	1.2 (1.1-1.4)
Larynx	**282**	270 (96)	7.2 (6.8-7.7)	4 (1)	0.1* (0.1-0.2)	8 (3)	0.2* (0.2-0.3)	**115**	3.2 (2.9-3.5)
Oral cavity	**140**	129 (92)	3.4 (3.2-3.7)	7 (5)	0.2* (0.1-0.3)	4 (3)	0.1* (0.1-0.2)	**62**	1.7 (1.5-1.9)
Total	**694**	645 (93)	17.1 (16.5-17.8)	29 (4)	0.8 (0.6-0.9)	20 (3)	0.6 (0.5-0.7)	**237**	6.5 (6.1-6.9)
Total[c]	**272**	246 (90)	6.4 (6.0-6.9)	18 (7)	0.5 (0.4-0.6)	8 (3)	0.2 (0.2-0.3)	**60**	1.6 (1.4-1.8)

Data source: Québec cancer registry and death registry.

[a] Adenosquamous carcinoma, small-cell neuroendocrine carcinoma and other carcinomas.

[b] Incidence rate (all morphological types combined) = 7.0/100,000 PY.

[c] Excluding cancer of the larynx and cancer of the oral cavity, rarely associated with HPV.

* 16.66% < coefficient of variation ≤ 33.33%. This figure must be interpreted with caution.

** Coefficient of variation > 33.33%. The figure is provided solely for information purposes.

[7] Number of cases reported to the cancer registry, regardless of HPV status.

[8] Rates standardized for the population of Québec in 2001, both sexes combined.

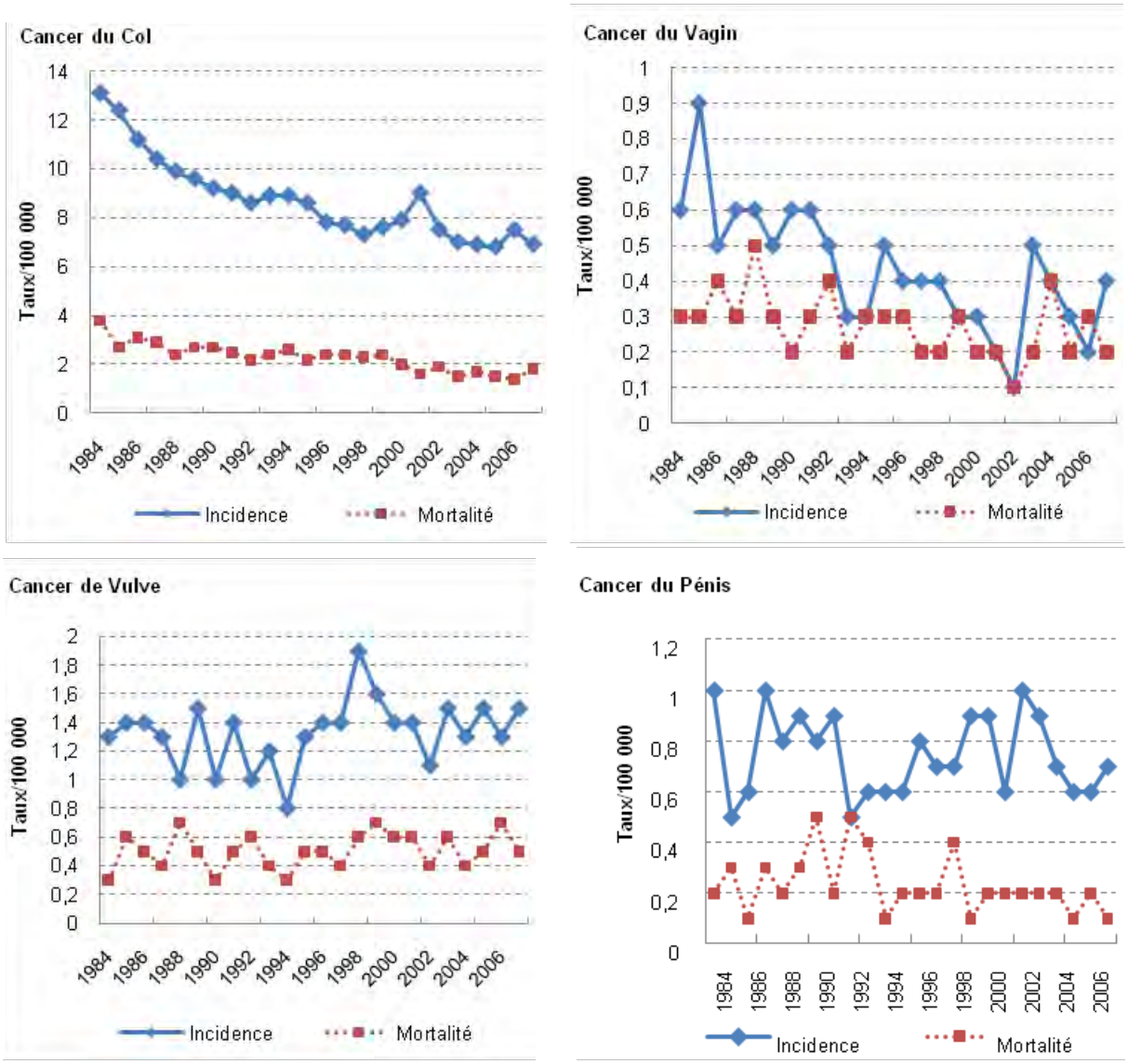
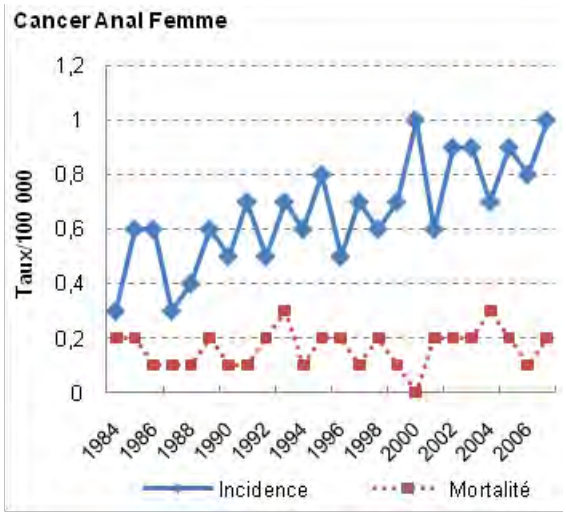
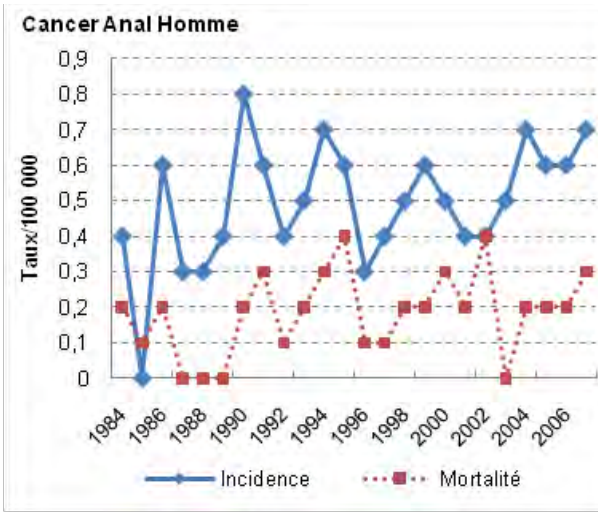


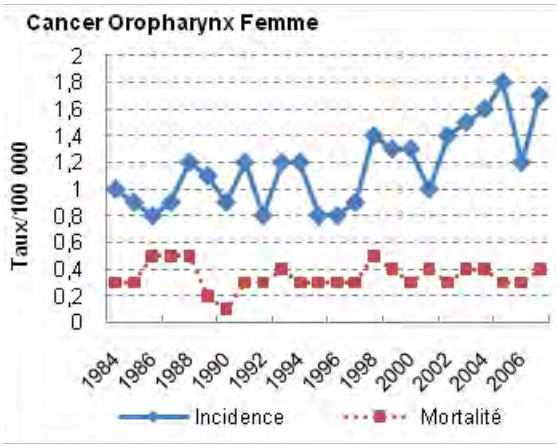
Figure 3 **Time trends in the standardized incidence and mortality rates, by cancer site and sex, Québec, 1984-2007**

N.B.: For incidence, with the exception of cervical cancer, only squamous cell carcinomas were included.

Cancer du col: Cervical cancer; *Cancer du vagin*: Vaginal cancer; *Cancer de la vulve*: Vulvar Cancer; *Cancer du pénis*: Penile cancer; *Taux/100 000*: Rate/100 000; *Incidence*: Incidence; *Mortalité*: Mortality.







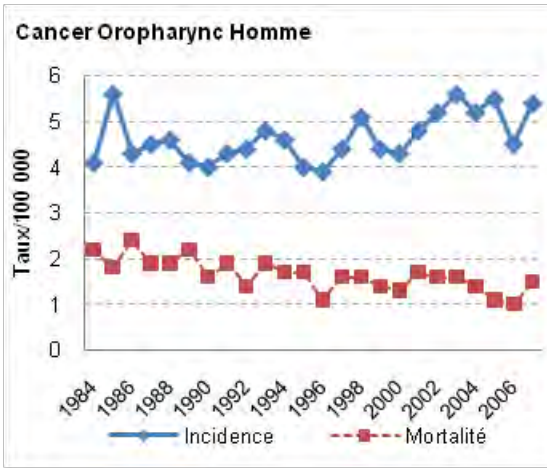


Figure 3 Time trends in the standardized incidence and mortality rates, by cancer site and sex, Québec, 1984-2007 (cont'd)

Cancer anal femme: Anal cancer females; *Cancer anal homme*: Anal cancer males; *Cancer oropharynx femme*: Oropharyngeal cancer females; *Cancer oropharynx homme*: Oropharyngeal cancer males; *Taux/100 000*: Rate/100 000; *Incidence*: Incidence; *Mortalité*: Mortality.

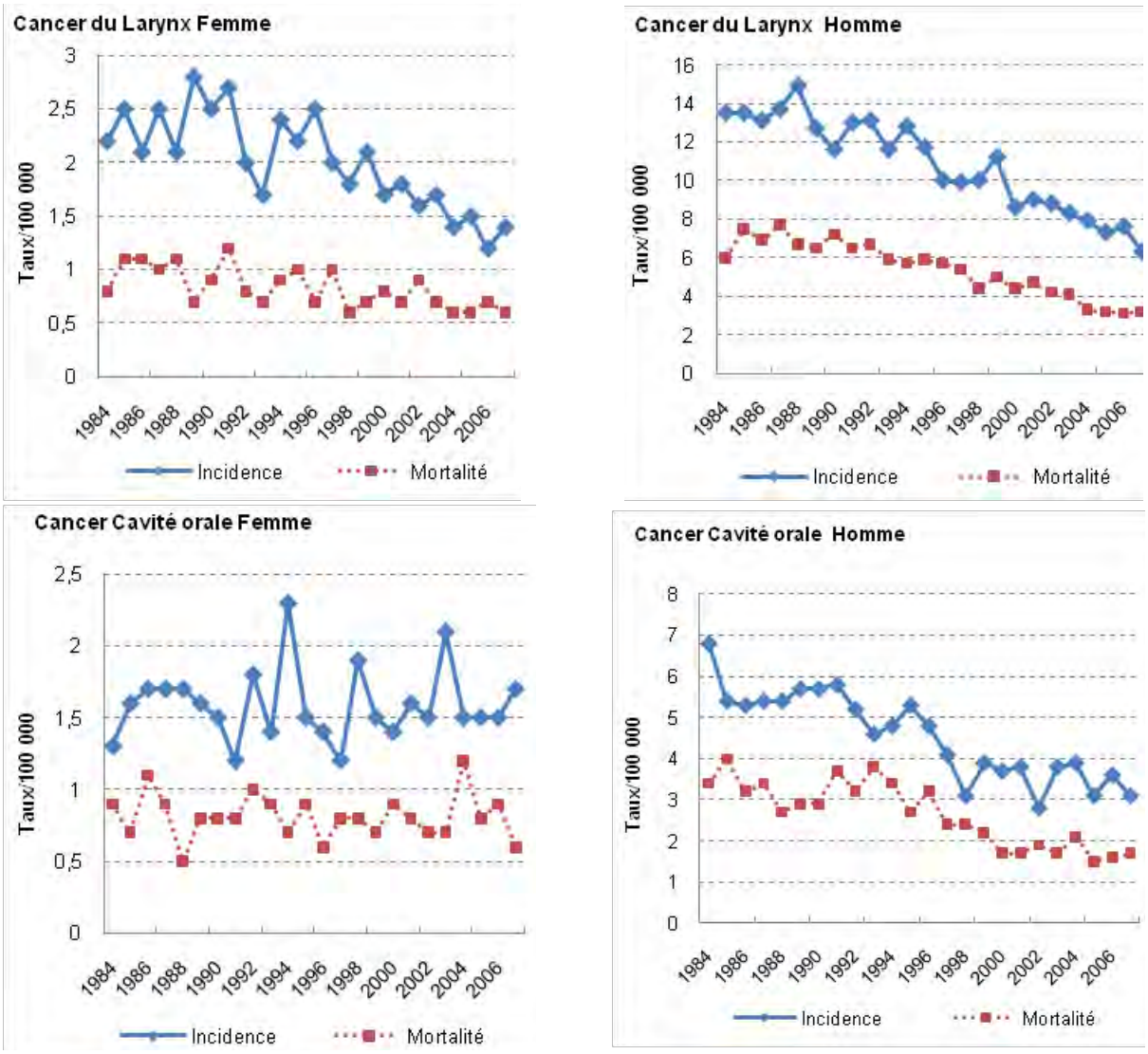


Figure 3 Time trends in the standardized incidence and mortality rates, by cancer site and sex, Québec, 1984-2007 (cont'd)

Cancer du larynx femme: Laryngeal cancer females; *Cancer du larynx homme*: Laryngeal cancer males; *Cancer cavité orale femme*: Oral cavity cancer females; *Cancer cavité orale homme*: Oral cavity cancer males; *Taux/100 000*: Rate/100 000; *Incidence*: Incidence; *Mortalité*: Mortality.

Table 7 Variations in incidence and mortality rates, by cancer site and sex, Québec, 1984-2007

	Incidence		Mortality	
Cancer site	**Period**	**APC (95% CI)**	**Period**	**APC (95% CI)**
Female				
Cervix	**1984-2007**	**–2.4 (–2.9, –1.9)**	**1984-2006**	**–3.1 (–3.6, –2.5)**
	1984-1989	–6.6 (–10.0, –3.1)	1984-1998	–2.3 (–2.4, –1.2)
	1989-2007	–1.6 (–2.3, –1.0)	1998-2007	–4.6 (–6.9, –2.3)
Vulva	1984-2007	0.7 (–0.1; 1.5)	1984-2007	0.8 (–0.4, 2.0)
Vagina	**1984-2007**	**–3.7 (–5.1, –2.3)**	**1984-2007**	**–2.0 (–3.4, –0.6)**
Anus	**1984-2007**	**3.1 (2.2, 3.9)**	1984-2007	1.0 (–1.1, 3.2)
Oropharynx	**1984-2007**	**2.6 (1.7, 3.6)**	1984-2007	–0.1 (–1.6, 1.3)
	1984-1996	0.8 (–2.0, 3.6)	1990-2007	1.7 (0.1, 3.4)
	1996-2006	4.3 (1.8, 6.8)		
Larynx	**1984-2007**	**–2.6 (–3.3, –2.0)**	**1984-2007**	**–2.2 (–2.9, –1.4)**
	1984-1988	–0.7 (–2.1, 0.8)		
	1988-2007	–4.9 (–6.6, –3.2)		
Oral cavity	1984-2007	0.1 (–0.7, 0.9)	1984-2007	0 (–0.9, 0.9)
Male				
Anus	**1984-2007**	**1.6 (0.1, 3.2)**	1984-2007	5.2 (–0.6, 11.3)
Penis	1984-2007	–0.3 (–1.4, 0.8)	**1984-2007**	**–3.4 (–5.4, –1.4)**
			1984-1990	11 (–7.5, 33.1)
			1990-2007	–5.4 (–7.9, –2.7)
Oropharynx	**1984-2007**	**0.8 (0.3, 1.4)**	**1984-2007**	**–2.2 (–2.8, –1.6)**
	1984-1990	–2.7 (–7.4, 2.2)		
	1990-2007	1.5 (0.7, 2.3)		
Larynx	**1984-2007**	**–3.1 (–3.5, –2.6)**	**1984-2007**	**–3.7 (–4.3, –3.2)**
	1984-1993	–1.1 (–2.7, 0.4)	1984-1991	–0.1 (–2.5, 2.3)
	1993-2006	–4,1 (–4,8, –3.4)	1991-2007	–4.8 (–5.4, –4,2)
Oral cavity	**1984-2007**	**–3.0 (–3.5, –2.4)**	**1984-2007**	**–3.8 (–4.7, –3.0)**

APC: Annual percent change is estimated by a Joinpoint regression model developed by the National Cancer Institute (Bethesda, USA).

2.4 SUMMARY OF THE CLINICAL BURDEN OF HPV-ASSOCIATED CANCERS BY SEX AND ATTRIBUTABLE RISK FRACTION

HPV-associated cancers constitute a major health problem. In Québec, the average annual number of new cancer cases and deaths (recorded in the death registry) by site, sex and age, estimated for the 2004-2007 period, is presented in Figure 4. During this period, on average 646 new cases of cancer and 199 deaths, all sites combined, were reported annually for women. For men, there were 694 new cases and 237 deaths. With the exception of cervical cancer (71% of new cases and 51% of deaths before age 60), cancers involving all the other anatomical sites mainly affected persons 60 years of age or older.

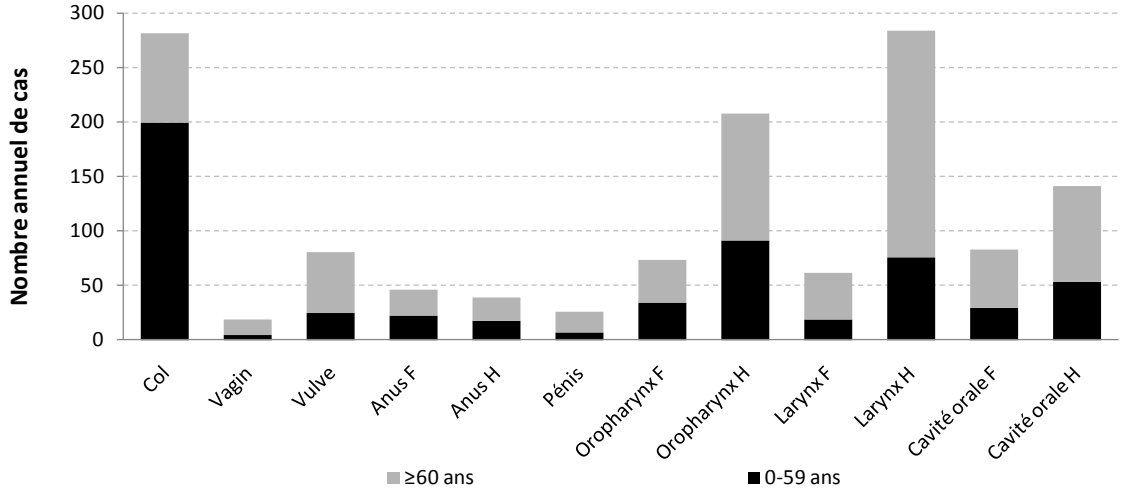


Figure 4a **Distribution of the average annual number of new cancer cases (all morphological types combined) by site, sex and age, Québec, 2004-2007**

Nombre annuel de cas: Annual number of cases; *Col*: Cervical; *Vagin*: Vaginal; *Vulve*: Vulvar; *Anus F*: Anal (F); *Anus H*: Anal (M); *Pénis*: Penile; *Oropharynx F*: Oropharyngeal (F); *Oropharynx H*: Oropharyngeal (M); *Larynx F*: Laryngeal (F); *Larynx H*: Laryngeal (M); *Cavité orale F*: Oral cavity (F); *Cavité orale H*: Oral cavity (M); *≥ 60 ans*: ≥ 60 years old; *0-59 ans*: 0-59 years old.

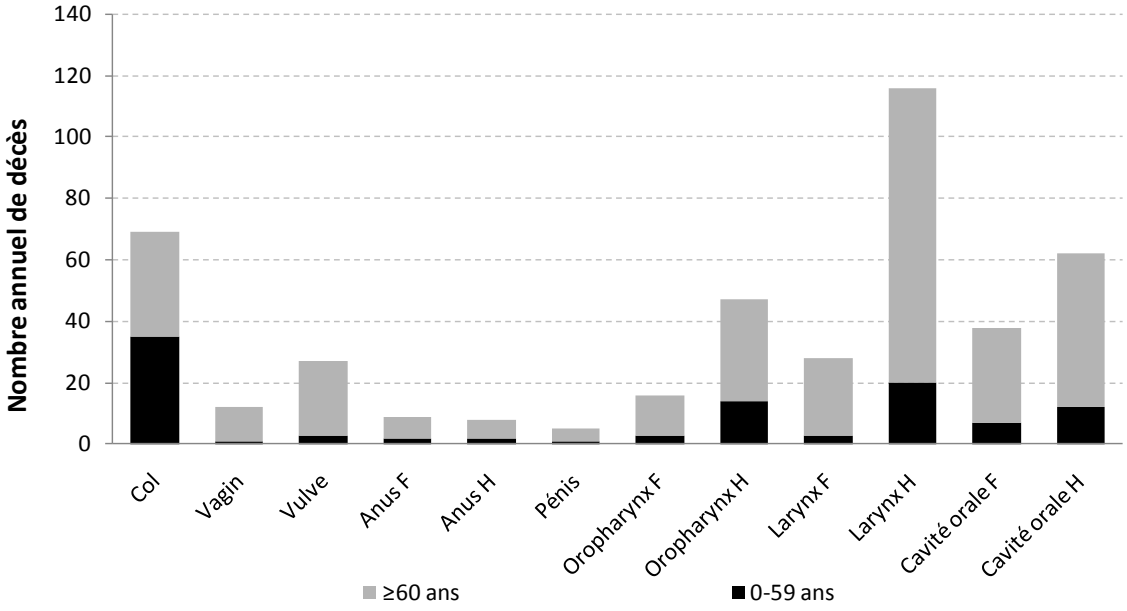


Figure 4b **Distribution of the average annual number of deaths by site, sex and age, Québec, 2004-2007**

Nombre annuel de décès: Annual number of deaths; *Col*: Cervical; *Vagin*: Vaginal; *Vulve*: Vulvar; *Anus F*: Anal (F); *Anus H*: Anal (M); *Pénis*: Penile; *Oropharynx F*: Oropharyngeal (F); *Oropharynx H*: Oropharyngeal (M); *Larynx F*: Laryngeal (F); *Larynx H*: Laryngeal (M); *Cavité orale F*: Oral cavity (F); *Cavité orale H*: Oral cavity (M); *≥ 60 ans*: ≥ 60 years old; *0-59 ans*: 0-59 years old.

By applying the specific prevalence of HPV 16 and 18 to the number of cancer cases by cancer site, it is estimated that 356 of the 646 female cancer cases and 179 of the 694 male cancer cases could have been prevented by HPV vaccination with the current vaccines (Figure 5), without taking into account the protection that the vaccines could provide against other genotypes. Excluding the cases of cancer of the larynx and oral cavity, the number of potentially vaccine-preventable cases would be 339 in women and 129 in men.

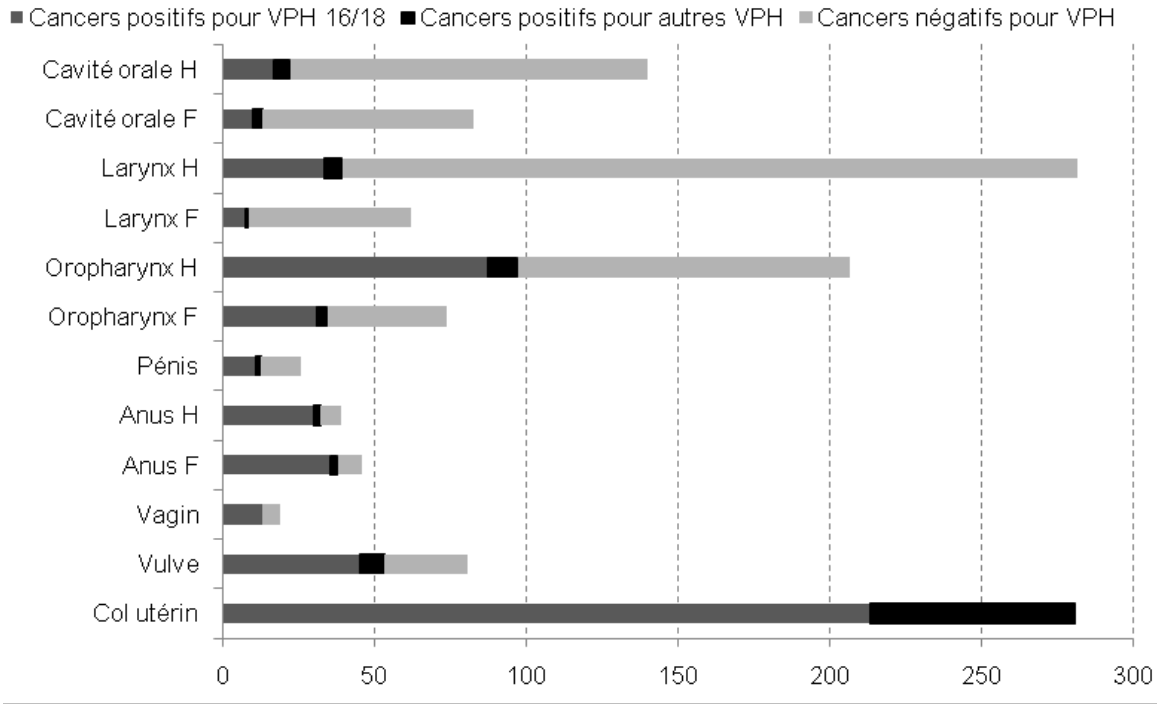


Figure 5a **Distribution of the average annual number of new cancer cases potentially preventable by vaccination, by site and sex, Québec, 2004-2007**

Cancers positives pour VPH 16/18: HPV 16-18-positive cancers; *Cancers positifs pour autres VPH*: Cancers positive for other HPV types; *Cancers négatifs pour VPH*: HPV-negative cancers; *Cavité orale H*: Oral cavity (M); *Cavité orale F*: Oral cavity (F); *Larynx H*: Laryngeal (M); *Larynx F*: Laryngeal (F); *Oropharynx H*: Oropharyngeal (M); *Oropharynx F*: Oropharyngeal (F); *Pénis*: Penile; *Anus H*: Anal (M); *Anus F*: Anal (F); *Vagin*: Vaginal; *Vulve*: Vulvar; *Col utérin*: Cervical.

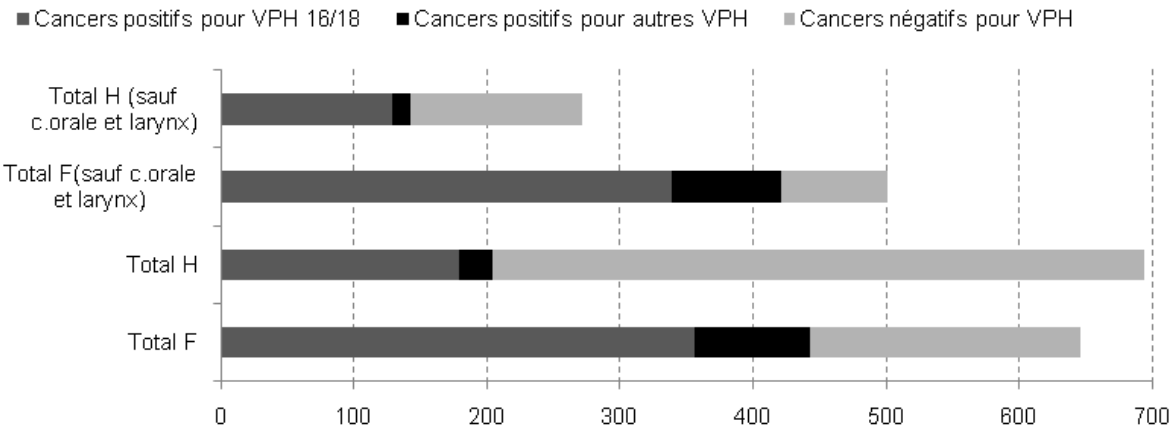


Figure 5b Distribution of the average annual number of new cancer cases potentially preventable by vaccination, by sex (all sites combined), Québec, 2004-2007

Cancers positifs pour VPH 16/18: HPV 16/18-positive cancers; *Cancers positifs pour autres VPH*: Cancers positive for other HPV types; *Cancers négatifs pour VPH*: HPV-negative cancers; *Total H (sauf c. orale et larynx)*: Total M (excluding oral and laryngeal cancer); *Total F (sauf c. orale et larynx)*: Total F (excluding oral and laryngeal cancer); *Total H*: Total M; *Total F*: Total F.

With current Québec cancer registry data, it is impossible to precisely determine the clinical burden in MSM, but the epidemiological trends observed elsewhere suggest that this group may account for a disproportionate number of cancers at certain sites, such as the anal region.[28, 88]

3 QUÉBEC DATA ON DISEASES ASSOCIATED WITH LOW-RISK HPV TYPES

3.1 ANOGENITAL WARTS

There are insufficient Québec population-based data to document the burden associated with AGW. However, by applying Manitoba and British Columbia data to the Québec population, the number of AGW cases diagnosed annually in both men and women in Québec can be estimated at 14,000.[80, 81, 89]

3.2 RECURRENT RESPIRATORY PAPILLOMATOSIS

Based on a registry of all cases recorded in university pediatric hospitals between 1994 and 2007, the estimated incidence of the juvenile form of RRP in Canada was 0.24 per 100,000 children under the age of 14, and the estimated prevalence was 1.11 per 100,000.[90] Of the 243 cases recorded, the median age at the time of diagnosis was 4.4 years (0.1-14 years) and the median number of medical procedures was 7 (1-134). It is possible that milder forms of the disease also exist but were not recorded.

In Québec, 31 cases were recorded from 1995 to 2008, which works out to an average of 2.2 new cases a year.[91] Research is continuing in order to provide a more accurate assessment of the burden of the disease.

4 CERVICAL CANCER SCREENING

The incidence and mortality rates for cervical cancer have fallen considerably over the last few decades. In Québec, the incidence rate decreased from 13.1 to 6.9 cases per 100,000 between 1984 and 2007, and the mortality rate declined from 3.8 to 1.8 per 100,000 during the same period, a reduction of 47% and 53% respectively (see Figure 3 in the previous section). We sometimes tend to forget that this significant reduction was only made possible through dedicated efforts to offer screening to the population on a widespread basis. This section will present an overview of the interventions undertaken to maintain such low incidence and mortality rates. Because there is no organized screening program and screening-specific information system in Québec, certain data will be extrapolated from the data of other Canadian provinces.

According to the MSSS, 1,186,371 cytological tests (Pap tests) were performed in 2010-2011.[9] The proportion of the tests performed specifically for screening purposes is unknown, but if we apply the estimated proportion in the context of the British Columbia screening program in 2010 (95%),[10] the number of screening tests, as opposed to tests performed for diagnostic purposes, would be approximately 1,127,000 a year in Québec. According to the combined data of six Canadian provinces, for the 2006-2008 period[11] 4.7% of screening results were abnormal, which, assuming that the same proportion is applicable to Québec, represents approximately 53,000 women a year for whom a follow-up examination or colposcopy investigation would be necessary.

The number of treatments required is difficult to estimate, since, while there is a consensus on the need to treat the serious precursor states (CIN2 and CIN3), except in the case of very young women the treatment of low-grade abnormalities has increasingly been replaced by watchful waiting, given the high rate of spontaneous regression and the risk of fertility complications following certain treatments.

Data from the RAMQ (Québec health insurance plan) registry of medical procedures indicate that 89,126 medical procedures related to the investigation or treatment of cytological abnormalities were billed by general practitioners or obstetricians/gynecologists in 2010, nearly 3,500 of which were for the treatment of high-grade lesions. The following table lists the main procedures recorded. Colpectomies and hysterectomies are not included since their indications relate more to the treatment of invasive cancer than precursors. In addition, in the case of hysterectomies, the clinical indications include conditions other than invasive cervical cancers or cervical cancer precursors.

[9] Source: MSSS, Direction générale des services de santé et médecine universitaire, personal communication.

[10] BC Cancer Agency. 2010 Annual Report. Accessible on-line at: http://www.bccancer.bc.ca/NR/rdonlyres/A6E3D1EC-93C4-4B66-A7E8-B025721184B2/50262/2010CCSPAnnualReport.pdf.

[11] Canadian Partnership Against Cancer, Cervical Cancer Screening in Canada. Monitoring Program Performance 2006-2008. December 2011. Accessible on-line at: http://www.partnershipagainstcancer.ca/wp-content/uploads/CPAC_Cervical_CS_Report_E_WEB_Final.pdf.

Table 8 Number of medical procedures related to the investigation or treatment of cytological abnormalities in 2010 (based on RAMQ data)

	Billing code	Number
Colposcopy (first)	06074	50,417
Colposcopy (subsequent)	06075	29,985
Diagnostic conization	06146	1,275
Treatment of high-grade lesion	06810	3,487
Treatment of low-grade lesion	06811	2,938
Treatment of benign lesion	06812	1,024
TOTAL NUMBER		89,126

Source: RAMQ registry of medical procedures, personal communication.

The following figure summarizes the data used to estimate the screening burden for Québec.

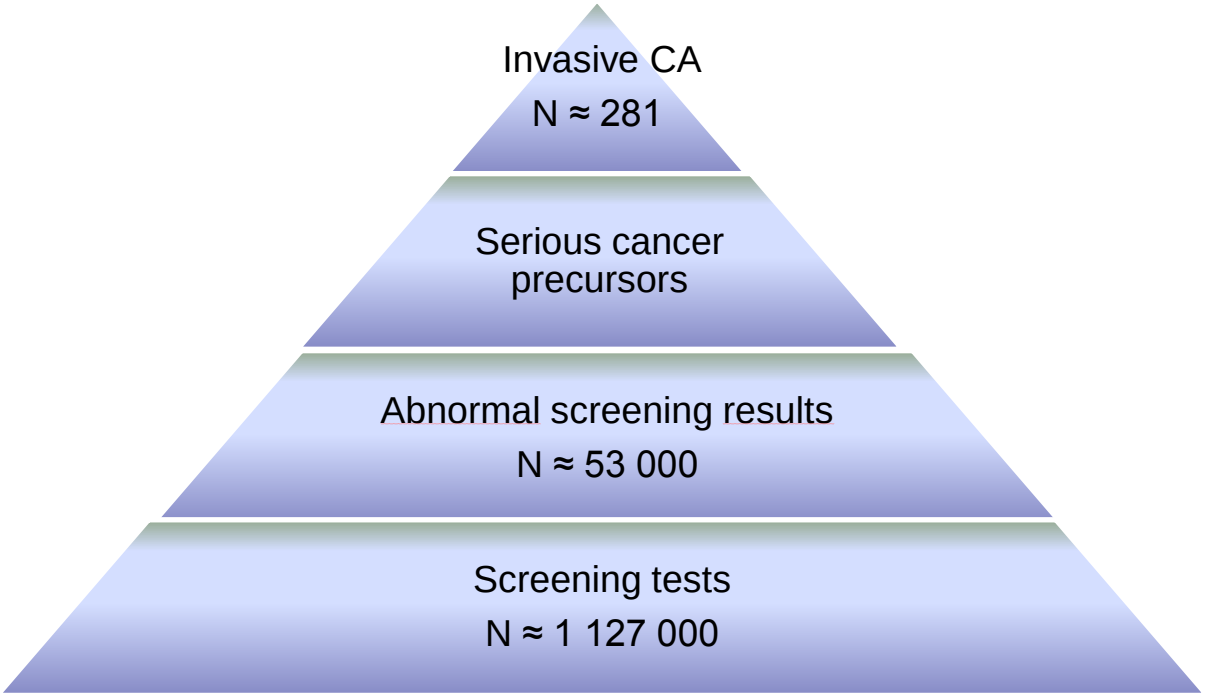


Figure 6 Estimate of the clinical burden of cervical cancer, including screening, on an annual basis in Québec

According to RAMQ data, the total cost of the procedures listed in Table 8 (including anesthesia in certain cases) was $4,688,844, which is in addition to the approximately $18 million estimated by the INSPQ for screening tests in 2009 (excluding medical visits).[12]

[12] Goggin P, Mayrand MH, et al. Recommendations on optimizing cervical cancer screening in Quebec. INSPQ. 2009. Accessible on-line at: http://www.inspq.qc.ca/pdf/publications/10815_CervicalScreening.pdf.

Compared with 2009 and 2008, the total number of procedures has been decreasing by approximately 3% a year, despite an increase in the population. These trends are probably attributable to changes in the recommendations for screening and follow-up of abnormal results issued by various organizations in the last few years. We note in particular that the number of colposcopies in young women aged 14-19 declined from 2,675 in 2008 to 1,651 in 2010, a decrease of 38%. It is difficult to determine how much of this reduction may be attributable to the fact that some young women vaccinated against HPV may also have fewer abnormal cytology results.

In November 2011, clinicians were provided with a set of new cervical cancer screening guidelines for Québec, developed by a group of experts under the coordination of the INSPQ.[92] By delaying the start of screening tests until age 21 and by spacing the tests two to three years apart, the number of screening tests should fall significantly over the coming years, since, until recently, annual screening beginning in adolescence was the standard practice. In addition, since cytological abnormalities are more frequent in young women, the number of diagnostic evaluations should continue to decrease.

All these trends will have an impact on the number of screening procedures performed and screening costs, regardless of vaccination. The arrival of vaccinated cohorts in the near future and the eventual use of the oncogenic HPV detection test for primary (i.e. first-line) screening will also have significant impacts, and there is currently no information system for tracking all these data. One option to consider would be systematic recording of the serious precursors of cervical cancer in the new cancer registry, since simply monitoring invasive cancers is not sufficiently sensitive to estimate the true burden of the disease or the impact of public health policies and interventions.

5 HPV VACCINES

5.1 VACCINE CHARACTERISTICS

The two vaccines Gardasil® and Cervarix™ are recombinant vaccines that protect against HPV. They are in the form of a sterile liquid suspension prepared from the highly purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV.

The Gardasil® vaccine contains recombinant L1 proteins of HPV types 6, 11, 16 and 18. The L1 proteins are produced by separate fermentation in recombinant *Saccharomyces cerevisiae* (yeast), then self-assembled into VLPs. The L1 proteins in Gardasil® are adjuvanted with amorphous aluminum hydroxyphosphate sulfate (AASH).[93]

The Cervarix™ vaccine contains recombinant L1 proteins from HPV types 16 and 18. The HPV 16 and HPV 18 L1 antigens are produced by a Baculovirus expression vector system in *Trichoplusia ni* cells. The L1 antigens in Cervarix™ are adjuvanted with AS04.[94]

Table 9 Dosage form/composition of the two HPV vaccines

Quadrivalent (Gardasil®)	Bivalent (Cervarix™)
Each 0.5 mL dose contains: 20 µg of HPV 6 L1 protein, 40 µg of HPV 11 L1 protein, 40 µg of HPV 16 L1 protein, 20 µg of HPV 18 L1 protein. Approximately 225 µg of aluminum (as amorphous aluminum hydroxyphosphate sulfate [AAHS] adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 µg of polysorbate 80, 35 µg of sodium borate and water for injection.	Each 0.5 mL dose contains: 20 µg of HPV 16 L1 protein, 20 µg of HPV 18 L1 protein. 3-*0*-desacyl-4'-monophosphoryl lipid A (MPL), hydrated aluminum hydroxide, sodium chloride, sodium dihydrogen phosphate dihydrate and water for injection.

The two HPV vaccines authorized for use in Canada do not contain any infectious agents or antibiotics.[95, 96]

As is the case with any vaccine, vaccination with the HPV vaccines may not result in protection in all recipients.[97-99]

Neither of the two vaccines is intended to be used for the treatment of active external genital lesions, cervical, vulvar, vaginal or anal cancers, or their precursors (CIN, VIN, VaIN or AIN).[100, 101]

5.2 VACCINE APPROVAL

Approval of the two HPV vaccines for women aged 16-25 (bivalent) and 16-45 (quadrivalent) was based on the results of efficacy studies. The approval for girls aged 9-15 was based exclusively on immunogenicity data (bridging immunogenicity studies). In the field of vaccine studies, once the efficacy of a vaccine is clearly established in one study population, efficacy studies are rarely conducted in other similar populations (e.g. females of a different age category). The underlying premise of immunogenicity bridging studies is that if the trial population attains similar (not lower) antibody levels to those in the population in which efficacy is already established, efficacy results can be bridged or inferred with respect to the new population. In addition, and specifically for the HPV vaccines, efficacy studies could not be done in preadolescent girls because it would have been considered unethical to conduct cervical examinations in this group. In addition, few or no infections or lesions would be expected in this young group.[102]

The quadrivalent vaccine is authorized in Canada for use in **girls and women 9 to 45 years of age** for the prevention of the following diseases caused by HPV types 6, 11, 16 and 18, included in the vaccine:

- cervical, vulvar and vaginal cancers caused by HPV 16 and 18;
- genital warts (condyloma acuminata) caused by HPV 6 and 11;

and the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16 and 18:

- cervical adenocarcinoma *in situ* (AIS);
- cervical intraepithelial neoplasia (CIN) grades 1, 2 and 3;
- vulval intraepithelial neoplasia (VIN) grades 2 and 3;
- vaginal intraepithelial neoplasia (VaIN) grades 2 and 3.

The quadrivalent vaccine is approved for use in **girls and women 9 to 26 years of age** for the prevention of the following diseases:

- anal cancer caused by HPV types 16 and 18;
- anal intraepithelial neoplasia (AIN) grades 1, 2 and 3, caused by HPV types 6, 11, 16 and 18.

The quadrivalent vaccine is approved for use in **boys and men 9 to 26 years of age** for the prevention of infection caused by HPV types 6, 11, 16 and 18 and the following diseases caused by these HPV types, included in the vaccine:

- anal cancer caused by HPV types 16 and 18;
- genital warts caused by HPV types 6 and 11;
- AIN grades 1, 2 and 3, caused by HPV types 6, 11, 16 and 18.[93]

The bivalent vaccine is approved for use in **girls and women 10 to 25 years of age** to prevent cervical cancer (squamous cell carcinoma and adenocarcinoma) by conferring protection against the following precancerous or dysplastic lesions caused by oncogenic HPV types 16 and 18:

- CIN grades 2 and 3;
- AIS;
- CIN grade 1.[94, 103, 104]

6 HPV VACCINE IMMUNOGENICITY

6.1 SEROLOGICAL TESTS

There is no “standard” for serological tests, and the two vaccine manufacturers use different tests during clinical research.[97, 105] In addition, since the HPV vaccines were approved, independent laboratories have developed new tests. In the most recently published studies, these new tests often replace the initial tests, which complicates the interpretation of the results of longitudinal studies.[106]

ELISA (enzyme-linked immunoassay) is the most commonly used test to measure the presence of antibodies by type. In this test, VLP are used as antigens to detect antibodies against HPV.[107] ELISA measures polyclonal antibodies and does not differentiate between neutralizing antibodies and non-neutralizing antibodies.

Neutralization tests detect total immunoglobulins (IgM, IgA and IgG) and measure functional immune response after vaccination or natural infection.[108] These tests are complex and have a relatively high coefficient of variation between results.[109] Studies have shown that neutralization tests can be 20-30 times less sensitive than ELISA.[110]

The Luminex serology platform represents a third method, which is a robust and sensitive method for detecting HPV antibodies by type. With this platform, up to 100 analyses can be performed simultaneously. The competitive Luminex assay (cLIA) measures functional immune response by simultaneous quantification of neutralizing antibodies against HPV types 6, 11, 16 and 18. This test requires monoclonal antibodies.[111] It is type-sensitive and type-specific. However, the competitive Luminex assay measures only a part of the antibodies because only one epitope is recognized. As a result, the test may underestimate the total level of protective antibodies. However, the non-competitive Luminex assay does not have this disadvantage. It measures total IgG antibodies specific for type. This test is sensitive, reproducible and easy to use.[112]

When the same test is used, it is possible to measure and compare antibody geometric mean titres (GMT) in vaccine recipients and those obtained after natural infection. It is also important to point out that the antibody titres produced by natural infection do not necessarily confer protection against subsequent infections by the same or a different HPV type.[113, 114]

6.2 GENERAL CONSIDERATIONS CONCERNING VACCINE IMMUNOGENICITY

According to the World Health Organization, protection against HPV is mediated by neutralizing antibodies.[115] This conclusion is based mainly on results obtained from animal models, in which passive antibody transfer has been shown to be protective against a challenge with the virus.[116, 117]

Studies also show that serum antibodies against HPV develop in only about half of infected persons.[23]

Clinical studies consistently demonstrate that both HPV vaccines are immunogenic. More than 98% of the non-immunosuppressed individuals who participated in the clinical studies had antibodies against the vaccine HPV types one month after the third dose.[118-122] Both vaccines are more immunogenic when administered to preadolescents and adolescents 9-14 years of age.[123, 124] In fact, two doses of the quadrivalent or bivalent vaccine, or even a single dose of the bivalent vaccine, induce detectable antibody titres in almost all individuals 9-13 years old, regardless of the serological tests used.[122, 123, 125, 126]

An increase in antibody titres is generally observed in the first 4-6 weeks after administration of HPV vaccines, followed by a significant decrease in antibody titres up to 18-24 months after vaccination. A certain plateau effect is then observed for at least 5-7 years.[127-129] This plateau effect is consistent with the assumption that a certain proportion of cells, which secrete antibodies, are transformed into long-lived plasma cells. These cells continue to ensure that there is serologic memory.[130]

Based on clinical study data, mathematical models suggest antibody persistence for several years, even decades, after vaccination. At least one mathematical model suggests that a detectable level of antibodies persists after vaccination with the bivalent vaccine for up to 50 years.[131, 132]

There do not appear to be any significant differences in the immunogenicity of HPV vaccines between males and females of the same age.[133, 134]

The manufacturer of the bivalent vaccine conducted a randomized, head-to-head comparison trial of the immunogenicity of the two vaccines in a study population of 1,106 women. The bivalent vaccine proved to be more immunogenic in all three study age groups, i.e. 18-26, 27-35 and 36-45 years old. One month after the third dose of Cervarix™, the GMT of neutralizing antibodies against HPV 16 were 2.2-3.7 times higher than after administration of the quadrivalent vaccine; titres against HPV 18 were 5.7-8.0 higher after the bivalent vaccine.[122] The same trend was observed at months 12 and 24 of the study.[135] In addition, a higher proportion of subjects vaccinated with the bivalent vaccine had neutralizing antibodies in cervicovaginal secretions (81.3% versus 50.9% for HPV 16 and 33.3% versus 8.8% for HPV 18).[122]

It should also be noted that a linear correlation was observed between antibody titres in serum and antibody titres in cervicovaginal secretions.[94]

There is currently no consensus on the seroprotective titre after HPV vaccination. However, even if the magnitude of the immune response to HPV vaccination necessary for long-term protection remains unknown, it is biologically plausible that higher titres in the short and medium term are predictive of longer antibody persistence. Since we still do not fully understand the role of cell-mediated immunity, the long-term presence of high antibody titres is encouraging.

An anamnestic response was reported in the majority of the women vaccinated 60 months earlier with the quadrivalent vaccine, whereas this response occurred in all the women vaccinated with the bivalent vaccine 84 months earlier.[136, 137] Generally, an anamnestic

response demonstrates the presence of memory B cells, which are capable of establishing rapid antibody production (3-7 days) after a booster dose or a challenge with the virus.[130]

However, in the case of HPV, there have been relatively few studies on the role of immune memory in protection against clinical diseases,[130, 138] and the response to a vaccine booster dose cannot be directly extrapolated to a generally local infection. Some experts even question whether antibodies constitute the only mechanism involved in protecting against HPV after vaccination.[139] In addition, there are no data on the duration of immune memory beyond 5-8 years.

The magnitude of the immune response after HPV vaccination, antibody persistence and immune memory should be considered especially in the context of a vaccination program for adolescents and preadolescents, who will be at high risk of HPV infections several years after HPV vaccination and for whom there are currently no efficacy data.

6.3 IMMUNOGENICITY IN OLDER INDIVIDUALS

The immunogenicity of HPV vaccines decreases with age.

In one study of the quadrivalent vaccine in women 24-45 years old, seroconversion one month after the third dose of the vaccine was 98.4%, 98.1%, 98.8% and 97.3% for HPV 6, 11, 16 and 18 respectively. Four years after HPV vaccination, 91.5%, 92.0%, 97.4% and 47.9% of them still had detectable antibodies (using cLIA) against these genotypes. Generally, the women who were seropositive for a given HPV type at the time of recruitment had higher titres for this virus type after vaccination. Four years after HPV vaccination, the GMT of antibodies in women who had had a positive serological test but a negative DNA test (DNA-negative) for HPV 6, 11, 16 and 18 at the beginning of the study were 8, 13, 4, and 15 times higher respectively than in women who were seronegative at the beginning of the study.[140]

In another study, this time with the bivalent vaccine, very high and similar seroconversion rates among the age groups were observed. However, a downward trend in the GMT of antibodies with age was reported. In fact, the GMT of antibodies against HPV 16 and HPV 18 were approximately 30% lower in women in the 36-45 age group than women in the 18-26 age group.[122]

6.4 CROSS-PROTECTION

Cross-protection refers to the potential effect of a vaccine in protecting against certain HPV types that are not found in the vaccine but that are genetically closely related to the vaccine types.

Some degree of cross-protection has been demonstrated for both vaccines. However, although it is difficult to compare the studies conducted with the two HPV vaccines and with the proviso that the studies were not originally designed to measure cross-protection, it appears that the Cervarix™ vaccine provides broader cross-protection.[141-144]

In the head-to-head comparison trial on the immunogenicity of the two HPV vaccines, the presence of neutralizing antibodies against HPV 31 and 45 was analyzed.[122] In the three age groups, one month after the third dose a higher proportion of the women vaccinated with the bivalent vaccine had detectable antibody titres with a clear trend toward higher GMT (in 11 out of 12 comparisons). In the same study, ELISA was also used to measure antibodies against HPV 31 and HPV 45 before vaccination and at months 7, 12, 18 and 24 of the study. The proportions of women who had detectable antibodies and GMT were fairly similar in both study groups. These results suggest that both vaccines induce antibodies against HPV 31 and 45, but the bivalent vaccine appears to induce more neutralizing antibodies in a higher proportion of vaccinated individuals.

In the same study, tests for the presence of CD4 cells specific to HPV 31 and HPV 45 that express at least two cytokines were performed in a subsample of participants. The results show that the GMT of these cells were higher in the group vaccinated with the bivalent vaccine than in the group vaccinated with the quadrivalent vaccine. Tests to detect memory B cells specific to HPV 31 and HPV 45 were also performed, but because of the small number of subjects per group and the heterogeneity of the results, conclusions cannot be drawn regarding a significant difference between the two vaccines.

Analysis of clinical trials data indicates a certain degree of correlation between antibody titres against HPV 16 and 18 and the degree of cross-protection.[143]

As in the case of induced immunity against the vaccine HPV types, the duration, robustness and clinical impact of the cross-protection needs to be further studied.

6.5 IMMUNOGENICITY USING DIFFERENT VACCINATION SCHEDULES

A study conducted by the Program for Appropriate Technology in Health initiative measured the immunogenicity of the quadrivalent vaccine administered according to the following four schedules: 0, 2 and 6 months; 0, 3 and 9 months; 0, 6 and 12 months; and 0, 12 and 24 months. The immunogenicity of the 0, 3 and 9 month and the 0, 6 and 12 month schedules was not inferior to that observed in the group vaccinated according to the schedule recommended by the manufacturer, i.e. 0, 2 and 6 months. The 0, 12 and 24 month schedule induced lower antibody titres.[145] However, since the girls vaccinated according to the 0, 12 and 24-month schedule were older, the impact of the participants' age on immune response cannot be ruled out. In addition, it appears that other vaccines were administered to the participants during the study period, And so some interference between the vaccines in one or more of the study groups was possible.

The manufacturer of the bivalent vaccine conducted a comparison study on the immunogenicity of the 0, 1 and 12 month schedule versus the 0, 1 and 6 month schedule. Non-inferiority with respect to seroconversion rates and GMT was observed.[146]

Two studies, one with the quadrivalent vaccine and the other with the bivalent vaccine, measured the immunogenicity of the two-dose schedule (0 and 6 months) and compared it with that of the three-dose schedule (0, 1-2 and 6 months).

In the Canadian study (British Columbia, Nova Scotia and Québec) with the quadrivalent vaccine,[147] 825 participants were recruited. Group 1 (260 girls aged 9-13) received two doses of vaccine at 6 month intervals; group 2 (260 girls aged 9-13) and group 3 (305 women aged 16-26) received three doses of vaccine according to the 0, 2 and 6 month schedule. Blood samples were taken at months 7, 18, 24 and 36 of the study. At month 7, anti-HPV GMT by HPV type were 1.8 to 2.4 times higher in group 1 than in group 3 (women aged 16-26 vaccinated with three doses, comparison group selected on the basis of the primary study objective, for whom efficacy data were available) (Table 10).

Table 10 Geometric mean titre (GMT) ratios for groups 1 to 3 in the study with the quadrivalent vaccine (per-protocol population) – month 7

Test (cLIA)	GMT ratio (95% CI)		
	Group 1*/Group 3‡	Group 1/Group 2†	Group 2/Group 3
Anti-HPV 6	2.37 (1.78-3.14)	1.18 (0.89-1.57)	2.01 (1.51-2.66)
Anti-HPV 11	1.86 (1.53-2.25)	1.12 (0.92-1.37)	1.65 (1.37-2.00)
Anti-HPV 16	2.10** (1.62-2.73)	0.97 (0.74-1.25)	2.18 (1.68-2.82)
Anti-HPV 18	1.84** (1.47-2.31)	0.71 (0.56-0.89)	2.60 (2.08-3.26)

* Group 1: girls aged 9-13 vaccinated with two doses of vaccine.

† Group 2: girls aged 9-13 vaccinated with three doses of vaccine.

‡ Group 3: women aged 16-26 vaccinated with three doses of vaccine.

** Results associated with the primary study objective.

The conclusions of the same study at month 36 were as follows:

- A two-dose schedule with the doses administered six months apart in the 9- to 13-year-olds was **non-inferior** in terms of seroconversion and GMT at months 18, 24 and 36 compared with a three-dose schedule in the women aged 16-26;
- A two-dose schedule with the doses administered six months apart in the 9- to 13-year-olds was **non-inferior** in terms of seroconversion and GMT at months 18, 24 and 36 compared with a three-dose schedule in the girls aged 9-13, except for HPV 6 and HPV 18.[147]

In a study with the bivalent vaccine,[146] one group of 65 girls aged 9-14 received two doses of vaccine (0 and 6 months), and a second group of 114 young women aged 15-25 received three doses of vaccine (0, 1 and 6 months). The main conclusion of this study was as follows:

- In the girls aged 9-14, two doses of the bivalent vaccine induced immunity that was non-inferior (with a ratio of close to one) to that observed after three doses of vaccine administered to the women in the 15-25 age group in whom clinical efficacy was demonstrated. These results remained consistent at month 18 of the study.[146]

Table 11 GMT and GMT ratios of anti-HPV-16/18 antibodies obtained one month after HPV vaccination in girls aged 9-14 years who received two doses of the bivalent vaccine six months apart compared to women aged 15-25 years who received three doses of the bivalent vaccine at 0, 1 and 6 months[148]

Group	n	GMT (ELU/mL)	GMT ratio (3-dose/2-dose) (95% CI)
Bivalent 0 and 6 months – 9-14 years			
HPV 16	65	11,067	0.93 (0.68-1.28)
HPV 18	64	5,510	0.77 (0.59-1.01)
Bivalent 0, 1 and 6 months – 15-25 years			
HPV 16	111	10,322	
HPV 18	114	4,262	

ELU: ELISA (enzyme-linked immunosorbent assay) units.

The results of at least four other studies with alternative schedules involving females and males (NCT01381575; NCT01184079; NCT00862810 and NCT00572832)[13] are expected in the coming months.

6.6 INTERACTION WITH OTHER VACCINES AND MEDICATIONS

In all the clinical studies with the two HPV vaccines, subjects who had received blood products or immunoglobulins in the 3-6 months preceding the first dose of vaccine were excluded.

6.6.1 Use with other vaccines

Clinical study results indicate that the quadrivalent vaccine can be coadministered with Menactra, Adacel and RECOMBIVAX-HB®. In one coadministration study, a non-significant decrease of 1% in the anti-HBs seroprotection rates and a 33% decrease in GMT (534.9 mIU/mL versus 792.5 mIU/mL; $p < 0.05$) were observed in the group of women aged 16-23 who had received the three doses of the quadrivalent HPV and RECOMBIVAX-HB® vaccines simultaneously.[149]

In another placebo-controlled study, an increase in cases of swelling at the injection site after concomitant administration of the quadrivalent HPV vaccine with the meningococcal polysaccharide vaccine (groups A, C, Y and W-135) and with the DTaP vaccine was observed. The majority of the reported cases of swelling at the injection site were mild or moderate in intensity.[93]

The bivalent HPV vaccine can be administered simultaneously with the Tdap, Tdap-IPV and quadrivalent meningococcal (MCV-4) vaccines without clinically relevant interference with the antibody response to the individual antigens in the various vaccines.[150] However, a tendency

[13] Clinical trials. Gov, available at: http://clinicaltrials.gov/.

toward lower GMT against HPV 16 and 18 was observed following sequential administration of the combined Tdap-IPV vaccine and the bivalent HPV vaccine one month later, as compared with administration of the bivalent vaccine only.[150]

In another study, no clinically significant interference in the antibody response to the HPV and hepatitis A antigens was found following concomitant administration of the bivalent HPV vaccine and Twinrix in preadolescent girls. However, the GMT of anti-HBs antibodies were lower after coadministration of the two vaccines. The percentage of subjects who attained an anti-HBs titre of ≥ 10 mIU/mL was 98.3% after concomitant vaccination and 100% after vaccination with Twinrix only.[151]

In a Québec study, coadministration of the quadrivalent HPV vaccine and Twinrix Junior and sequential administration of the two vaccines in girls aged 9-10 were studied. The anti-HBs seroprotection rates one month after the second dose of Twinrix were 97.5% in both study groups. The GMT of the anti-HBs antibodies were 1,679 mIU/mL (95% CI 1,314-2,146) in the group receiving the coadministered vaccines and 2,006 mIU/mL (95% CI 1,586-2,537) in the group in which the vaccines were administered sequentially (non-statistically significant difference of 16% in the GMT).[152]

In the same study, the anti-HA seroconversion rates were 100% in both study groups, and the GMT of anti-HA antibodies were higher in the group in which the quadrivalent vaccine was coadministered with the Twinrix Junior vaccine: 2,955 (95% CI 2,623-3,330) and 2,130 (95% CI 1,809-2,508) respectively.[152] The results for the HPV vaccine components were not available at the time of writing.

The clinical significance of these observations is not known.

6.6.2 Use with medications

In clinical studies of HPV vaccines, 4% to 30% of participants were taking analgesics, anti-inflammatories, antibiotics, antihistamines or vitamin preparations. Vaccine immunogenicity, efficacy and safety do not appear to have been affected by these medications.[93, 94] In addition, 50% to 60% of the female participants were taking hormonal contraceptives. There is no evidence that the use of hormonal contraceptives had any impact on immune response.[93, 94]

A small percentage (< 1.8%) of the clinical study participants received inhaled, topical or parenteral corticosteroids. These medications do not appear to have influenced immune response to the HPV vaccine.[93]

Very few data are available on the immunogenicity and efficacy of HPV vaccines in individuals receiving immunosuppressive therapy. As is the case with other vaccines, a satisfactory response may not be obtained in patients receiving therapy with immunosuppressive agents.[93, 94]

Generally, vaccines are less immunogenic in immunosuppressed individuals. However, fairly high seroconversion rates (≥ 95%) were observed in at least one study of the quadrivalent vaccine in HIV-seropositive individuals.[153] In another study with the same vaccine involving individuals with an inherited immunodeficiency syndrome, levels of neutralizing antibody titres were reported to be 64-80 times lower than in individuals considered immunocompetent.[154] Several other studies with immunodepressed individuals are under way or have just been finalized, and more robust data for these population groups are expected in the near future.

7 HPV VACCINE EFFICACY

7.1 GENERAL CONSIDERATIONS CONCERNING HPV VACCINE EFFICACY

The main criteria used in the clinical trials to determine vaccine efficacy were as follows:

- Reduction in the incidence of persistent infections due to the vaccine HPV types and certain other related types;
- Reduction in the number of cases of moderate and severe intraepithelial neoplasia (CIN2/3) and carcinoma *in situ*;
- Reduction in other HPV-associated cancers and precursors (e.g. VIN/VaIN, AIN, penile intraepithelial neoplasia [PIN]);
- Reduction in genital warts (condyloma acuminata).

It should also be pointed out that relying on cervical cancer as the primary criterion for measuring the efficacy of HPV vaccines in clinical studies would be unethical, since screening can prevent most of these cancers by identifying and treating the precancerous pathologies.[93, 94]

Comparing the two available vaccines is difficult for the following reasons:

- The studies were conducted in different countries, with different prevalence rates of the HPV types (rate in the population and proportion due to types 16/18).
- There was a lack of consistency among studies as to whether or not to exclude high-grade lesions before the beginning of the study.
- The number of sexual partners before the beginning of the study varied in different studies.
- The time at which case counting began was different.
- Different tests were used, for both antigen detection and antibody measurement.
- Co-infections were managed differently, depending on the study.
- The results were analyzed differently, depending on the study.

7.2 EFFICACY IN WOMEN

There are currently no data on efficacy measured in terms of prevention of cervical lesions in preadolescent and adolescent girls vaccinated at the age of 15 years or younger, since the groups vaccinated at this age have not yet reached the age at which these lesions develop.

7.2.1 Efficacy against precancerous and cancerous cervical lesions in the female population 15-26 years of age

In women with no evidence of prior exposure to the vaccine HPV types (negative for HPV DNA in cervical samples and seronegative), efficacy against the vaccine types was very high for both vaccines. Several cohorts were analyzed. The populations studied in the clinical trials that seem to be most similar are the Total Vaccinated Cohort - Naïve (TVC-naïve) (PATRICIA) for the bivalent vaccine and the Restricted Modified Intention-To-Treat-2

(RMITT-2) (FUTURE I/II) for the quadrivalent vaccine (Table 12). This section deals mainly with the results obtained from the analysis of these last two cohorts (one per vaccine).

Table 12 Description of two clinical trial populations considered the most comparable

Population (study)	**Bivalent**[98, 155, 156]	**Quadrivalent**[157]
	TVC-naïve (PATRICIA)	RMITT-2 (FUTURE I/II)
Eligible age	15-25 years old	16-26 years old
Cytology at the beginning of the study	Normal	Normal
Serological status at the beginning of the study	Seronegative for HPV 16/18	Seronegative for HPV 6/11/16/18
HPV DNA status at the beginning of the study	Negative for 14 HPV types	Negative for 14 HPV types
Doses received	≥ 1 dose	≥ 1 dose
Average follow-up	3.7 years	3.6 years

In women aged 16-26 initially HPV DNA-negative, the two vaccines demonstrated very high efficacy in preventing persistent infections and high-grade cervical lesions (CIN2/3) due to the vaccine HPV types for up to 4-6 years after HPV vaccination (Tables 13, 14, 15).[158, 159]

More specifically, in the analyses of the per-protocol and RMITT-2 populations receiving the quadrivalent vaccine, vaccine efficacy against high-grade cervical lesions (CIN2+) associated with types 16 and 18 was 98-100%.[160]

An evaluation of the efficacy of the quadrivalent vaccine against non-vaccine HPV types was also carried out. According to the analysis of the RMITT-2 population, efficacy against persistent infections (six months) was 46% (95% CI 15-66%) for type 31[157] (Table 13). Efficacy against CIN2+ (including the lesions in which type 16 or 18 were found) for this same type was 70% (95% CI 32-88%)[161] (Table 14). When lesions co-infected with HPV 16 or 18 were excluded from the analysis, efficacy against CIN2+ was no longer statistically significant for any of the non-vaccine types[161] (Table 15). Efficacy against persistent lesions or CIN2 lesions (including or excluding lesions co-infected with HPV 16/18) for the other non-vaccine types (other than type 31), evaluated individually, was not statistically significant. Efficacy against CIN2+ (including lesions co-infected with type 16 or 18) for all the HPV types measured was 51% (95% CI 33-64%)[161] (Table 14).

For the bivalent vaccine, per-protocol vaccine efficacy against high-grade cervical lesions (CIN2+) associated with types 16 and 18 was 93% (and 98% depending on the HPV type assignment algorithm, when there were infections or lesions caused by more than one HPV type).[98] According to the analysis of the TVC-naïve cohort, the efficacy of the bivalent vaccine against high-grade cervical lesions (CIN2+) associated with types 16 and 18 was 98-100%.[162]

Again, according to the analysis of the TVC-naïve cohort, efficacy against persistent infections (six months) was statistically significant for types 31, 33, 45 and 52, ranging from 19% to 79% (Table 13). The efficacy of the bivalent vaccine against CIN2+ (including lesions co-infected with type 16 or 18) was 89% (95% CI 66-98%) for type 31, 82% (95% CI 53-95%) for type 33 and 100% (95% CI 42-100%) for type 45[98, 159, 162] (Table 14). When lesions co-infected with type 16 or 18 were excluded from the analysis, efficacy against CIN2+ persisted and remained statistically significant for types 31 and 33 (Table 15). Efficacy against CIN2+ for the other non-vaccine types (other than types 31 and 33) evaluated individually was not statistically significant. Efficacy against CIN2+ (including lesions co-infected with type 16 or 18) for all the types measured was 70%.[162]

Table 13 Vaccine efficacy against persistent infection (≥ 6 months) in the HPV-naïve population[155, 157, 161-163]

HPV type	Bivalent (%)	95% CI	Quadrivalent (%)	95% CI
HPV 16	94.7	(91.8-96.7)	95.5	(90.0-98.4)
HPV 18	92.3	(86.5-96.0)	95.8	(84.1-99.5)
HPV 31	77.1	(67.2-84.4)	46.2	(15.3-66.5)
HPV 33	43.1	(19.3-60.2)	28.7	(–45.1-65.8)
HPV 45	79.0	(61.3-89.4)	7.8	(–67.0-49.3)
HPV 52	18.9	(3.2-32.2)	18.4	(–20.6-45.0)
HPV 58	–6.2	(–44.0-21.6)	5.5	(–54.3-42.2)
HPV 31/33/45/52/58	33.8	(24.5-41.9)	25.1	(5.0-41.0)
All non-vaccine HPV types tested	19.0	(11.5-25.9)	19.3	(0.4-34.6)
All types tested	N/A	N/A	44.0	(32.1-53.9)

Table 14 Vaccine efficacy against CIN2+, including lesions co-infected with HPV 16/18, in the HPV-naïve population[155, 157, 161-163]

HPV type	Bivalent (%)	95% CI	Quadrivalent (%)	95% CI
HPV 16	98.8	(93.2-100)	100.0	(93.5-100.0)
HPV 18	100	(79.9-100)	100.0	(73.7-100.0)
HPV 31	89.4	(65.5-97.9)	70.0	(32.1-88.2)
HPV 33	82.3	(53.4-94.7)	24.0	(–71.2-67.2)
HPV 45	100	(41.7-100)	-51.9	(–17.8-82.6)
HPV 52	30.4	(–45.0-67.5)	25.2	(–46.3-62.5)
HPV 58	36.1	(–58.6-75.6)	18.9	(–64.7-60.7)
HPV 31/33/45/52/58	58.0	(34.8-73.6)	32.5	(–0.3-55.0)
All non-vaccine types tested	56.2	(37.2-69.9)	32.5	(6.0-51.9)
All types tested	69.8	(57.8-78.8)	51.0	(33.1-64.4)

Table 15 Vaccine efficacy against CIN2+, excluding lesions with HPV 16/18 co-infection, in the HPV-naïve population[155, 157, 161-163]

HPV type	Bivalent (%)	95% CI	Quadrivalent (%)	95% CI
HPV 31	83.4	(43.3-96.9)	57.4	(–2.0, 83.9)
HPV 33	76.3	(35.5, 93.0)	–21.6	(–214.2, 51.9)
HPV 45	100	(–429.7, 100)	N/A	N/A
HPV 52	–132.3	(–637.5, 16.2)	–1.3	(–111.0, 51.4)
HPV 58	–11.9	(–233.4, 61.7)	–15.8	(–156.3, 47.0)
HPV 31/33/45/52/58	N/A	N/A	9.1	(–39.5, 40.9)
All non-vaccine types tested	17.1	(–25.5, 45.4)	4.9	(–36.6, 33.9)
All types tested	-	-	-	-

In another study of the bivalent vaccine in women aged 15-25, vaccine efficacy against CIN2/CIN3+ in the TVC-naïve cohort was 98-100%, with no differences between women in the 15-17 and 18-25 age groups.[140, 159] However, in the TVC cohort, a clear downward trend in efficacy against CIN2/CIN3+ was observed in older women. For example, efficacy against CIN2 was 44% in 15- to 17-year-olds and 23.5% in 18- to 25-year-olds; efficacy against CIN3+ was 65.5% and 33.1% respectively. The authors indicated that this decrease in efficacy with age could be due to a higher proportion of women aged 18-25 exposed to the virus at the beginning of the study (30% among 18- to 25-year-olds versus 20% among 15- to 17-year-olds).[140, 159]

7.2.2 Efficacy against vulvar and vaginal cancers and their precursors (VIN and VaIN) in women aged 15-26 years

The efficacy of the quadrivalent vaccine against VIN/VaIN 2/3 associated with types 16 and 18 was 95-97% (95% CI 82-100%) for the RMITT-2 cohort.[93, 158]

The efficacy of the bivalent vaccine against VIN/VaIN was also measured. According to the analysis for the TVC-naïve cohort, efficacy against VaIN1+ was 82% (95% CI 17-98%). All the other results were not statistically significant.[164] Analyses of the efficacy of the bivalent vaccine against VIN/VaIN were not originally planned as part of the study protocol and were carried out on a smaller sample of subjects, which may explain why the results are not statistically significant. Given that the majority of cases of VIN and VaIN are due to HPV 16 and 18, it is biologically plausible that both vaccines protect against VIN/VaIN.

7.2.3 Efficacy against anogenital warts in women aged 16-26 years

The efficacy of the quadrivalent vaccine against AGW was evaluated in two randomized, placebo-controlled studies. A total of 17,599 women aged 16-26 (average age 20) who had had an average of 2.1 lifetime sexual partners (maximum 4 partners) participated. In the population naïve for the HPV vaccine types, efficacy against AGW due to HPV 6 and HPV 11 four years after vaccination was estimated at approximately 99%, and against all AGW at approximately 83%.[93, 158, 165]

The efficacy of the bivalent vaccine against anogenital warts was not studied.

7.2.4 Efficacy in older women (> 24 years)

Efficacy in preventing precancerous lesions or genital lesions was demonstrated in women over the age of 26 for both the quadrivalent[140, 166] and bivalent vaccines.[167] It appears that the efficacy of both vaccines decreases when administered at a later age.[140, 159]

In a study of women aged 24-45, efficacy of the quadrivalent vaccine was estimated four years after HPV vaccination. In the per-protocol population, efficacy against persistent infection, CIN or external genital lesions due to the vaccine HPV types was 91.3% in women aged 24-34 and 83.8% in women aged 35-45. Specifically, it was 100% against AGW, 89.6% against persistent infection, 94.1% against all CIN and 83.3% against CIN2/3+.[140] In the total population (intention-to-treat population), efficacy against persistent infection, CIN or external genital lesions due to the vaccine HPV types was 44.1% in women aged 24-34 and 51.2% in women aged 35-45.

In another randomized, placebo-controlled study, the efficacy of the bivalent vaccine in women aged ≥ 26 years was investigated. In the per-protocol cohort, an efficacy of 81.1% against intraepithelial neoplasias and persistent infections due to the vaccine HPV types was reported. In the same cohort, the efficacy of the vaccine against CIN1+ was 91.1% in the women who were seronegative at the beginning of the study and 86.1% in all the women regardless of their serological status. Efficacy of the vaccine against persistent infection with HPV 31 and HPV 45 was 79.1% (95% CI 27.6-95.9%) and 76.9% (95% CI 18.5-95.6%) respectively.[167]

7.2.5 Efficacy in women previously exposed to HPV 16 and HPV 18

For both vaccines, some degree of efficacy in preventing the occurrence of subsequent lesions was demonstrated in women previously exposed to HPV 16 and 18. More specifically, this efficacy was measured in women aged 16-26 who were seropositive (antibodies) and DNA-negative for HPV 16 and 18 at recruitment. It is important to note the very limited number of cases and the importance of conducting further studies that will confirm or refute these data.[168, 169]

Table 16 Efficacy of HPV vaccines in women previously exposed to HPV 16 and 18

Efficacy	Quadrivalent	Bivalent
CIN2+	100% (0-100%) 0/1,243 cases versus 4/1,283	89% (11-100%) 1/1,710 cases versus 9/1,777
AGW	100% (40-100%) 0/1,268 cases versus 7/1,301	N/A

In addition, some degree of efficacy of both vaccines against CIN2+ was demonstrated in women who had previously received treatment for cervical pathologies associated with HPV.[170-172]

7.2.6 Efficacy against recurrence of anogenital warts and respiratory papillomatosis

Some recent studies have shown a possible decrease in the risk of recurrence of AGW and RRP after HPV vaccination with the quadrivalent vaccine in individuals who previously had either of these diseases.[173, 174] If these results are confirmed by more robust studies, targeted use of the quadrivalent vaccine could be considered in order to decrease the burden of these diseases.

7.2.7 Efficacy data on the frequency of use of certain procedures (Pap test, colposcopy, etc.)

The efficacy of both vaccines against cytological abnormalities and against the need for subsequent procedures has been demonstrated.

In women aged 16-26 who were DNA-naïve and seronegative for the vaccine HPV types, a 19.8% reduction in the number of colposcopies and a 22% reduction in the number of cervical excisions were observed three and a half years after vaccination with the quadrivalent vaccine.[158]

In women aged 15-25 who were DNA-naïve and seronegative for the vaccine HPV types, a 29% reduction in the number of colposcopies and a 33.2% reduction in the number of cervical excisions were reported for the four years following vaccination with the bivalent vaccine.[140, 159]

However, because of the different experimental designs, it is difficult to compare the results obtained in these two studies. Also, since the experimental design of the two studies involved a screening, investigation and treatment protocol different from the protocols used in Québec and in Canada, the impact observed should not be extrapolated to the general population of women in the same age group.

7.3 EFFICACY IN MEN

To the best of our knowledge, there are no efficacy data on boys under the age of 15.

7.3.1 Efficacy against anogenital warts and cancerous and precancerous penile/perineal/perianal lesions in men aged 16-26 years

The efficacy of the quadrivalent vaccine against infections and diseases due to HPV was estimated in a randomized, placebo-controlled study involving 4,065 men aged 16-26. In the per-protocol population, at follow-up of nearly three years after the start of vaccination, efficacy against external lesions was 90.4% against the vaccine types and 83.8% against all the types measured. In the total study population (intention-to-treat population), efficacy was 65.5% and 60.2% respectively. In the per-protocol cohort, specific efficacy against AGW

caused by the vaccine HPV types was 89.4%. Because of the small number of PIN cases, the efficacy observed was not statistically significant.[175, 176]

In a substudy, the efficacy of the quadrivalent vaccine in MSM was evaluated. Its efficacy against persistent anal infections due to the vaccine HPV types was 94.9% in the per-protocol cohort and 59.4% in the total study cohort (intention-to-treat population). Vaccine efficacy against AIN grades 2 and 3 due to the vaccine HPV types was 74.9% in the per-protocol cohort and 54.2% in the total study cohort. However, it should be noted that given the very small number of anal neoplasias, the confidence intervals were very large. The authors also indicated that the participants in this substudy had to have a maximum of five sexual partners and that the study results may not be generalizable to the general population of MSM of the same age. However, the results of this study are encouraging and should be similar for boys who are not yet or not very sexually active.[177]

7.4 POPULATION-LEVEL HPV VACCINE EFFECTIVENESS

In Australia, the quadrivalent vaccine was offered free of charge during the period from mid-2007 to the end of 2009 to all girls aged 12-18 years and to women aged 26 years or under. After this period, only girls aged 12-13 had access to the vaccine free of charge. The quadrivalent vaccine has been approved in Australia for boys and men since 2007 but was not included in the publicly funded program until 2012. In 2009, 65.1% of the female residents of Australia who were eligible for free vaccination received the HPV vaccine. The results of three evaluations of the impact of the vaccination program against AGW have been published.[178-180]

The most recent evaluation, based on the results from a clinic specializing in the treatment of sexually transmitted disease, shows that during the 2004-2007 period, the proportion of patients with AGW was on the rise or stable in all age groups. After the introduction of the vaccination program, a decline in the proportion of patients with AGW was observed. In fact, the comparison of two 12-month periods in 2010-2011 and 2007-2008 showed that the proportion of females under 21 years of age who had AGW fell from 18.7% to 1.9%. Among heterosexual males in the same age group, a decrease from 22.9% to 2.9% was observed. For the same period, there was no significant decrease among women and men aged 30 and older. The authors concluded that four years after the start of the program, the reproductive rate[14] of AGW was less than one.[180]

In another publication, the prevalence of AGW before and after the introduction of the vaccination program was estimated among 112,083 new patients who consulted for medical treatment in sexually transmitted disease clinics. Before vaccination, 9% of the patients had AGW. Three years after introduction of the program, a 59% decrease in the frequency of AGW diagnoses was observed in women covered by the free vaccination; a 28% decline was observed in heterosexual men in the same age group. There was no significant decrease among women 26 years of age or older at the start of the vaccination program or among MSM.[179]

[14] Average number of persons infected in a susceptible population by an infected person during his/her infectious phase.

The results of the first evaluation carried out in 2008 showed the same trend.[178]

The Australian data demonstrated that the quadrivalent vaccine has the potential to quickly decrease the frequency of AGW after introduction of the vaccination program. However, it should be pointed out that the individual vaccination status of the patients was not known in the three above-mentioned evaluations. In addition, caution must be exercised in generalizing the results, since the evaluations were performed ecologically and exclusively among patients who consulted for a sexually transmitted disease.

7.5 EFFICACY OF A ONE- OR TWO-DOSE SCHEDULE

The efficacy of a schedule of one, two or three doses of the bivalent vaccine was measured approximately four years after vaccination. In total, 5,967 women aged 18-25 were initially randomly assigned to receive the bivalent HPV vaccine or a control vaccine; 802 of these women received two doses and 384 received only one dose of the vaccine. The incidence of persistent infections that lasted one year or more was unrelated to the number of vaccine doses received. In fact, the efficacy of one, two and three doses of the bivalent vaccine against persistent HPV 16 and HPV 18 infections was, respectively, 100% (95% CI 66.5-100%), 84.1% (95% CI 50.2-96.3%) and 80.9% (95% CI 71.1-87.7%).[181]

The authors pointed out that it is important to evaluate the efficacy of a single dose of the vaccine, that these Costa Rican data cannot necessarily be extrapolated to another HPV vaccine, and that the duration of protection and the level of cross-protection should be further studied. They also indicated that evidence from immunogenicity studies supports their findings. On the basis of their results, the authors concluded that a two-dose regimen that covers more women could provide a greater reduction in the number of cervical cancer cases than a three-dose regimen that uses the same number of total vaccine doses but covers fewer women. They also noted that surveillance data from regions where programs with extended intervals are used (Québec and Mexico) could be used to monitor the efficacy of a vaccine schedule using fewer than three doses.

To the best of our knowledge, there are no published data on the efficacy of a reduced-dose schedule for the quadrivalent vaccine.

7.6 CROSS-PROTECTION AND EFFICACY AGAINST NON-VACCINE TYPES

The detailed data by HPV type were presented in the previous sections. Cross-protection has been demonstrated for both vaccines and appears to be higher after vaccination with the bivalent vaccine than with the quadrivalent vaccine. However, direct comparisons are difficult since the studies were not originally designed to measure cross-protection. Standardization calculations of the efficacy of a clinical trial were carried out using data on the placebo cohort that had participated in the studies of the other vaccine: the differences do not appear to be explained solely by the differences between the cohorts (or the countries where the studies were conducted[161]).

In addition, in a nine-year study conducted with the bivalent vaccine in Brazil, efficacy against the vaccine types (16 and 18) persisted over the entire period. However, this study did not demonstrate efficacy against the non-vaccine types, in contrast to the findings of the main efficacy study with the bivalent vaccine.[162] It should be noted that the number of subjects in this Brazilian study was small and the number of CIN1+ cases due to a given HPV type ranged from 0 to 4 in the vaccinated group and from 0 to 6 in the placebo group.[182]

Some authors believe that HPV type 16 could progress faster to CIN3+.[3, 183, 184] There may be a stronger association between type 16 and the lesions observed during the first few years of follow-up, which increases the probability that the vaccine will prove to have high efficacy against all HPV types. However, the longer the follow-up period, the more lesions could be attributable to types other than type 16, which would imply lower efficacy against all types.

There may be a greater potential for classification error when efficacy against lesions (e.g. CIN2+) caused by non-vaccine types is calculated, since the lesion is usually attributable to only one HPV type. The efficacy of cross-protection in cases of co-infection may then be overestimated. This tends to be less of a problem when efficacy against persistent infection is measured. Furthermore, how robust this cross-protection is and how long it lasts are not known, nor do we have this information for the vaccine HPV types. Further studies must be carried out on the clinical impact of cross-protection.

8 VACCINE SAFETY

Both vaccines are well tolerated. The most frequently observed injection site reactions are pain at the injection site, edema, swelling and pruritus. The most frequently observed systemic symptoms are fatigue, headache and myalgia. In the clinical trials, the onset of autoimmune diseases was very rare and comparable between vaccine recipients and those who received a placebo. There was no increase in local reactions or systemic symptoms with the number of vaccine doses administered. In the 30 days after vaccination, fewer symptoms were reported in 10- to 14-year-olds than in 15- to 25-year-olds.[93, 94]

A higher proportion of participants reported adverse reactions at the injection site in clinical studies of the bivalent vaccine than in studies of the quadrivalent vaccine (injection site pain: 91.8% versus 81.5%). However, it should be pointed out that for both vaccines, more than 90% of the injection site adverse reactions were considered mild or moderate by vaccine recipients. Generally, the frequency of systemic symptoms after administration of the vaccine was similar for both vaccines.[93, 94] However, in the head-to-head comparison study of the two vaccines, a higher proportion of subjects vaccinated with the bivalent vaccine reported fatigue (49.8% versus 39.8%) and myalgia (27.6% versus 19.6%). No difference was observed for symptoms considered serious.[142]

In the Québec study, 59-61% of girls aged 9-10 reported a local reaction and 44-45% at least one systemic symptom after vaccination with the quadrivalent vaccine. Injection site pain was the most frequently reported local reaction (56-58%). Fatigue (23-26%) and headache (23%) were the most frequently reported general symptoms. More than 98% of local reactions and systemic symptoms were considered mild or moderate. All reported local reactions and systemic symptoms resolved without medical intervention. More than 95% of local reactions and 99% of systemic symptoms lasted for less than four days.[152, 185] A team also reviewed the published and unpublished international postmarketing safety data[186] for the two vaccines and concluded that both vaccines are safe; the majority of the adverse events that may occur after vaccination are local reactions at the injection site.

9 ACCEPTABILITY OF HPV VACCINATION

This section provides an update on the publications dealing with knowledge, attitudes and practices (KAP) regarding HPV vaccination since 2007. The surveys of the public and of health care professionals in Canada and the Western world are briefly described. When available, the data from Québec or Canada are presented in greater detail.

The publications cited in this section refer to studies conducted with different methodologies, questionnaires and recruitment methods, with often low response rates and funding sometimes provided by the vaccine manufacturers.[187] Caution must therefore be exercised when interpreting the results.

9.1 ACCEPTABILITY OF HPV VACCINATION AMONG PARENTS

In countries similar to Canada, studies carried out among young women under 18 (or their parents)[188-191] show that the acceptability of the vaccine remains generally high. This is particularly true when the vaccine is offered free of charge and through a school-based program.

In Canada, data from a telephone survey conducted in 2007 indicated that a majority of parents were in favour of their daughters being vaccinated against HPV.[192] Nearly 74% of the parents questioned intended to have their daughters vaccinated, and this proportion rose to 77.5% among Québec parents.

The purpose of a recent survey conducted in Québec was to identify the factors that influenced HPV vaccination decisions among 1,318 14- to 18-year-old girls and 1,319 parents.[193] In this study, 78% of the teenaged girls had received at least one dose of the HPV vaccine. The encouragement of school professionals and parents, the consent of at least one of the two parents, living in an area where the school-based HPV program was widespread, sufficient knowledge of HPV and vaccination, vaccination habits and the perceived benefits of vaccination played a positive role among vaccinated participants. Seventy-six percent of the parents who participated in this survey reported that their daughters had been vaccinated against HPV. For parents, the factors that influenced their willingness to have their daughters vaccinated against HPV were being in favour of vaccination, having positive attitudes and beliefs toward vaccination in general, having received a positive recommendation from a health care professional, living in a region where the school-based HPV program was widespread, having a lower level of education than their daughters, or anticipating regret if their daughters were not vaccinated.[193]

A study conducted in Nunavik in 2008-09[194, 195] provides some interesting information about the knowledge and attitudes of 175 Inuit women in Québec. Only half of the women questioned had heard about cervical cancer and 23% about HPV. Despite this low level of awareness, 72% of the participants would agree to have their child vaccinated against HPV.

Finally, the estimated vaccine coverage rates of 81% in elementary grade 4 and 80% in Secondary III obtained in Québec in 2008-09,[196] during the first year of the school vaccination program, were encouraging and demonstrated high acceptability of vaccination

of girls against HPV in the general population. However, these rates declined in 2009-10: in both groups, vaccine coverage was 76%. In 2010-11, vaccine coverage rates were virtually unchanged, i.e. 78% in elementary grade 4 and 77% in Secondary III. The estimated vaccine coverage varied considerably in the various regions of Québec. In 2010-11, vaccine coverage rates ranged from 66% to 96% depending on the region.

9.2 ACCEPTABILITY OF HPV VACCINATION AMONG WOMEN AGED 18-26 YEARS

Psychosocial studies have been mainly interested in describing the acceptability of the vaccines for girls under 18, although HPV vaccines are approved for older women.

At the international level, some 20 recent studies dealing with the KAP of women over the age of 18 relating to HPV vaccination have been conducted in Western countries, including four in Canada. These publications are summarized in Table A1 in Appendix 2. They show a significant disparity between the intention to receive the vaccine and the vaccination status of the participants. A physician's recommendation, social norms and young age were strongly associated with vaccination or intention to receive the vaccine. Cost was the main barrier identified.

In Canada, a study carried out among 100 mothers recruited in Ontario clinics[197] showed that the acceptability of HPV vaccination was high, for both boys and girls. However, only a small proportion of the female participants intended to get vaccinated themselves. Another survey[198] was conducted among 400 female students at the University of Saskatchewan. The results indicated that if the vaccine were offered free of charge 60% would agree to receive it, 31% would be undecided, and 8% would refuse. The main barriers were the cost of the vaccine and concerns about possible side effects.

In Québec, three recent studies described the acceptability of vaccination among women over the age of 18. A postal survey of a representative sample of 2,400 24-year-old women was conducted in 2009.[199] Only 5% of the 1,347 participants had received the HPV vaccine. These young women did not perceive themselves as being at risk of HPV infections and indicated that they were dissatisfied with the information received on this subject.

Another survey, conducted on the Internet in 2009,[200] solicited the opinions of 1,005 women between the ages of 18 and 30. The results indicated that only 5% had been vaccinated. Among those who had heard about HPV and the vaccine but had not been vaccinated, 31% intended to receive the HPV vaccine if it were offered free of charge. Having recently had a Pap test was associated with a higher intention to receive the vaccine. Lack of knowledge and higher age were associated with negative intention.

Finally, an Internet survey[201] was conducted of female students (average age 20 years) at McGill University who did not intend to receive the vaccine (n = 223), did intend to receive it (n = 102) or had already received it (n = 122). In this study, the main factors associated with intention to be vaccinated or not were the perception of negative health consequences associated with the vaccine, the recommendation of a health care professional, positive attitude toward the vaccine and subjective norms. The factors associated with having been

vaccinated were the recommendation of a health care professional, subjective norms and the perception of susceptibility to HPV.

9.3 ACCEPTABILITY OF HPV VACCINATION AMONG BOYS AND MEN

To the best of our knowledge, there are no published data on HPV vaccine coverage in boys and men in Canada. In the United States, it is estimated that less than 2% of boys aged 13-17 have been vaccinated against HPV.[202]

In a review of the literature, some 20 articles published between 2000 and 2009 on the acceptability of HPV vaccination for boys and young men were examined.[203] These studies had involved three types of respondent: the parents of boys (under 18), men over 18 and health care professionals.

9.3.1 Studies among parents of boys under 18

In this review of the literature, the 11 studies conducted among parents[197, 204-213] generally showed fairly high acceptability of the vaccination of boys (59% to 100%). The parents preferred a vaccine that prevented both AGW and cervical cancers. In the studies in which the parents had a son and a daughter, there was a slight preference for vaccinating girls, in particular when the vaccine was not free. The results of a national study[208] conducted among Canadian parents are also included in this review of the literature. Of the 1,381 parents of boys questioned, 68% intended to have their sons vaccinated against HPV. By comparison, 74% of the parents intended to have their daughters vaccinated. Positive attitudes toward vaccination in general, the recommendation of a health care professional and the belief that being vaccinated will have little impact on sexual behaviour were identified as factors influencing vaccination decisions.

A review of the articles published since this review of the literature[203] identified five other studies targeting the parents of boys. Although the proportion of respondents who were in favour of vaccinating their sons was fairly high, this proportion was generally lower than the proportion of those in favour of vaccinating their daughters. Whether or not the vaccine was free was a factor that influenced the parents' opinion. Table A2 in Appendix 3 summarizes these articles.

9.3.2 Studies among men over 18

The review of the literature by Liddon and colleagues[203] compared six studies[214-219] carried out among males over 18. The acceptability of the vaccine was generally fairly high, and the proportion of men who intended to receive the vaccine ranged from 33% to 78%. Preference was given to a vaccine that prevented both AGW and cervical cancers, rather than to a vaccine that prevented only cervical cancers in their partners. Intention to receive the vaccine was generally higher among MSM. Stronger intention was associated with a larger number of sexual partners, better knowledge about HPV, subjective norms and generally positive attitudes toward vaccination.

Since the publication of this review of the literature,[203] other articles on the acceptability of HPV vaccination among men have been reviewed or identified. The data presented in most of these articles were collected from convenience samples, which are not very representative of the general population. Three of the publications referred to the same survey carried out among men over 18.[220-222] Intention to receive the vaccine was quite variable. Of heterosexual men, 5% to 37% would agree to be vaccinated. Intention was higher among homosexuals and bisexuals (73%). One publication[223] presented the reasons why homosexual men had accepted or refused the offer of the HPV vaccine in a clinic. More than one-third had refused, the main cause being the cost of the vaccine. Another article[224] reported results obtained from men who participated in a study on HPV prevention; intention to receive the vaccine was 94% among these respondents, who were well informed about the issue. Several recent publications[225-229] have reported the findings of studies carried out among young men recruited mainly at universities. Intention to receive the vaccine ranged from 36% to 79% and was positively associated with favourable attitudes toward vaccination and with certain sexual practices, in particular oral sex.[229] The cost of the vaccine and concerns about the long-term effects of the vaccine were the main barriers.

Table A3 in Appendix 4 summarizes these articles on the acceptability of the HPV vaccine among adult men not included in the review of the literature by Liddon and colleagues.[203]

9.4 Acceptability to Health Care Professionals of HPV vaccination for women aged 18-26 years and for boys

Liddon and colleagues[203] reviewed six studies on the attitudes of health care professionals toward the HPV vaccine. Three[230-232] of the four American studies were surveys of pediatricians; the fourth[233] targeted family physicians. The respondents expressed three preferences: a vaccine that would prevent both AGW and cervical cancer, administration at an older age (> 16 years in general) and a slight preference for vaccinating girls over boys. Depending on the study and on the age of administration, intention to recommend the vaccine for boys varied from 37% to 92%, whereas for girls the figure ranged from 46% to 98%.

A survey of Italian pediatricians[234] reported a preference for offering vaccination to both girls and boys.

The sixth study solicited the opinions of Québec nurses[235] in parallel to a survey of Canadian physicians in 2006.[236] In these surveys, the proportion of respondents in favour of vaccinating girls was always higher than for boys, for all categories of health care professionals surveyed (nurses, general practitioners, pediatricians and obstetricians-gynecologists). The results of the surveys, conducted between 2006 and 2009, indicated that Québec health care professionals preferred to administer HPV vaccines before the start of sexual activity and that they more strongly recommended vaccination of girls than boys.

Several articles that reported the opinions of health care professionals concerning the vaccination of women aged 18-26 years or the vaccination of men appeared after the publication of Liddon's literature review. These articles are summarized in Table A4 in Appendix 5.

Australia's experience is noteworthy, since this country offered free HPV vaccination to all females from 12 to 26 years of age in 2007 and 2008. A survey of 836 Australian gynecologists[237] conducted in 2009 showed that 94% of the respondents recommended vaccination to women aged 19-26. A high proportion of the respondents would also recommend the vaccine for women aged 27-45 (67% agreed); for women over 45, 20% agreed. Physicians who considered themselves less knowledgeable about HPV were less likely to recommend vaccination in all age groups.

An American survey[238] of more than 1,000 physicians (pediatricians and family physicians) sought to measure the acceptability of vaccination of men and boys. The results indicated that most physicians would recommend vaccination of boys, although in a slightly lower proportion than for girls. For example, 70% would recommend vaccinating 11- and 12-year-old girls, compared with 64% for boys of the same age. The physicians questioned were also more favourable to vaccination given at an older age, preferably between 13 and 18. The perceived benefits of vaccination of boys were the prevention of cervical cancer in female partners (96% agreed), the prevention of HPV infection in women (94% agreed), the prevention of AGW (89% agreed) and the prevention of anal and penile cancers in men (83%).

A recent American publication[239] presented the views of physicians concerning the priority of HPV vaccination for their patients. The physicians questioned generally considered vaccination a lower priority for married women or women in a stable monogamous relationship. This is contrary to the universal recommendation of the Advisory Committee on Immunization Practices (ACIP) that all women from 11 to 26 years of age should be vaccinated, regardless of marital status.[240]

9.5 SURVEY OF QUÉBEC HEALTH CARE PROFESSIONALS WITH REGARD TO THE HPV VACCINATION PROGRAM

In Québec, as part of the work carried out for this advisory report, Internet and postal surveys were conducted in the fall of 2010 of general practitioners (GPs) (n = 1,000), pediatricians (n = 577), obstetricians-gynecologists (n = 469), nurses (n = 1,000) and public health specialists (PH) (representatives of the Table de concertation nationale en santé publique, of the Table de concertation nationale en maladies infectieuses and of the Comité sur l'immunisation du Québec; n = 54).

The main purpose of the questionnaire was to solicit the opinions of these professionals on HPV vaccination, particularly for boys (9-18 years), men aged 18-26 and women aged 18-26. The questionnaire included five questions on the participants' demographic and professional characteristics and 12 questions about HPV and its prevention by vaccination. For most of the questions, a six-level Likert scale was used (three levels of agreement, three levels of disagreement). A few introductory sentences on vaccine approval and the free vaccination program were included in the questionnaire (essentially a reminder of the dates), as well as information on the different HPV types and associated diseases (AGW, cervical cancer and other HPV-related cancers).

- The response rates for this survey were relatively low (20% for nurses and general practitioners and 24% for obstetricians-gynecologists), except for pediatricians (48%) and public health specialists (67%).

Generally, the participants considered themselves sufficiently knowledgeable about HPV (Figure 7). However, the proportion of nurses who considered their knowledge about the HPV vaccine satisfactory for their practice was somewhat lower (40% strongly agreed or agreed), whereas nearly 95% of obstetricians-gynecologists strongly agreed that their knowledge was satisfactory ($p < 0.0001$). There was no correlation between how the different health care professionals rated their knowledge of the subject and characteristics such as number of years of practice, workplace or the number of vaccines administered per month in the workplace. Most of the participants who had the opportunity to do so in the course of their practice also indicated that they recommended the HPV vaccine to their patients (Figure 8). However, 40% of public health specialists, 31% of nurses, 10% of general practitioners and 6% of pediatricians indicated that this question was not applicable to them.

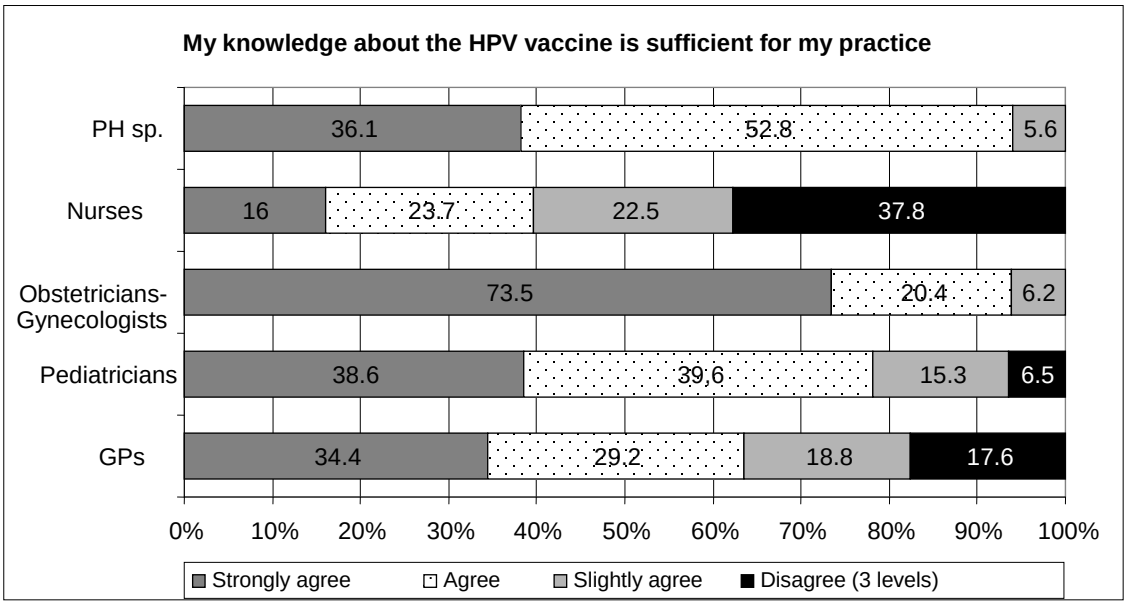


Figure 7 Knowledge about the HPV vaccine by type of professional

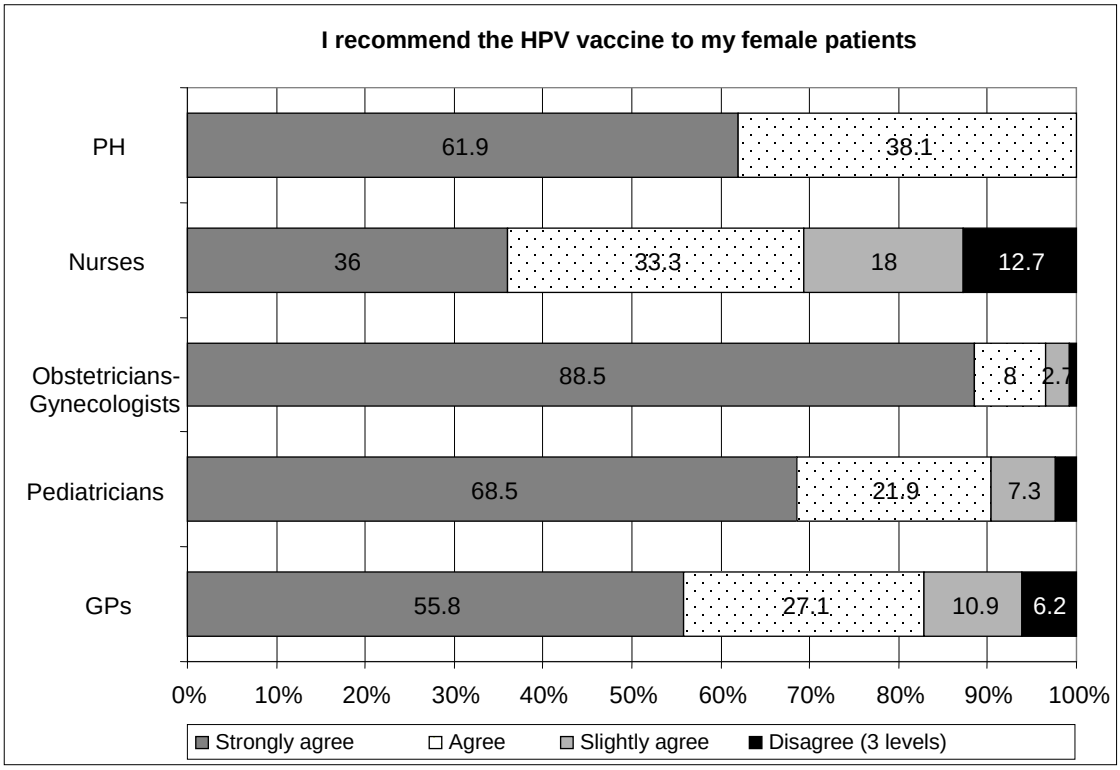


Figure 8 Recommendation of the HPV vaccine to female patients by type of professional

The respondents' perceptions about the frequency, severity and burden of the various diseases attributable to HPV are presented in Table 17. Generally, cervical cancers were perceived as the most serious and as representing a greater burden on the health care system than AGW and other HPV-related cancers. However, taking into account the quality of life of the persons affected, all three conditions were considered to have a significant negative impact. While the differences in perceptions observed among health care professionals were significant at a general level, paired comparison tests did not reveal any one category of professionals as being different from the others.

Table 17 Perceptions about the frequency, severity and burden of the various diseases attributable to HPV

The following diseases attributable to HPV are significant in terms of their… % agree + strongly agree (% strongly agree)	**GPs**	**Pedia-tricians**	**Ob-Gyn**	**Nurses**	**PH prof.**	**All**
Frequency	n = 140	n = 254	n = 110	n = 148	n = 34	n = 686
AGW	80.1 (42.6)	69.3 (23.7)	87.5 (58.0)	58.8 (27.0)	94.1 (50.0)	73.4 (35.1)
Cervical cancer	66.9 (17.0)	70.7 (34.2)	67.0 (33.0)	66.9 (27.2)	44.1 (14.7)	64.2 (28.1)
Other HPV-related cancers (e.g. anal cancer)	20.0 (4.3)	32.3 (9.1)	34.5 (8.2)	41.9 (8.1)	23.5 (5.9)	31.8 (7.6)
Severity	n = 142	n = 251	n = 110	n = 147	n = 34	n = 684
AGW	22.5 (4.9)	35.7 (6.0)	33.6 (15.5)	47.6 (6.8)	17.7 (2.9)	34.3 (7.3)
Cervical cancer	88.7 (57.8)	90.2 (62.5)	98.2 (82.7)	83.9 (52.4)	91.2 (55.9)	89.9 (62.2)
Other HPV-related cancers (e.g. anal cancer)	73.8 (39.4)	70.5 (39.0)	80.9 (50.0)	69.4 (32.0)	82.4 (52.9)	73.1 (40.1)
Burden on the health care system	n = 142	n = 249	n = 111	n = 147	n = 34	n = 685
AGW	46.5 (19.7)	53.2 (13.8)	73.0 (38.7)	49.0 (17.0)	70.6 (23.5)	54.9 (20.2)
Cervical cancer	78.2 (40.9)	86.2 (49.0)	84.8 (53.6)	71.8 (35.6)	79.4 (47.1)	80.9 (45.1)
Other HPV-related cancers (e.g. anal cancer)	52.1 (21.8)	59.8 (34.1)	58.0 (28.6)	60.1 (26.4)	55.9 (29.4)	57.8 (24.8)
Negative impact on the quality of life of the persons affected	n = 141	n = 249	n = 112	n = 145	n = 34	n = 685
AGW	80.3 (47.9)	80.6 (44.4)	88.4 (58.0)	69.8 (30.2)	85.3 (44.1)	79.7 (44.3)
Cervical cancer	89.2 (59.2)	93.7 (71.9)	100 (83.0)	84.0 (52.7)	100 (61.8)	92.1 (66.4)
Other HPV-related cancers (e.g. anal cancer)	87.9 (56.0)	89.2 (62.7)	94.6 (75.0)	80.0 (50.3)	100 (64.7)	88.4 (60.8)

These four criteria (frequency, severity, burden on the health care system and negative impact on quality of life) were analyzed and assigned a score. The following values were attributed to the various response choices:

Strongly disagree	Disagree	Slightly disagree	Slightly agree	Agree	Strongly agree
-3	-2	-1	1	2	3

For each HPV-related disease, the responses for the four criteria were totalled (total score obtained). A score, in the form of a percentage, was calculated for each disease as follows:

$$\% = \frac{\text{total score of the disease for the 4 criteria}}{\text{total score of the 3 diseases for the 4 criteria}} \text{ X } 100$$

By professional group, the following results were obtained (CC: cervical cancer, OC: other HPV-related cancers and AGW: anogenital warts):

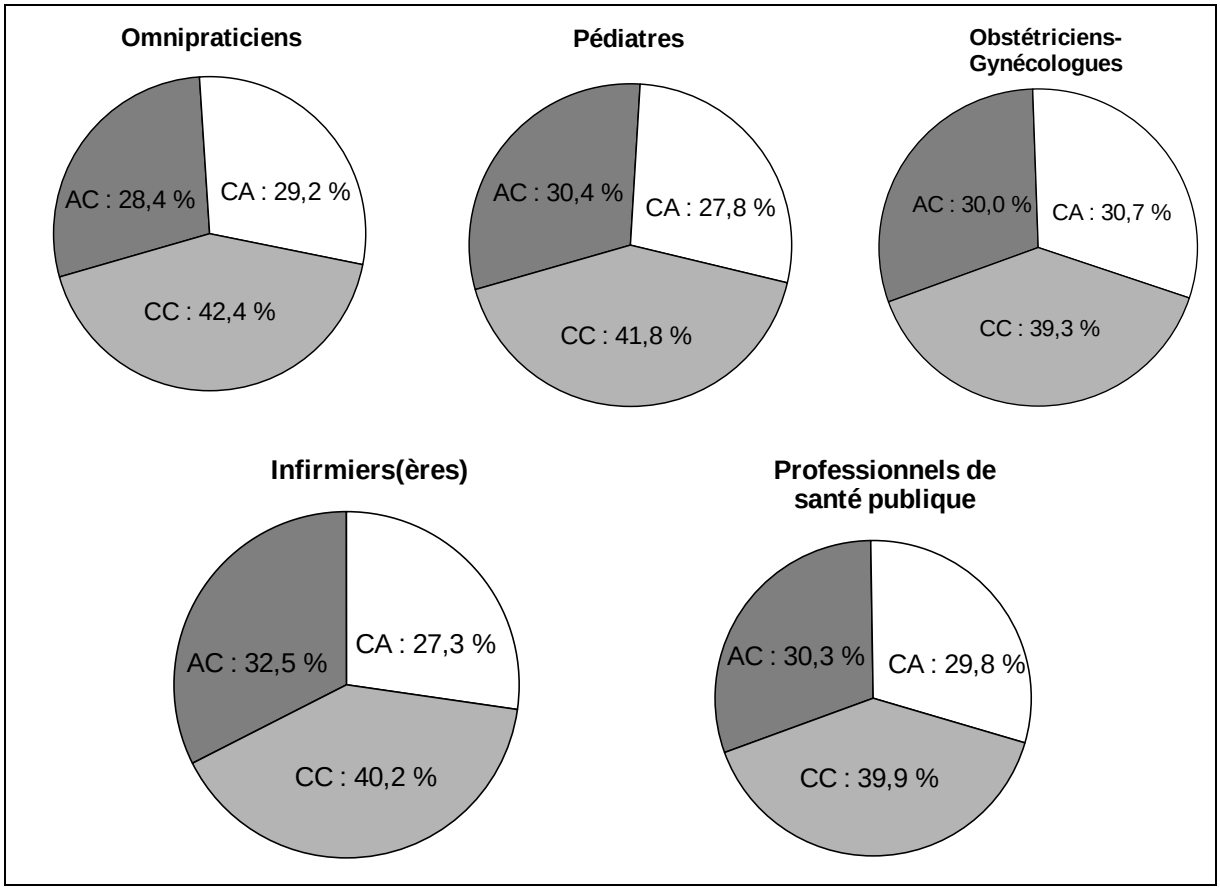


Figure 9 Scores calculated for each disease by professional group

Omnipraticiens: General Practitioners: AGW 29.2%, CC 42.4%, OC 28.4%.
Pédiatres: Pediatricians: AGW 27.8%, CC 41.8%, OC 30.4%.
Obstétriciens-Gynécologues: Obstetricians/Gynecologists: AGW 30.7%, CC 39.3%, OC 30.0%.
Infirmiers(ères): Nurses: AGW 27.3%, CC 40.2%, OC 32.5%.
Professionnels de santé publique: Public Health Professionals: AGW 29.8%, CC 39.9%, OC 30.3%.

The variations observed in the percentages were not statistically significant.

The following overall ranking (including all the professional groups) was obtained:

1. Cervical cancer: 41.06%;
2. Other HPV-related cancers: 30.34%;
3. AGW: 28.61%.

When the participants were asked what should be the objective of the free HPV vaccination program, the majority chose all diseases attributable to HPV (Table 18). There was no significant difference among the groups.

In addition, a higher proportion of the respondents who indicated that they preferred all HPV-related diseases as the program objective (compared with the other two objectives) agreed with the question on the burden of AGW on the health care system ($p < 0.05$). There were no other differences for the other three criteria studied (frequency, severity, impact on quality of life). A higher proportion of the respondents who indicated that they preferred cervical cancer as the program objective (compared with the other two objectives) agreed with the question on the burden of cervical cancers on the health care system ($p < 0.05$). Once again, no other differences were observed for the other three criteria.

Table 18 Opinions about the objective of the publicly funded HPV vaccination program

	GPs n = 145	Pedia-tricians n = 271	Nurses n = 152	PH prof. = 34	Ob-Gyn n = 112	All n = 714
	%	%	%	%	%	%
Prevention of **cervical cancers**	24.1	32.5	17.1	32.4	19.6	25.5
Prevention of **all HPV-related cancers**	26.2	22.1	27.6	23.5	19.6	23.8
Prevention of **all diseases attributable to HPV**, including all HPV-related cancers and AGW caused by the low oncogenic risk HPV types	45.5	40.6	48.7	44.1	60.7	46.6
No opinion	4.1	4.8	6.6	0	0	4.1

N.B.: Only one answer was possible.

When they were asked which group should be the main target of this program, the majority of the professionals surveyed considered that both girls and boys should be able to benefit from free vaccination (Figure 10). For the pediatricians, general practitioners and nurses, the choice of targeting girls and boys in the program was associated with the prevention of all diseases as the objective of the publicly funded HPV vaccination program ($p < 0.05$). More than 75% of the professionals who had chosen “girls only,” answered “cervical cancer” or “all HPV-related cancers” as the program objective.

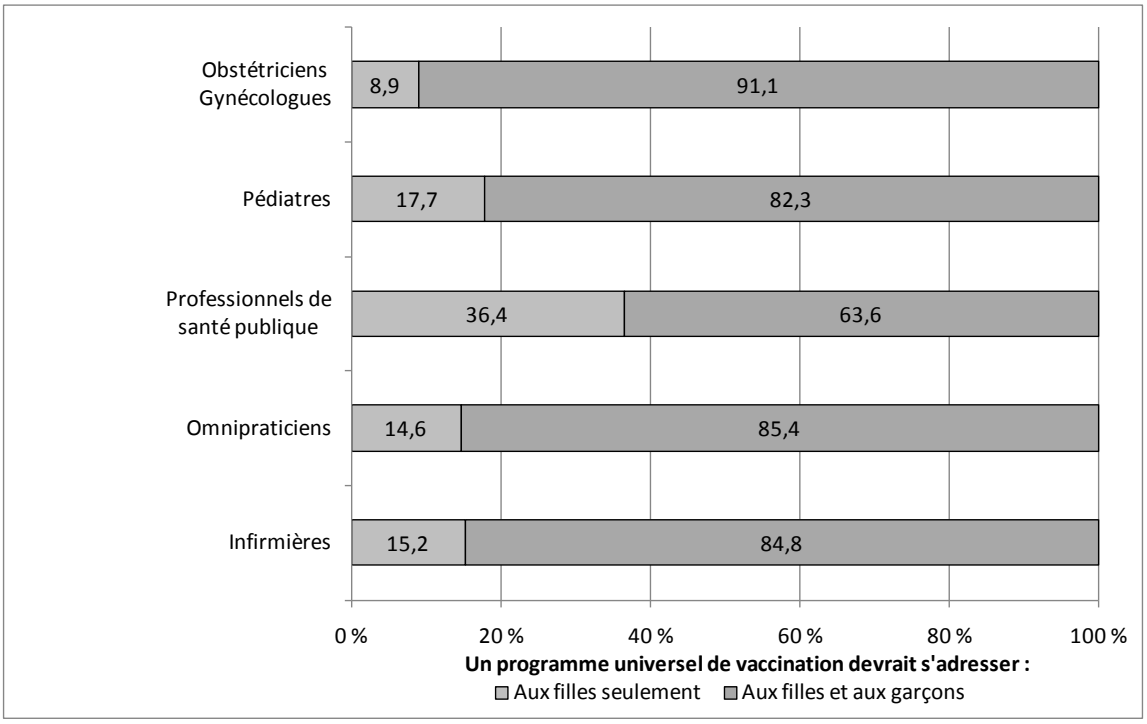


Figure 10 Perceptions of health care professionals concerning the preferred target group of a universal HPV vaccination program

Obstétriciens Gynécologues: Obstetricians/Gynecologists; *Pédiatres*: Pediatricians; *Professionnels de santé publique*: Public Health Professionals; *Omnipraticiens*: General Practitioner; *Infirmières*: Nurses; *Un programme universel de vaccination devrait d'adresser*: A universal vaccination program should target; *Aux filles seulement*: Girls only; *Aux filles et aux garçons*: Girls and boys.

Finally, if the free program were to be expanded, the majority of the professionals surveyed indicated that the priority target group should be women aged 18-26 (Figure 11).

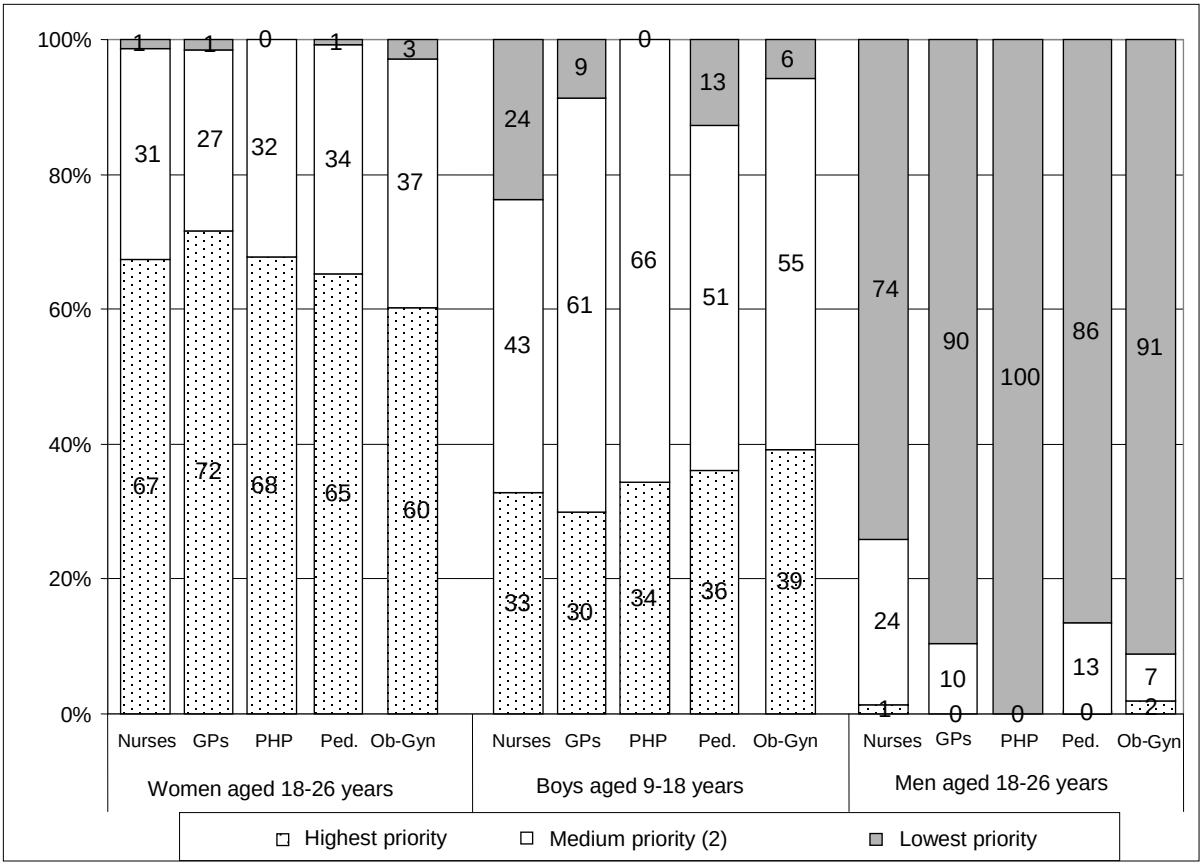


Figure 11 Priorities in the event of publicly funded program expansion

We were also interested in the differences between participants depending on whether or not they recommended the HPV vaccine as part of their regular practice. For nurses, no significant differences were observed on any of the questions between those who did and those who did not recommend HPV vaccination. For public health specialists, those who indicated that they did not recommend the vaccine tended to place higher priority on the prevention of cervical cancer as the objective of the free vaccination program (50% compared with 20% for the other public health specialists, $p = 0.02$). General practitioners and pediatricians[15] who did not recommend the vaccine believed that they were not sufficiently knowledgeable; a lower proportion of these respondents considered that HPV-related cancers were as significant in terms of their severity as other cancers, and considered other cancers to be more frequent and AGW less frequent than did those general practitioners and pediatricians who recommended the HPV vaccine in their practice. Nonetheless, like the general practitioners, the pediatricians held similar views concerning the priorities for an expanded program.

In short, the results of the survey of Québec health care professionals must be interpreted with caution in light of the low response rate and the possibly limited knowledge of some professionals. Indeed, since knowledge was not measured objectively, the way the question

[15] A lower proportion of general practitioners and pediatricians reported that they did not recommend the HPV vaccine in their practice.

was worded ("knowledge sufficient for your practice") makes it more difficult to compare professionals on this point. Obstetricians-gynecologists probably have a greater need to be aware of the latest advances concerning HPV since their patients are at higher risk. In addition, 6% to 40% of the participants (except gynecologists) reported that they did not recommend the HPV vaccine in their practice. Hence, there is some divergence of opinion among the participants, which is why we always presented the results by professional category. The aggregated results are provided for information only, without any assigned weighting.

9.6 CONCLUSIONS ON THE ACCEPTABILITY OF HPV VACCINATION

The recent data in the literature indicate that the public and health care professionals continue to be in favour of vaccinating girls aged 9-17. They also approve of the vaccination of boys and of women aged 18-26. The cost of the vaccine is the greatest barrier, and a physician's recommendation remains the most important factor influencing the acceptability of vaccination. It is important to note that women over 26 could also benefit from the protection conferred by vaccination. Some articles document the opinion of these women or of health care professionals concerning expansion of the targeted age group but were not included in the present report.

HPV vaccine coverage in Québec exceeded 75% in 2010-11, indicating high acceptability of vaccination among parents for their daughters and among teenaged girls. However, the debate over the pros and cons of HPV vaccination is a subject that comes up regularly in media reports[241-245] and in the scientific community.[246, 247] This indicates that the current program is not free of controversy and that promotion efforts must be maintained.

Finally, the results of the survey of Québec health care professionals, although they must be interpreted with caution given the low response rate, indicate significant support for the idea of vaccinating boys. However, according to the respondents, if the free vaccination program were to be expanded, women in the 18-26 age group should be the first priority.

10 FEASIBILITY

10.1 FEASIBILITY OF HPV VACCINATION FOR WOMEN AGED 18-26 YEARS

The management of a vaccination program for women in the 18-26 age group represents a major logistical challenge. At this age, the target clientele cannot generally be reached through school-based programs. Therefore, more appropriate methods for vaccine delivery must be identified. Many young women see their family physicians on a regular basis to discuss contraception; they could thus be vaccinated during a medical visit. However, handling HPV vaccines would pose a problem for physicians who generally do not offer other vaccines. Managing the purchase, reimbursement and storage of the vaccines (which require refrigeration) would pose a major problem, as was noted in the publications cited earlier (see Table A1, Appendix 2).

Using the services offered by certain pharmacies represents another avenue for improving access to HPV vaccination for these women. Some vaccines are now offered in pharmacies, where they are administered by nurses.[248] HPV vaccines could be included via this channel. This would also make it possible to reach women living in more remote areas, since there is a pharmacy in virtually every municipality.

Finally, vaccine administration by nurses in private agencies or travel health clinics could increase the geographic accessibility of HPV vaccination services. However, this option has the disadvantage of generating administration costs for women.

10.2 FEASIBILITY OF HPV VACCINATION FOR BOYS UNDER 18

Expanding HPV vaccination to the entire school population rather than girls only could be done relatively easily. Although the costs associated with buying and administering the vaccines would obviously be doubled, the logistics of the program would not be too complex to manage. The current documentation (information brochures, consent forms) could be easily adapted. It can be assumed that such a program would achieve vaccine coverage rates comparable with those for girls (76% to 81%) or with those in hepatitis B vaccination programs (85% in 2010-11).[249]

Another major advantage of vaccinating boys in the school setting is that this would better protect boys who will later have sex with men, by vaccinating them before the start of sexual activity.

10.3 CONCLUSIONS ON FEASIBILITY

Expanding the school vaccination program for boys appears to be easier to achieve than offering the vaccine to older women. With either approach, it would be essential to devote more effort to promote and educate the public and health care professionals about the important role of vaccines in preventing HPV infections.

11 METHODS FOR EVALUATING AN HPV IMMUNIZATION PROGRAM THAT WOULD INCLUDE BOYS AND/OR OLDER WOMEN

Measuring vaccine coverage of women in the 18-26 age group is a complex task. Outside the school setting or early childhood, it is difficult to determine the effectiveness of a vaccination program in reaching the target population. Establishing a provincial vaccination registry would allow documentation of vaccine coverage for the entire population and assessment of whether vaccine coverage objectives are being met. In the meantime, vaccine coverage surveys remain the main source of data.

On this subject, the Australian experience[250] is informative, since in that country HPV vaccination was offered to all females 12 to 26 years of age during the first two years of the program. Relatively high vaccine coverage rates were quickly achieved. In fact, 58% of the females aged 15-26 had received at least one dose of the vaccine 10 months after the start of the program, outside of the school setting.

A vaccination program for women aged 18-26 would probably have a faster impact on decreasing lesions caused by HPV. If the quadrivalent vaccine were chosen and a monitoring system established, the impact on the need for treatment of AGW would probably also be observed fairly quickly, as in Australia.[178, 179]

If the decision is made to vaccinate boys, the effects of the program would likely be evident in the medium term, with a decrease in the number of consultations for AGW. However, there is currently no effective system in place in Québec to measure the incidence and prevalence of AGW.

12 ETHICAL ISSUES AND CONSIDERATIONS

Several ethical issues surrounding HPV vaccination were identified in the 2007 report,[251] using the ethical framework of Québec's National Public Health Program. Some of the issues were related to concern about the possibility that HPV vaccination might send a negative moral message (promotion of sexual promiscuity among young people, conflicts of values on the part of health care professionals who would be called on to recommend the vaccine, etc.), to false expectations about the vaccine (protection against all sexually transmitted infections), its cost[16] and informed consent (for example, if a girl under 14 wanted to receive the vaccine without her parents' permission).[252-254] These remain real issues, regardless of the objective chosen for the publicly funded vaccination program. The approval of the bivalent vaccine for girls and young women aged 10-25 and the quadrivalent vaccine for boys and young men aged 9-26 poses new ethical issues.

First, the lack of a publicly funded HPV vaccination program targeting women over 18 and young men raises ethical issues associated with social justice. Indeed, in the context of a program that targets only girls under 18, access to the vaccine is not equitable since some individuals for whom the vaccine is recommended will have to pay in order to obtain it. It is also necessary to ensure that the conditions for implementation of the program do not generate further inequalities, as was the case during the Québec program for the vaccination of girls under 18 in 2008. In fact, at the regions' request, the decision was left to their discretion as to how to organize the delivery of vaccination to girls under 18 not covered by the school-based catch-up program in Secondary III. Those regions where a school-based vaccination program was organized for girls in Secondary IV and V (and sometimes even in College [*Cégeps*]) provided greater access to vaccination than those where vaccination was only available through the local community services centres (*CLSC*s),[193] resulting in some degree of inequity in access to vaccination for these women, currently aged 18-21.

There would also be risks of stigmatization if, for epidemiological and/or logistical reasons, HPV vaccines were offered free of charge only to certain subgroups of the population (MSM and seropositive individuals). In addition, even if vaccine coverage in girls is high, certain men, particularly MSM, will not benefit from the indirect protection that this provides.

Finally, the choice of the objective of the publicly funded vaccination program may raise issues regarding the principle of utility (cost/benefit). Indeed, the mandate of public health is to optimize its interventions by favouring those that maximize the benefits for as many as possible while minimizing any negative effects, at a reasonable cost relative to the benefits obtained. Hence, the ultimate criteria for judging the utility of a public health intervention are its consequences on the fundamental common goods of health and well-being.[255] In this context, economic studies can be useful in guiding decision making. For instance, if the results of the economic analyses indicate that HPV vaccination of men is not cost-effective, the decision to include the vaccination of men in the publicly funded program, although it would promote gender equity in preventing lesions associated with HPV, would not be consistent with the ethical principle of utility.

[16] Health care professionals who recommended the HPV vaccine knowing that some of their patients will not be able to afford the vaccine would be confronted with an ethical dilemma.

13 CONSISTENCY WITH PLANNED OR EXISTING PROGRAMS IN OTHER JURISDICTIONS/COUNTRIES

From 2007 to 2009, all Canadian provinces and territories introduced routine HPV vaccination programs for preadolescent and adolescent girls. All these programs use the quadrivalent vaccine. Québec had the most extensive program, offering free HPV vaccination to all girls under 18, starting in 2008.

In January 2012, the National Advisory Committee on Immunization (NACI) updated its recommendations on the use of HPV vaccines.[256] In addition to recommending the vaccination of girls and women aged 9-26 with the bivalent and quadrivalent vaccines, NACI added a recommendation concerning the use of the quadrivalent vaccine for males aged 9-26. NACI stressed that the provinces and territories, in considering the potential inclusion of males in their routine vaccination programs, should take several factors into account, including a cost-effectiveness analysis based on parameters specific to the Canadian context. At the present time, no Canadian jurisdiction has announced the introduction of a universal vaccination program for boys.

In October 2011 ACIP voted in favour of routine vaccination with three doses of the quadrivalent vaccine for all 11- and 12-year-old boys. The ACIP also recommended catch-up vaccination for all males between the ages of 13 and 21.[202] This recommendation was supported by favourable cost-effectiveness analyses,[17] particularly in light of the low HPV vaccine coverage (< 50%) of girls in the United States.

In Australia, the government has provided free HPV vaccination for girls and women between the ages of 12 and 26 since 2007. In November 2011, the Pharmaceutical Benefits Advisory Committee[18] recommended expanding the national immunization program to include the prevention of HPV-associated diseases in 12- and 13-year-old boys. This committee also recommended catch-up vaccination for 14-year-old boys for a two-year period.[19] However, no official announcement concerning the introduction of a universal vaccination program for boys in Australia had been made as of July 2012.

Finally, HPV vaccines are used in publicly funded vaccination programs in some 30 countries around the world for the vaccination of girls 18 and under. With the exception of the United States, there are currently no universal HPV vaccination programs for boys and men.

[17] H. Chesson. HPV Vaccine Cost-effectiveness Updates and Review, Advisory Committee on Immunization Practices (ACIP) Summary Report of June 22-23, 2011, p. 94-99. Available on-line at: http://www.cdc.gov/vaccines/recs/acip/downloads/min-jun11.pdf.

[18] This committee formulates recommendations and provides advice to the Minister of Health concerning medications and other medical products that should be made available. The recommendations of this committee are necessary for a new vaccine to be included in the Australian national immunization program. Information available on-line at: http://www.health.gov.au/internet/main/publishing.nsf/content/health-pbs-general-listing-committee3.htm. Web page accessed on March 7, 2012.

[19] Information available on-line at: http://www.health.gov.au/internet/main/publishing.nsf/Content/pbacrec-nov11-positive. Web page accessed on March 7, 2012.

14 POPULATION-LEVEL EFFECTIVENESS AND ECONOMIC ANALYSES OF HPV VACCINATION PROGRAMS

This section is based on the following report, submitted to the INSPQ in April 2012: Laprise JF, Drolet M, Van de Velde N, Malagon T, Boily MC, Brisson M. *Efficacité populationnelle et coût-efficacité des programmes de vaccination contre les VPH au Québec* (Population-level effectiveness and cost-effectiveness of HPV vaccination programs in Québec). The English version has not been revised by the authors.

The results of an analysis of the population-level effectiveness and cost-effectiveness of HPV vaccination in the Québec context are presented. The objectives of the analysis were 1) using the HPV-ADVISE model for Québec, to estimate the population-level effectiveness and cost-effectiveness ratio of vaccinating girls only with the bivalent or quadrivalent vaccine and vaccinating boys/men in addition to girls; 2) to compare the results obtained with those of other published studies on the cost-effectiveness of HPV vaccines; and 3) to determine the key factors that influence the cost-effectiveness ratio of the various vaccination strategies.

14.1 METHOD

14.1.1 Model structure

HPV-ADVISE[257, 258] (Agent-based Dynamic Model for Vaccination and Screening Evaluation) is the first dynamic, individual-based transmission model, which is based on sequential partnership formation and dissolution, and the natural history of HPV infections and HPV-associated diseases.[258] The model has six components: 1) socio-demographic characteristics, 2) sexual behaviour and HPV transmission, 3) natural history of HPV-associated diseases, 4) vaccination, 5) screening and treatment, and 6) economic aspects.

14.1.1.1 Socio-demographic characteristics

The model population is heterosexual,[20] open and stable. Individuals enter the simulated population at 9 years of age and are assigned three different risk factors: gender, level of sexual activity and screening behaviour.

14.1.1.2 Sexual behaviour and HPV transmission

HPV transmission depends on 1) sexual behaviour (e.g. level of sexual activity and contact matrix), 2) the risk of transmission by sexual relations and 3) the natural history of the infection (its duration and the probability of natural immunity developing following clearance of the infection). Partnership formation/dissolution is dictated by the partnership formation rate, the separation rate and the contact matrix; these parameters depend on gender, age and level of sexual activity.

[20] The model represents a heterosexual population, but the analyses consider the fact that a proportion of the population is composed of MSM.

Eighteen HPV types are modelled individually: 16/18/6/11/31/33/45/52/58/35/39/51/56/59/66/68/73/82. These types are considered to be independent of each other with respect to transmission and persistence; hence, all combinations of multiple infections are possible. After clearance of an infection, natural immunity may develop depending on a probability that is specific to gender and HPV type (i.e. reinfection by a HPV type previously cleared is possible).

14.1.1.3 Natural history of HPV-related diseases

HPV-ADVISE offers the capability to evaluate the potential impact of prophylactic HPV vaccination on condyloma acuminata, cervical cancers (squamous cell carcinomas and adenocarcinomas) and other HPV-associated cancers (cancers of the vulva/vagina, anus, oropharynx and penis).

Anogenital warts

Individuals infected by HPV 6 and 11 may develop AGW or clear the infection, depending on the respective probabilities of each event. In the baseline scenario, HPV 6 and 11 are considered responsible for 85% of all AGW.[76] Sensitivity analyses were based on the assumption that HPV 6 and 11 cause 70% to 90% of AGW (Table 19).

Squamous cell carcinomas

The natural history of cervical squamous cell carcinomas is represented by nine mutually exclusive states: three states relating to HPV infection (susceptible, infected and immune), three grades of cervical intraepithelial neoplasia (CIN1, CIN2 and CIN3) and three stages of cancer (localized [stage I], regional [stage II] and distant [stage III]). The rate of transition between these nine states are specific to each HPV type.

Other HPV-associated cancers

Although there are few available data on the natural history of other HPV-associated cancers, it is assumed that a certain proportion of HPV infections will progress to cancers of the vulva, vagina, penis, anus and oropharynx. Section 14.1.3 presents the method used to estimate these proportions.

Economic analysis

The economic analysis is based on the perspective of the MSSS. An annual discount rate of 3% is applied to costs and benefits. The time horizon is 70 years (i.e. approximately the life expectancy of the first cohort), and the cost per dose of the vaccine is $95, including administration costs. Table 19 presents the values used for the economic parameters in the baseline scenario and shows the minimum and maximum burdens (QALYs[21] lost, costs and mortality) for AGW[77, 80, 81, 89] and cancers[259-267] that were used in the sensitivity analyses conducted on the economic parameters.

[21] Quality-adjusted life-years.

Table 19 Resources used, costs, loss of quality of life and mortality[80, 81, 89, 259-267]

	Baseline scenario	Sensitivity analysis	
		Minimum	Maximum
% AGW caused by HPV 6/11	85%	70%	90%
Consultations per AGW episode			
Women	1.11	1.08	1.14
Men	1.19	1.13	1.24
Costs ($ CAN)			
Per AGW episode for women	227	180	274
Per AGW episode for men	200	193	207
Normal cytology	44	15	117
Colposcopy/biopsy	162	59	733
LEEP	1,050	86	2,101
Cervical cancer (stages 1, 2-3, 4)	12.365, 19.211, 26.251	5.012, 9.605, 12.365	31.444, 48.137, 71.631
Relative costs vs cervical cancer			
Vulvar/vaginal cancer	87%	83%	91%
Anal cancer	102%	87%	118%
Oropharyngeal cancer	120%	100%	141%
Penile cancer	71%	64%	77%
QALYs lost			
Per episode			
AGW	2%	1%	4%
CIN1 or LSIL	0.60%	0.60%	0.80%
CIN2/3 or HSIL	1.00%	0.90%	1.20%
Instantaneous (disutility)			
Cervical cancer (stages 1, 2-3, 4)	30%, 30%, 38%	19%, 29%, 29%	51%, 58%, 64%
Vulvar/vaginal cancer	32%		
Anal cancer	51%		
Oropharyngeal cancer	25%		
Penile cancer	29%		
Mortality[a]			
Cervical cancer (stages 1, 2-3, 4)	8%, 42%, 83%		
Vulvar/vaginal cancer	38%	19%	56%
Anal cancer	19%	19%	58%
Oropharyngeal cancer	24%	24%	42%
Penile cancer	21%	21%	42%

LEEP: loop electrosurgical excision; CIN: cervical intraepithelial neoplasia; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion.

[a] The probability of mortality is calculated as follows: mortality = 100% – (5-year survival probability [%]).

14.1.1.4 Vaccination

HPV-ADVISE operates on the assumption that HPV vaccination is effective in preventing HPV infection but has no impact on the natural history of infection and disease in individuals already infected at the time of vaccination. Different vaccine efficacy values can be applied to

any of the 18 HPV types included in the model. The values for HPV vaccine types 6, 11, 16 and 18 are based on the PATRICIA[98] and FUTURE I/II clinical trials.[268, 269] A systematic review of the literature was conducted in order to determine the vaccine efficacy values of cross-protection for each non-vaccine HPV type.[161] Table 20 presents the vaccine efficacy values used in the model for the bivalent and quadrivalent vaccines. In the baseline scenario, the vaccines offer lifelong protection, and vaccine efficacy against persistent infections was used since these estimates are less likely to be biased by classification errors of the HPV types in the lesions.[161] Sensitivity analyses were conducted by reducing the duration of protection of the vaccines to 20 years for the vaccine types and 10 years for the non-vaccine types, and using the values of vaccine efficacy against CIN2+ (excluding lesions co-infected with HPV 16/18). Since these vaccine efficacy values are higher for the bivalent than the quadrivalent vaccine, this scenario therefore favours the bivalent vaccine.

Table 20 Vaccine efficacy

HPV type	Baseline scenario VE against persistent infections		Sensitivity analysis VE against CIN2+ (excluding lesions co-infected with HPV 16/18)	
	Bivalent (%)	Quadrivalent (%)	Bivalent (%)	Quadrivalent (%)
16/18	95.0[a]	95.0[a]	100.0[a]	100.0[a]
6/11	0.0[b]	95.0[b]	0.0[b]	100.0[b]
31	77.1[155]	46.2[157]	83.4[155]	57.4[161]
33	43.1[155]	28.7[157]	76.3[155]	0.0[e,161]
45	79.0[155]	7.8[157]	100.0[155]	0.0[161]
52	18.9[162, 163]	18.4[157]	0.0[c,d]	0.0[e,161]
58	0.0[e,162, 163]	5.5[157]	0.0[c,d]	0.0[e,161]
Other HR types[f]	0.0[c]	0.0[c]	0.0[c]	0.0[c]

VE: vaccine efficacy, CIN: cervical intraepithelial neoplasia, HR: high risk (oncogenic).

[a] We consider the vaccine efficacy against types 16/18 of the bivalent vaccine and the quadrivalent vaccine to be equal and the same for both boys and girls.

[b] We consider the vaccine efficacy against types 6/11 to be zero for the bivalent vaccine, equal to the efficacy against types 16/18 for the quadrivalent vaccine and the same for both boys and girls.

[c] Considered to be zero.

[d] VE against CIN2+ for this HPV type was not estimated in the literature.

[e] A value of zero was used in the model for negative VE estimates.

[f] Other HR HPV types: 35, 39, 51, 56, 59, 66, 68, 73 and 82.

14.1.1.5 Screening and treatments

HPV-ADVISE reproduces various individual screening algorithms by simulating the screening history of each woman. In the present study, the model reproduces cervical cancer screening by cytology in Canada. Each woman in the model is assigned a screening behaviour, which represents the average interval between two normal routine tests. The five screening behaviour levels range from one screening test every 1.25 years (level 0) to never having been screened (level 4). The screening behaviours were estimated from Canadian population-level data.[270, 271] The screening rates depend on the screening behaviour of each

woman, the previous screening test result and age. Algorithms for the management of women with abnormal cytology results depend on the cytology test results and are based on the Québec and Canadian guidelines and Canadian empirical data.[92, 270, 272-274] Finally, women who have cervical cancer have a probability, specific to each stage, of symptoms developing and of their being diagnosed outside of routine screening.

14.1.2 Men who have sex with men (MSM)

The burden and risks of HPV-associated diseases for MSM and for heterosexuals are different. In addition, MSM probably do not benefit as much as heterosexual men from the indirect protection conferred by the vaccination of girls. In order to take these differences into account, the costs and benefits for MSM were estimated separately, then incorporated into the efficacy and cost-effectiveness predictions for the various vaccination scenarios analyzed. Table 21 presents the data from the literature[175, 270, 275] used to estimate the fraction of new cases of AGW and HPV-associated cancers occurring in MSM compared with the total male population in Québec. The baseline scenario assumes that MSM represent 3% of the Québec male population[270] and that they have a 17-fold higher risk of developing anal cancer than heterosexual men[275] and a three-fold higher risk of AGW or penile and oropharyngeal cancers.[175] Sensitivity analyses were conducted by varying the proportion of MSM in Québec and the relative risk of development of HPV-related cancers and AGW.

Table 21 MSM-related parameters

	Baseline scenario	Sensitivity analysis
	Median (80% UI)	Maximum burden
Proportion of MSM in the male population (%)	3[270]	10
Relative risk[a]		
Anal cancer	17 (8; 36)[275]	17
AGW and other cancers	3[175]	17

80% UI: 80% uncertainty interval; MSM: men who have sex with men.

[a] Relative risk in MSM compared with the male heterosexual population.

14.1.3 Calibration of the model

The HPV-ADVISE calibration procedure is described in detail in Van de Velde et al.[258] This procedure identifies multiple parameter sets, which simultaneously fit highly stratified Canadian data on sexual behaviour, natural history of the infection and disease, as well as screening. These data are derived from the literature, population-level databases and original studies.[4, 14, 15, 44, 77, 264, 270, 271, 276-279] Some 285,000 different combinations of parameters were sampled (1,850,000 runs and $2 \times 10^{[270]}$ person-years simulated) from ranges of pre-calibration parameters. Ten parameter sets produced results within the 731 pre-specified targets determined from empirical data and were included in the post-calibration parameter sets. This procedure makes it possible to reproduce the epidemiological data for AGW and cervical cancers and to generate estimates that take parameter uncertainty into account.

For the other cancers (cancers of the vulva/vagina, penis, anus and oropharynx), the proportion of HPV infections that progress to cancer and the period of time necessary for the cancer to develop were estimated in order to reproduce the incidence of cancers in heterosexuals (Québec data [see section 2]) and the HPV-type distribution for each cancer site.[47, 48, 51, 280]

14.1.4 Vaccination scenarios

In this study, three vaccination strategies were modelled: 1) girls only with the bivalent vaccine, 2) girls only with the quadrivalent vaccine and 3) girls and boys with the quadrivalent vaccine. The schedule used in the model for routine vaccination was two doses at age 9 and one dose at age 14. The schedule used for catch-up vaccination was three doses at age 14 for the first five years of the program. In all the scenarios, the routine vaccination program included the same vaccine coverage and number of doses for both girls and boys. However, no catch-up vaccination for boys was considered, since it is assumed that the catch-up program for girls would quite likely be ended by the time vaccination of boys started. In the baseline scenario, vaccine coverage with the routine vaccination program is 80% for the first two doses, and it is assumed that, subsequently, 90% of those who received two doses at age 9 receive the third dose at age 14. It is further assumed that, of the 20% of girls who did not receive the first two doses at age 9 in the routine program, 20% will be vaccinated with three doses at age 14 (20% x 20% = additional 4%). For the catch-up program, the model assumes a vaccine coverage of 80%. The vaccine efficacy values used in the simulations are against persistent infections (Table 20) with lifelong vaccination protection. The vaccination of boys starts five years after the start of the vaccination of girls.

14.1.5 Model predictions

The main yardstick used to represent the population-level effectiveness of vaccination is the relative reduction (compared with the scenario of no vaccination) in the incidence of HPV-associated diseases at 30 years, 50 years and 70 years after the start of vaccination. Hence, the incidence represents the number of cases in the 30^{th}, 50^{th} or 70^{th} year after the start of vaccination and not the cumulative total of cases over these years. This measurement was chosen in order to illustrate the changes in incidence over time. The predictions of the economic analysis are presented in costs per QALY.

Univariate sensitivity analyses were performed by varying the following parameters: 1) vaccine efficacy and duration of protection, 2) economic parameters (costs and QALYs lost) and 3) proportion of MSM in the population and relative risk of disease for MSM compared with heterosexuals. The minimum and maximum values of the parameters that were varied in the sensitivity analyses are presented in Tables 19, 20 and 21.

The variability of the model predictions (reflecting parameter uncertainty) is expressed as the median and the 10^{th} and 90^{th} percentiles of the results from the 10 post-calibration parameter sets, referred to as the “80% uncertainty intervals” (80% UI).

14.2 RESULTS AND DISCUSSION OF THE ECONOMIC ANALYSES

14.2.1 Vaccination of girls/women

14.2.1.1 Population-level effectiveness in Québec

Table 22 presents the relative reduction in the incidence of HPV-related diseases at 30 years, 50 years and 70 years after the start of vaccination of girls only with the bivalent or quadrivalent vaccine (baseline scenario), and Table 23 presents the burden of HPV-related diseases that would be prevented on average per year, in Québec, totalled over the first 70 years of the program for each vaccine.

HPV-ADVISE predicts that a vaccination program for girls only with the quadrivalent vaccine would produce a rapid decline in the incidence of AGW, culminating after 70 years in a reduction of 85% (80% UI: 85-85%) for women and 77% (80% UI: 77-77%) for men as a result of herd immunity. The lower reduction for men than for women may be explained by the fact that a certain proportion of AGW (approximately 9%) would occur in MSM and that the model assumes no benefit for MSM from the indirect protection afforded to heterosexual men by the vaccination of girls. Vaccination with the bivalent vaccine would have no impact on the incidence of AGW.

According to the model predictions, the bivalent and quadrivalent vaccines would produce very similar reductions in the incidence of CIN2/3 and cervical cancers in the short term. However, in the long term, the bivalent vaccine would result in a greater decrease in the incidence of CIN2/3 (73% [80% UI: 69-81%]) and cervical cancers (85% [80% UI: 75-88%]) compared with the quadrivalent vaccine (CIN2/3 = 68% [80% UI: 63-78%]; cervical cancers = 80% [80% UI: 73-85%]).

The reductions in the incidence of other HPV-associated cancers (vulvar/vaginal, anal, penile and oropharyngeal cancers) would be very similar for both vaccines. For example, with the bivalent vaccine, the decrease in the incidence of anal cancers 70 years after the start of vaccination would be 74% for men (80% UI: 73-74%) and 44% for women (80% UI: 43-45%), whereas with the quadrivalent vaccine the figures would be 73% (80% UI: 72-74%) and 43% (80% UI: 43-45%) respectively. This result may be explained by the fact that the great majority of these cancers are attributable to types 16 and 18,[47, 48, 51] against which the two vaccines have similar efficacy (see Table 20).

Use of the bivalent vaccine for girls only would prevent, on average, an additional 135 CIN2/3 episodes and four cervical cancers a year over the first 70 years of the program compared with the use of the quadrivalent vaccine (Table 23). However, use of the bivalent vaccine would have no effect on the incidence of AGW, whereas vaccination with the quadrivalent vaccine would prevent an average of 3,089 cases of AGW a year in men and 3,308 cases in women (6,397 cases a year in total) over the first 70 years of the program. For the other cancers, there would be no difference in the number of cases prevented (e.g. an average of 11 and 5 cases of anal cancer a year would be prevented over the same period in women and heterosexual men, respectively, regardless of the vaccine used).

Table 22 Impact of the vaccination of girls only

Relative reduction in the incidence[a] of HPV-related diseases at 30 years, 50 years and 70 years after the start of the vaccination of girls only (baseline scenario) compared with the scenario of no vaccination

Time since the start of vaccination	Females						Males					
	30 years		50 years		70 years		30 years		50 years		70 years	
Vaccine	Biv.	Quad.	Biv.	Quad.	Biv.	Quad.	Biv.	Quad.	Biv.	Quad.	Biv.	Quad.
	Med. % (80% UI)	Med. % (80% UI)	Med. % (80% UI)	Med.% (80% UI)	Med. % (80% UI)	Med. % (80% UI)	Med. % (80% UI)	Med. % (80% UI)	Med. % (80% UI)	Med. % (80% UI)	Med. % (80% UI)	Med. % (80% UI)
Consultations for AGW[b]	1 (–2; 3)	85 (85; 85)	–1 (–4; 4)	85 (85; 85)	–2 (–5; 2)	85 (85; 85)	1 (–2; 3)	77 (77; 77)	–1 (–3; 4)	77 (77; 77)	–1 (–4; 1)	77 (77; 77)
CIN2/3 episodes	71 (64; 80)	66 (61; 75)	73 (69; 82)	68 (64; 77)	73 (69; 81)	68 (63; 78)	-	-	-	-	-	-
HPV-associated cancers												
Cervical	29 (23; 40)	28 (24; 36)	71 (56; 79)	69 (50; 73)	85 (75; 88)	80 (73; 85)	-	-	-	-	-	-
Anal	10 (10; 10)	10 (9; 10)	34 (33; 35)	34 (33; 34)	74 (73; 74)	73 (72; 74)	3 (3; 3)	3 (3; 3)	21 (20; 23)	21 (20; 22)	44 (43; 45)	43 (43; 45)
Oropharyngeal	1 (1; 1)	1 (1; 1)	18 (18; 19)	18 (18; 19)	43 (43; 43)	43 (42; 43)	1 (1; 1)	1 (1; 1)	17 (16; 18)	17 (15; 18)	36 (36; 38)	36 (36; 37)
Vulvar/vaginal	2 (2; 2)	2 (1; 2)	22 (21; 23)	22 (21; 22)	60 (59; 61)	59 (59; 60)	-	-	-	-	-	-
Penile	-	-	-	-	-	-	1 (1; 2)	1 (1; 2)	10 (9; 10)	9 (9; 10)	34 (32; 35)	33 (31; 34)

80% UI: 80% uncertainty interval.

[a] Calculation of the reduction in incidence X years after the start of vaccination:

$$\text{(reduction in incidence at X years)} = 1 - \frac{\text{(incidence at X years)}}{\text{(incidence at year 0)}}$$

[b] The relative reductions in the incidence of AGW for the bivalent vaccine are not exactly zero because of stochastic fluctuations in the simulations.

Table 23 Impact of the vaccination of girls on the burden of HPV-associated diseases in Québec (baseline scenario)

	Average number of events per year	Average number of events per year prevented over 70 years	
	Prevaccination	Bivalent	Quadrivalent
	Median	Median	Median
HPV-ASSOCIATED DISEASES			
AGW			
Women	5,013	0	3,089
Heterosexual men	5,578	0	3,308
MSM	583	0	0
Abnormal cytologies	33,695	10,616	10,376
CIN2/3 episodes	3,187	1,910	1,775
HPV+ CANCERS			
Cervical	259	89	85
Anal			
Women	41	11	11
Heterosexual men	21	5	5
MSM	13	0	0
Oropharyngeal			
Women	34	8	8
Heterosexual men	98	23	22
MSM	10	0	0
Vulvar/vaginal	59	12	12
Penile			
Heterosexual men	13	2	2
MSM	1	0	0
All HPV-related cancers[a]			
Women	394	120	116
Heterosexual men	132	30	30
MSM	24	0	0
All	550	150	146
COSTS (IN MILLIONS $)			
Vaccination		11.7	11.7
Costs avoided		5.8	6.9
Total cost		5.9	4.8

MSM: men who have sex with men; CIN: cervical intraepithelial neoplasia.

[a] Based on Québec data from 2004 to 2006.

14.2.1.2 Cost-effectiveness of the vaccination of girls

Table 23 also presents the estimates of the costs associated with the vaccination of girls with the bivalent or quadrivalent vaccine. The decrease in health care costs resulting from vaccinating girls would be, on average, $1 million a year greater for the quadrivalent than the

bivalent vaccine over the first 70 years of the program. This additional reduction in costs would be attributable to the burden of AGW prevented with the quadrivalent vaccine.

Table 24 compares the cost-effectiveness ratios of vaccinating girls only with the bivalent or quadrivalent vaccine and presents the impact on the cost-effectiveness estimates of 1) considering all the HPV-associated diseases or just cervical cancer and AGW, 2) using different durations of protection for the vaccine HPV types and 3) varying the economic parameters (costs and QALYs lost).

The analysis predicts cost-effectiveness ratios for HPV vaccination that are significantly below the generally accepted cost-effectiveness threshold of $50,000/QALY, whether all HPV-related diseases or just cervical cancer and AGW are considered. Under the baseline scenario (including all HPV-related diseases), the model predicts cost-effectiveness ratios of $15,000/QALY and $12,000/QALY for use of the bivalent and quadrivalent vaccines respectively.

The results of the sensitivity analysis of the vaccine parameters suggest that the cost-effectiveness ratio of the bivalent vaccine is more sensitive than that of the quadrivalent vaccine to variation in the duration of vaccine protection. This is because the duration of vaccine protection has less influence on the predictions of population-level effectiveness against AGW. The vaccination scenario most favourable to the bivalent vaccine (bivalent/quadrivalent: vaccine coverage = 80%/80%; vaccine efficacy = persistent infections/persistent infections, duration of protection of vaccine types = lifetime/20 years and duration of cross-protection = lifetime/10 years) yields cost-effectiveness ratios of $15,000/QALY and $13,000/QALY respectively for the bivalent and quadrivalent vaccines. The bivalent vaccine therefore remains less cost-effective than the quadrivalent vaccine, even in a scenario with very favourable vaccine parameters.

In the sensitivity analysis of the parameters of the economic burden (costs and QALYs lost for AGW and cancers), the bivalent vaccine remains less cost-effective than the quadrivalent vaccine even assuming a minimum economic burden for AGW. Only the scenario combining a maximum economic burden for cancers with a minimum burden for AGW yields a cost-effectiveness ratio for the bivalent vaccine ($3,000/QALY) that is lower than the quadrivalent vaccine ($4,000/QALY). This stems from the fact that a higher efficacy of the bivalent vaccine against the non-vaccine types (Table 20) would produce a greater decline in the incidence of cervical cancers than with the quadrivalent vaccine (Table 23). In this scenario, the better cross-protection of the bivalent vaccine, combined with a high burden for cancers and a low burden for AGW, would thus provide quality of life gains and reductions in costs related to cervical cancers sufficient to obtain a lower cost-effectiveness ratio than that of the quadrivalent vaccine.

Table 24 Comparison of the cost-effectiveness of the bivalent and quadrivalent vaccines (vaccination of girls only, sensitivity analysis)

	Bivalent vaccine		Quadrivalent vaccine	
	Median ($/QALY)	(80% UI) ($/QALY)	Median ($/QALY)	(80% UI) ($/QALY)
Baseline scenario	15,000	(11,000; 19,000)	12,000	(9,000; 13,000)
Vaccine efficacy				
VE_x = CIN2+	13,000	(10,000; 16,000)	12,000	(10,000; 14,000)
VD_{type} = lifetime, VD_x = 10 years	16,000	(13,000; 18 000)	12,000	(10,000; 15,000)
VD_{type} = 20 years, VD_x = 10 years	18,000	(14,000; 22,000)	13,000	(10,000; 15,000)
Best scenario for the bivalent vaccine	15,000	(11,000; 19,000)	13,000	(10,000; 15,000)
Cost and QALYs				
Burden for AGW				
Minimum	15,000	(11,000; 19,000)	13,000	(10,000; 15,000)
Maximum	15,000	(11,000; 19,000)	9,000	(7,000; 10,000)
Burden for cancers				
Minimum	22,000	(18,000; 24,000)	16,000	(15,000; 18,000)
Maximum	3,000	(< 0; 7,000)	4,000	(2,000; 7,000)
Best scenario				
for the bivalent vaccine	3,000	(< 0; 7,000)	4,000	(2,000; 7,000)
for the quadrivalent vaccine	22,000	(18,000; 24,000)	12,000	(11,000; 14,000)

80% UI: 80% uncertainty interval; costs in $CAN; VE_X: vaccine efficacy of cross-protection against CIN2+ excluding HPV 16/18; VD_{type}: average duration of protection of the vaccine types; VD_x: average duration of cross-protection; Best scenario for the bivalent vaccine: 70% AGW caused by HPV 6/11, VE_x = CIN2+ excluding HPV 16/18, VD_x and VD_{type} (biv.) = lifetime, VD_x (quad.) = 10 years, VD_{type} (quad.) = 20 years, minimum burden for AGW, maximum burden for cancers; Best scenario for the quadrivalent vaccine: 90% AGW caused by HPV 6/11, maximum burden for AGW, minimum burden for cancers.

The results of the analysis of price differences per dose as a function of the cost-effectiveness ratio are provided in Table 25. In order to obtain an equal cost-effectiveness ratio for the two vaccines, the bivalent vaccine would have to cost approximately $12 (80% UI: $9-17) less per dose than the quadrivalent vaccine. It is also estimated that the quadrivalent vaccine would have to cost up to $35 more than the bivalent vaccine in order for its additional benefit, associated with the reduction in AGW, to be considered cost-effective at the $50,000/QALY threshold. In other words, the bivalent vaccine would have to cost $35 per dose less than the quadrivalent vaccine in order to represent an economically worthwhile alternative to the quadrivalent vaccine.

Table 25 Difference in price per dose between the quadrivalent and bivalent vaccines

	Equivalent CER		CER of the additional benefit of the quadrivalent vaccine = $50,000/QALY	
	Median ($)	(80% UI) ($)	Median ($)	(80% UI) ($)
Baseline scenario	12	(9; 17)	35	(29; 49)
Vaccine efficacy				
VE_x = CIN2+	5	(1; 7)	13	(5; 23)
VD_{type} = 100 years, VD_x = 10 years	13	(11; 16)	41	(27; 51)
VD_{type} = 20 years, VD_x = 10 years	17	(12; 22)	57	(26; 69)
Economic parameters (costs, QALYs)				
Burden				
minimum for AGW	7	(4; 11)	14	(6; 34)
maximum for AGW	19	(16; 26)	102	(93; 120)
minimum for cancers	16	(15; 20)	38	(33; 51)
maximum for cancers	3	(1; 10)	30	(19; 45)

CER: cost-effectiveness ratio; 80% UI: 80% uncertainty interval; VE_x = CIN2+: vaccine efficacy of cross-protection against CIN2+ excluding HPV 16/18; VD_{type}: average duration of the protection of the vaccine types; VD_x: average duration of cross-protection; Best scenario for bivalent vaccine: 70% AGW caused by HPV 6/11, VE_x = CIN2+ excluding HPV 16/18, VD_x and VD_{type} (biv.) = lifetime, VD_x (quad.) = 10 years, VD_{type} (quad.) = 20 years, minimum burden for AGW, maximum burden for cancers; Best scenario for quadrivalent vaccine: 90% AGW caused by HPV 6/11, maximum burden for AGW, minimum burden for cancers.

14.2.1.3 Discussion of the results obtained for girls/women

According to the results of this analysis, if the price of the two vaccines were the same in a vaccination program for girls only the quadrivalent vaccine would quite likely be more cost-effective than the bivalent vaccine. In addition, both the bivalent vaccine and the quadrivalent vaccine remain cost-effective in all the scenarios analyzed. Most of the studies that have estimated the cost-effectiveness of vaccinating girls in Canada,[259, 281, 282] the United States[265, 283-288] and the United Kingdom[266, 289, 290] reached similar conclusions.

In order for both vaccines to have an equivalent cost-effectiveness ratio, this analysis predicts that the bivalent vaccine would have to cost $12 less per dose than the quadrivalent vaccine (ranging from $3 to $19 in the sensitivity analysis). The magnitude of the price difference would depend mainly on 1) the costs and the QALYs lost associated with AGW and 2) the duration of protection conferred by the vaccines (including cross-protection).

This analysis did not examine the cost-effectiveness of expanding the current Québec vaccination program for girls to women 19 and older. However, if this strategy were to be considered, studies specific to Québec could be conducted with HPV-ADVISE in order to evaluate the impacts in the Québec population. The studies conducted in the United States, the United Kingdom and Australia predicted that catch-up vaccination of girls/women would be cost-effective up to 18 years of age but not up to age 24 or 26 .[265, 285, 289, 291, 292] In

addition, these studies concluded that vaccinating women aged 30 and older would not be a cost-effective intervention.[293] The cost-effectiveness ratio of the vaccination of older women would depend on two values that vary with age: 1) the percentage of individuals susceptible to the vaccine types and 2) the lifetime risk of infection.[265, 285, 289, 291-293] The study conclusions could therefore be different in the event of a high reinfection rate and high vaccine efficacy in women who have already cleared an infection by an HPV type included in the vaccine. These results, combined with the high coverage achieved by the vaccination program aimed at 9- to 18-year-old girls in Québec, seem to suggest that vaccinating women 19 and older in Québec would not be a cost-effective intervention.

What emerges from the present analysis is that the key factors to consider in the economic evaluation of girls-only vaccination strategies are 1) the duration of the protection conferred by vaccination (which is currently at least nine years; studies to determine the exact duration are continuing [see the *Vaccines* section]) and 2) the economic burden associated with AGW.

14.2.2 Vaccination of boys/men

14.2.2.1 Vaccination of boys

Population-level effectiveness of the vaccination of boys

Table 26 presents the impact of adding the vaccination of boys to the current girls-only vaccination programs (quadrivalent vaccine for both sexes) at 30 years, 50 years and 70 years after the start of vaccination. Vaccinating boys as well as girls (80% coverage for both sexes) would achieve an additional 6% reduction in the incidence of CIN2/3 episodes and cervical cancers in women 70 years after the start of vaccination. The additional reduction would be lower for the other HPV-associated cancers (3% for anal cancer and 2% for vulvar/vaginal and oropharyngeal cancers), and there would be no additional reduction for AGW in women. Seventy years after the start of vaccination, additional reductions of 34%, 3% and 9% would be achieved for men in the incidence of anal, penile and oropharyngeal cancers respectively and 9% for AGW. The additional reductions in the incidence of cancers observed in men attributable to the vaccination of boys would be mainly a result of the benefits for MSM, since it is assumed that MSM do not benefit from the indirect protection conferred by the vaccination of girls.

Table 26 Impact of the vaccination of boys and girls with the quadrivalent vaccine (relative reduction in the incidence of HPV-related diseases for the baseline scenario)

Time since the start of vaccination	Females			Males		
	30 years	50 years	70 years	30 years	50 years	70 years
	Median % (80% UI)	Median % (80% UI)	Median % (80% UI)	Median % (80% UI)	Median % (80% UI)	Median % (80% UI)
Impact of the vaccination of girls only						
AGW	85 (85; 85)	85 (85; 85)	85 (85; 85)	77 (77; 77)	77 (77; 77)	77 (77; 77)
CIN2/3	66 (61; 75)	68 (64; 77)	68 (63; 78)	-	-	-
Cancer						
Cervical	28 (24; 36)	69 (50; 73)	80 (73; 85)	-	-	-
Anal	10 (9; 10)	34 (33; 34)	73 (72; 74)	3 (3; 3)	21 (20; 22)	43 (43; 45)
Oropharyn-geal	1 (1; 1)	18 (18; 19)	43 (42; 43)	1 (1; 1)	17 (15; 18)	36 (36; 37)
Vulvar/ vaginal	2 (1; 2)	22 (21; 22)	59 (59; 60)	-	-	-
Penile	-	-	-	1 (1; 2)	9 (9; 10)	33 (31; 34)
Impact of the vaccination of girls and boys						
AGW	85 (85; 85)	85 (85; 85)	85 (85; 85)	86 (86; 86)	86 (86; 87)	86 (86; 87)
CIN2/3	72 (66; 82)	74 (70; 82)	74 (69; 84)	-	-	-
Cancer						
Cervical	28 (18; 37)	75 (59; 79)	87 (75; 91)	-	-	-
Anal	10 (10; 10)	35 (35; 36)	76 (76; 77)	5 (5; 5)	37 (35; 38)	78 (77; 79)
Oropharyn-geal	1 (1; 1)	19 (18; 19)	45 (44; 45)	1 (1; 1)	19 (18; 20)	45 (45; 45)
Vulvar/ vaginal	2 (2; 2)	22 (21; 24)	62 (60; 62)	-	-	-
Penile	-	-	-	2 (1;2)	10 (10;11)	37 (34;38)
Additional impact of vaccinating boys as well as girls						
AGW	0 (0;0)	0 (0;0)	0 (0;0)	9 (9;10)	9 (9;10)	9 (9;10)
CIN2/3	6 (5;7)	6 (5;8)	6 (5;8)	-	-	-
Cancer						
Cervical	0 (-6;5)	6 (1;9)	6 (2;8)	-	-	-
Anal	0 (0;1)	1 (1;2)	3 (3;4)	2 (2;2)	16 (15;16)	34 (33;35)
Oropharyn-geal	0 (0;0)	0 (0;1)	2 (2;2)	0 (0;0)	2 (2;2)	9 (8;9)
Vulvar/ vaginal	0 (0;0)	0 (0;1)	2 (1;3)	-	-	-
Penile	-	-	-	0 (0;0)	1 (1;1)	3 (3;4)

80% UI: 80% uncertainty interval.

CIN: cervical intraepithelial neoplasia.

Cost-effectiveness of the vaccination of boys

For the baseline scenario, the cost-effectiveness ratio of the vaccination of boys in Québec (while the current 80% coverage in girls with the quadrivalent vaccine is maintained) is estimated at $434,000/QALY and therefore far exceeds the threshold of cost-effectiveness generally accepted in Québec. The results of the analyses suggest that the cost per dose of the vaccine (including administration costs) would have to be $12 in order for the cost-effectiveness ratio of vaccinating boys to be under the $50,000/QALY threshold. The sensitivity analyses indicate that, even for the most favourable scenario for the vaccination of boys (maximum burden for MSM: proportion of MSM in the male population = 10% and relative risk of HPV-associated diseases = 17 for MSM compared with heterosexual men [Table 21]), the cost-effectiveness ratio would be $180,000/QALY. Under this scenario, in order to be cost-effective, the vaccine would have to cost $29 per dose, including administration costs.

Discussion of the results for boys/men

The results of the analyses suggest that vaccinating boys would not be cost-effective. This finding is explained mainly by our model's prediction that the vaccination of girls only would produce significant benefits for men owing to herd immunity. In Australia, where a girls-only vaccination program with the quadrivalent vaccine was introduced in 2007, a reduction in the proportion of heterosexual men under the age of 21 consulting for AGW has been observed since 2007, in addition to the reduction observed for women. However, no reduction has been observed in the proportion of MSM consulting for AGW. The reduction in AGW in heterosexual men is therefore attributed to the herd immunity conferred on boys/men by the vaccination of girls.[178, 180]

According to the results of the present analysis, an additional 34% reduction (80% UI: 33-35%) in the incidence of anal cancers would be observed for men 70 years after the introduction of a vaccination program for boys. The magnitude of this additional reduction may be explained by the model's prediction that more than one-third of anal cancers would be diagnosed in MSM (3% of men, Table 21) and that vaccinating girls would not protect MSM. This additional reduction represents, in absolute figures, 12 fewer new cases of anal cancer a year among men in Québec.

The additional reduction in the incidence of AGW observed in men (9% [80% UI: 9-10%]) 70 years after the start of vaccination is approximately equivalent to the fraction of AGW diagnosed in MSM (Table 21). This corresponds to an average additional reduction of 325 cases of AGW a year over 70 years, whereas the current program would be able to prevent approximately 6,400 cases a year, on average, over the first 70 years of the vaccination program (Table 23). According to the present analysis, the additional reduction in the incidence of anal cancers and AGW that would be achieved by the vaccination of boys/men would not be sufficient to make this a cost-effective intervention. To achieve cost-effectiveness the cost per dose of the vaccine would have to be $12 (including $10 administration costs) and at most $29 with a maximum burden in MSM (Table 21).

According to an American study conducted by Chesson et al.,[287] at equal coverage the incremental cost-effectiveness ratio of the vaccination of boys (versus the vaccination of girls only) increases exponentially with the increase in the vaccine coverage in girls, exceeding the cost-effectiveness threshold of $50,000/QALY (2008 $US) with vaccine coverage in girls of around 35%. Concurring with Chesson et al., with vaccine coverage in girls higher than 35% the majority of the cost-effectiveness estimates reviewed[265, 266, 291, 294] indicate that the vaccination of boys would not be a cost-effective intervention, given the indirect protection from which they already benefit through the vaccination of girls. Only the study published by Elbasha and Dasbach[295] indicates that vaccinating boys would be cost-effective, despite high coverage in girls. The lower cost-effectiveness ratios predicted by this study, compared with the other studies, could be explained by the estimate of a less significant impact of the vaccination of girls on the incidence of HPV-related cancers and AGW, which would make it possible to achieve greater additional reductions in the incidence by vaccinating boys as well as girls.[295]

Unlike previous cost-effectiveness studies on the vaccination of boys, the present analysis includes all HPV-associated cancers, as well as MSM. However, the model predictions are still subject to the limitations imposed by the lack of epidemiological data (on the transmissibility of HPV, natural immunity and its impact on the reinfection rate, the prevalence of the infection in men and the natural history of HPV infection and HPV-associated diseases) and the uncertainty surrounding existing data.

The following are key points to consider in analyzing the cost-effectiveness of vaccinating boys: 1) herd immunity in boys is likely quite significant, which results, in the analyses, in limited additional gains from vaccinating boys as well as girls and 2) even though the burden of HPV-associated diseases is high in MSM, who, unlike heterosexual males, do not benefit from the indirect protection conferred by the vaccination of girls, the burden of MSM would not represent (even with a maximum burden among MSM [Table 21]) a sufficient fraction of the HPV burden in the male population in Québec for the vaccination of boys to be cost-effective.

14.2.3 Targeted vaccination of MSM

HPV-associated diseases represent a significant burden among MSM, who probably benefit little from the indirect protection conferred by the vaccination of girls, as has been observed in Australia for AGW in the studies by Read et al.[180] and Fairley et al.[178] Targeted vaccination of MSM remains a strategy worth evaluating. However, in order to be efficacious and cost-effective, vaccination of MSM would have to be carried out when these men are still susceptible to the vaccine HPV types and vaccine efficacy is optimal, i.e. ideally before the start of sexual activity.

To date, the only analysis that has evaluated the cost-effectiveness ratio of targeted vaccination of MSM is the study by Kim in 2010, which suggests that the vaccination of MSM could be cost-effective if it reached enough MSM who were susceptible to the HPV vaccine types.[296] However, the results of this study must be interpreted with caution since the natural history of HPV infection and the transmission dynamics are not considered. Additional

studies are needed in order to estimate the cost-effectiveness ratio of targeted vaccination of MSM.

The percentage of MSM who are susceptible to the vaccine types and the vaccine efficacy in those who have cleared an infection with a vaccine HPV type will quite likely be key factors in estimating the cost-effectiveness of the intervention and should be the subject of future studies.

15 PROPOSALS

The MSSS requested the advice of the INSPQ on the following three questions:

1) Should the objective of the HPV vaccination program as recommended by the Comité sur l'immunisation du Québec (CIQ), namely to reduce the morbidity and mortality associated with cervical cancer, be maintained (or expanded)?
2) Depending on the answer to the previous question, can the two vaccines be considered to have the equivalent ability to achieve the health objective?
3) As a corollary, what is the INSPQ's recommendation concerning the inclusion of boys in the HPV vaccination program?

In its efforts to answer these questions, the INSPQ established an Ad Hoc Scientific Committee on HPV Vaccination composed of the members of the CIQ and experts and key individuals in the following fields: infectious diseases, gynecology, oncology, sexually transmitted infections, pediatrics, family medicine, nursing sciences, anthropology, ethics, epidemiology and public health. The objective that most of the participants in the Ad Hoc Scientific Committee agreed on is the following:

- ✓ Reduce the incidence, morbidity and mortality of cancers, precancerous lesions and other diseases associated with HPV.

The Committee believes that the available information on the immunogenicity and clinical efficacy of the quadrivalent HPV vaccine and the preliminary results of the Phase IV studies in other countries demonstrate that the Québec program consisting of routine vaccination of girls in grade 4 and a catch-up program up to the age of 18 with a quadrivalent vaccine will be effective in reducing the burden of precancerous lesions and cancers attributable to HPV, as well as AGW, in the target population. The vaccine coverage currently achieved (± 80%) in girls is also expected to have a considerable indirect impact on the male heterosexual population with respect to both AGW and certain cancers. The modelling results also indicate that the program will be cost-effective (< $20,000/QALY), on the basis of the standards generally accepted in Québec.

Replacing the quadrivalent vaccine (Gardasil®) with the bivalent vaccine (Cervarix™) would mean abandoning the goal of preventing diseases caused by HPV types 6 and 11, such as AGW and potentially laryngeal papillomatosis. However, the prevention of cancers would be slightly improved should the bivalent vaccine confer greater cross-protection against certain oncogenic types. Economic analyses conducted in Québec show that to be as cost-effective as the quadrivalent vaccine, the bivalent vaccine would have to cost much less. The majority of the members of the scientific committee expressed reservations about the possibility of abandoning protection against AGW (both in girls through direct protection and in boys through herd immunity). Abandoning such protection could also trigger negative reactions from health care professionals and the public. On the other hand, replacing the quadrivalent vaccine with the bivalent vaccine could minimize program costs should the bivalent vaccine cost significantly less than the quadrivalent vaccine.

The efficacy of the quadrivalent vaccine in men has been well demonstrated. However, adding universal vaccination of preadolescents would have only a marginal impact on the male heterosexual population, as long as vaccine coverage in the female population is maintained. The major benefit of a free vaccination program for boys would be to reduce the burden of AGW and certain cancers in men who will later have sexual relations with men, because they will have been vaccinated at the time when vaccine efficacy is highest (i.e. before the start of sexual relations). However, at the current cost of the quadrivalent vaccine, extending the program to all preadolescent boys in order to provide more protection to a minority of them would not be cost-effective (> $180,000/QALY) according to generally accepted standards. A free vaccination program for all boys could be justified by political and equity considerations, primarily with respect to MSM, but not by arguments of significant epidemiological impact or the efficiency of the program. In the event of a substantial reduction in the cost of the quadrivalent vaccine, such conclusions could change.

Extending the existing program in order to provide free vaccination to women aged 18 and over would probably have a limited impact on the burden of diseases caused by HPV in this population. The magnitude of the reduction is difficult to determine for each age group. Vaccine efficacy declines when vaccination takes place after the start of sexual activity. Approximately 50% of women aged 18-20 are already vaccinated, since they have been targeted by the catch-up program since 2008. Extending the existing program would be quite expensive, because three doses of the vaccine would have to be administered outside the school environment. The cost-effectiveness ratios of such an extension would definitely be less favourable than those achieved by the existing school-based program aimed at girls under the age of 18. There is also considerable uncertainty about the feasibility of such an addition to the program and the vaccine uptake that could be achieved.

The implementation of pilot projects for targeted vaccination of MSM could be explored, since free vaccination of all preadolescents is not an efficient strategy with the current cost of the vaccines. The scientific evidence suggests that the effectiveness of such a strategy, whereby the vaccine would in most cases be administered after the start of sexual relations, may be limited. Furthermore, the feasibility, acceptability and cost of such a program have not been carefully evaluated. Studies would have to be conducted to examine these aspects.

The vaccination of certain other population subgroups deemed at greater risk of acquiring HPV-associated diseases (e.g. Aboriginal people) or of experiencing complications (e.g. people with certain chronic diseases) could also be explored. A careful and specific analysis of this issue, which was not possible within the framework of this advisory report, should be undertaken.

16 OTHER CONSIDERATIONS

Since HPV vaccines do not protect against all oncogenic HPV types and since sexually active women may have been infected before vaccination, all women, vaccinated or not, should participate in existing cervical cancer screening activities in Québec. In addition, since HPV vaccination does not protect against all sexually transmitted infections, everyone, whether vaccinated or not, should adopt and maintain safe-sex practices and be screened in accordance with the applicable recommendations.

In the context of the present advisory report, the Committee did not study or discuss in detail vaccination schedules (for example, the extended schedule for vaccination in grade 4 [0, 6 and 60 months] and the need for a third dose at 60 months). The Committee members suggest that the vaccination schedules recommended in the INSPQ's 2007 report, *Prevention by Vaccination of Diseases Attributable to the Human Papillomavirus in Québec*, be maintained for the time being.

Research topics:

- Efficacy of an HPV vaccination program consisting of two doses administered six months apart;
- Immunogenicity and efficacy of a schedule using both vaccines;
- Long-term antibody persistence and immune memory, and the effect of a booster dose given 5, 10 or 15 years after primary vaccination;
- Impact of the program on the frequency of precancerous lesions, related interventions and resources;
- Acceptability of vaccination among boys and their parents;
- Efficacy of vaccination in immunosuppressed individuals;
- Strategies for reaching (effectively, efficiently and appropriately) subgroups to be vaccinated (e.g. MSM) if a selective approach is considered;
- Impact of the vaccination of boys on the transmission of HPV infections from boys to girls and on the prevention of precancerous and cancerous lesions in girls;
- Vaccine efficacy among individuals who have managed to clear an infection;
- Efficacy of the vaccine in preventing oropharyngeal cancers;
- Duration of vaccine efficacy against the vaccine types and against the non-vaccine types (cross-protection);
- Acceptable and effective strategies for promoting HPV vaccination in the context of a universal program, in order to maintain high vaccine coverage.

REFERENCES

1. Walboomers, J. M., Jacobs, M. V., Manos, M. M., Bosch, F. X., Kummer, J. A., Shah, K. V., et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1):12-9.

2. Bosch, F. X., Lorincz, A., Munoz, N., Meijer, C. J., Shah, K. V. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol. 2002;55(4):244-65.

3. Munoz, N., Bosch, F. X., de Sanjosé, S., Herrero, R., Castellsagué, X., Shah, K. V., et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Eng J Med. 2003;348(6):518-527.

4. Li, N., Franceschi, S., Howell-Jones, R., Snijders, P. J., Clifford, G. M. Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: variation by geographical region, histological type and year of publication. Int J Cancer. 2011;128(4):927-35.

5. Bouvard, V., Baan, R., Straif, K., Grosse, Y., Secretan, B., El Ghissassi, F., et al. A review of human carcinogens – Part B: biological agents. Lancet Oncol. 2009;10(4):321-2.

6. Bruni, L., Diaz, M., Castellsague, X., Ferrer, E., Bosch, F. X., de Sanjose, S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. J Infect Dis. 2010;202(12):1789-99.

7. Tricco, A. C., Ng, C. H., Gilca, V., Anonychuk, A., Pham, B., Berliner, S. Canadian oncogenic human papillomavirus cervical infection prevalence: systematic review and meta-analysis. BMC Infect Dis. 2011;11:235.

8. Giuliano, A. R., Nielson, C. M., Flores, R., Dunne, E. F., Abrahamsen, M., Papenfuss, M. R., et al. The optimal anatomic sites for sampling heterosexual men for human papillomavirus (HPV) detection: the HPV detection in men study. J Infect Dis. 2007;196(8):1146-52.

9. Nielson, C. M., Flores, R., Harris, R. B., Abrahamsen, M., Papenfuss, M. R., Dunne, E. F., et al. Human papillomavirus prevalence and type distribution in male anogenital sites and semen. Cancer Epidemiol Biomarkers Prev. 2007;16(6):1107-14.

10. Smith, J. S., Gilbert, P. A., Melendy, A., Rana, R. K., Pimenta, J. M. Age-specific prevalence of human papillomavirus infection in males: a global review. J Adolesc Health. 2011;48(6):540-52.

11. Giuliano, A. R., Lee, J. H., Fulp, W., Villa, L. L., Lazcano, E., Papenfuss, M. R., et al. Incidence and clearance of genital human papillomavirus infection in men (HIM): a cohort study. Lancet. 2011;377(9769):932-40.

12. Dunne, E. F., Nielson, C. M., Stone, K. M., Markowitz, L. E., Giuliano, A. R. Prevalence of HPV infection among men: a systematic review of the literature. J Infect Dis. 2006;194(8):1044-57.

13. Richardson, H., Franco, E., Pintos, J., Bergeron, J., Arella, M., Tellier, P. Determinants of low-risk and high-risk cervical human papillomavirus infections in Montréal University students. Sex Transm Dis. 2000;27(2):79-86.

14. Richardson, H., Kelsall, G., Tellier, P., Voyer, H., Abrahamowicz, M., Ferenczy, A., et al. The natural history of type-specific human papillomavirus infections in female university students. Cancer Epidemiol Biomarkers Prev. 2003;12(6):485-90.

15. Mayrand, M. H., Duarte-Franco, E., Coutlee, F., Rodrigues, I., Walter, S. D., Ratnam, S., et al. Randomized controlled trial of human papillomavirus testing versus Pap cytology in the primary screening for cervical cancer precursors: design, methods and preliminary accrual results of the Canadian cervical cancer screening trial (CCCaST). Int J Cancer. 2006;119(3):615-23.

16. Hamlin-Douglas, L. K., Coutlee, F., Roger, M., Franco, E. L., Brassard, P. Prevalence and age distribution of human papillomavirus infection in a population of Inuit women in Nunavik, Québec. Cancer Epidemiol Biomarkers Prev. 2008;17(11):3141-9.

17. Burchell, A. N., Tellier, P. P., Hanley, J., Coutlee, F., Franco, E. L. Human papillomavirus infections among couples in new sexual relationships. Epidemiology. 2010;21(1):31-7.

18. de Pokomandy, A., Rouleau, D., Ghattas, G., Vezina, S., Cote, P., Macleod, J., et al. Prevalence, clearance, and incidence of anal human papillomavirus infection in HIV-infected men: the HIPVIRG cohort study. J Infect Dis. 2009;199(7):965-73.

19. Kreimer, A. R., Bhatia, R. K., Messeguer, A. L., Gonzalez, P., Herrero, R., Giuliano, A. R. Oral human papillomavirus in healthy individuals: a systematic review of the literature. Sex Transm Dis. 2010;37(6):386-91.

20. Kreimer, A. R., Villa, A., Nyitray, A. G., Abrahamsen, M., Papenfuss, M., Smith, D., et al. The epidemiology of oral HPV infection among a multinational sample of healthy men. Cancer Epidemiol Biomarkers Prev. 2011;20(1):172-82.

21. Gillison, M. L., Broutian, T., Pickard, R. K., Tong, Z. Y., Xiao, W., Kahle, L., et al. Prevalence of oral HPV infection in the United States, 2009-2010. JAMA. 2012;307(7):693-703.

22. Pintos, J., Black, M. J., Sadeghi, N., Ghadirian, P., Zeitouni, A. G., Viscidi, R. P., et al. Human papillomavirus infection and oral cancer: a case-control study in Montréal, Canada. Oral Oncol. 2008;44(3):242-50.

23. Pagliusi, S. R., Dillner, J., Pawlita, M., Quint, W. G., Wheeler, C. M., Ferguson, M. Chapter 23: International Standard reagents for harmonization of HPV serology and DNA assays--an update. Vaccine. 2006;24 Suppl 3:S3/193-200.

24. Newall, A. T., Brotherton, J. M., Quinn, H. E., McIntyre, P. B., Backhouse, J., Gilbert, L., et al. Population seroprevalence of human papillomavirus types 6, 11, 16, and 18 in men, women, and children in Australia. Clin Infect Dis. 2008;46(11):1647-55.

25. Markowitz, L. E., Sternberg, M., Dunne, E. F., McQuillan, G., Unger, E. R. Seroprevalence of human papillomavirus types 6, 11, 16, and 18 in the United States: National Health and Nutrition Examination Survey 2003-2004. J Infect Dis. 2009;200(7):1059-67.

26. Moscicki, A. B., Schiffman, M., Kjaer, S., Villa, L. L. Chapter 5: Updating the natural history of HPV and anogenital cancer. Vaccine. 2006;24 Suppl 3:S42-51.

27. Trottier, H., and Franco, E. L. The epidemiology of genital human papillomavirus infection. Vaccine. 2006;24 Suppl 1:S1-15.

28. Schiffman, M., Kjaer, S. K. Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia. J Natl Cancer Inst Monogr. 2003(31):14-9.

29. Burchell, A. N., Richardson, H., Mahmud, S. M., Trottier, H., Tellier, P. P., Hanley, J., et al. Modeling the sexual transmissibility of human papillomavirus infection using stochastic computer simulation and empirical data from a cohort study of young women in Montréal, Canada. Am J Epidemiol. 2006;163(6):534-43.

30. Manhart, L. E., Koutsky, L. A. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. Sex Transm Dis. 2002;29(11):725-35.

31. D'Souza, G., Kreimer, A. R., Viscidi, R., Pawlita, M., Fakhry, C., Koch, W. M., et al. Case-Control Study of Human Papillomavirus and Oropharyngeal Cancer. N Engl J Med. 2007;356(19):1944-56.

32. Smith, E. M., Ritchie, J. M., Summersgill, K. F., Klussmann, J. P., Lee, J. H., Wang, D., et al. Age, sexual behavior and human papillomavirus infection in oral cavity and oropharyngeal cancers. Int J Cancer. 2004;108(5):766-72.

33. Gillison, M. L., D'Souza, G., Westra, W., Sugar, E., Xiao, W., Begum, S., et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst. 2008;100(6):407-20.

34. Koutsky, L. A., Galloway, D. A., Holmes, K. K. Epidemiology of genital human papillomavirus infection. Epidemiol Rev. 1988;10:122-63.

35. Syrjanen, K., Hakama, M., Saarikoski, S., Vayrynen, M., Yliskoski, M., Syrjanen, S., et al. Prevalence, incidence, and estimated life-time risk of cervical human papillomavirus infections in a nonselected Finnish female population. Sex Transm Dis. 1990;17(1):15-9.

36. Gillison, M. L., Chaturvedi, A. K., Lowy, D. R. HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. Cancer. 2008;113(10 Suppl):3036-46.

37. Insinga, R. P., Liaw, K. L., Johnson, L. G., Madeleine, M. M. A systematic review of the prevalence and attribution of human papillomavirus types among cervical, vaginal, and vulvar precancers and cancers in the United States. Cancer Epidemiol Biomarkers Prev. 2008;17(7):1611-22.

38. Ferlay, J., Shin, H. R., Bray, F., Forman, D., Mathers, C., Parkin, D. M. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127(12):2893-917.

39. de Sanjose, S., Quint, W. G., Alemany, L., Geraets, D. T., Klaustermeier, J. E., Lloveras, B., et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010;11(11):1048-56.

40. Clifford, G. M., Gallus, S., Herrero, R., Munoz, N., Snijders, P. J., Vaccarella, S., et al. Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. Lancet. 2005;366(9490):991-8.

41. Clifford, G. M., Rana, R. K., Franceschi, S., Smith, J. S., Gough, G., Pimenta, J. M. Human papillomavirus genotype distribution in low-grade cervical lesions: comparison by geographic region and with cervical cancer. Cancer Epidemiol Biomarkers Prev. 2005;14(5):1157-64.

42. Smith, J. S., Lindsay, L., Hoots, B., Keys, J., Franceschi, S., Winer, R., et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. Int J Cancer. 2007;121(3):621-32.

43. Castellsague, X., Diaz, M., de Sanjose, S., Munoz, N., Herrero, R., Franceschi, S., et al. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. J Natl Cancer Inst. 2006;98(5):303-15.

44. Coutlee, F., Ratnam, S., Ramanakumar, A. V., Insinga, R. R., Bentley, J., Escott, N., et al. Distribution of human papillomavirus genotypes in cervical intraepithelial neoplasia and invasive cervical cancer in Canada. J Med Virol. 2011;83(6):1034-41.

45. Khan, M. J., Castle, P. E., Lorincz, A. T., Wacholder, S., Sherman, M., Scott, D. R., et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. J Natl Cancer Inst. 2005;97(14):1072-9.

46. Kjaer, S. K., Frederiksen, K., Munk, C., Iftner, T. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. J Natl Cancer Inst. 2010;102(19):1478-88.

47. Kreimer, A. R., Clifford, G. M., Boyle, P., Franceschi, S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer Epidemiol Biomarkers Prev. 2005;14(2):467-75.

48. De Vuyst, H., Clifford, G. M., Nascimento, M. C., Madeleine, M. M., Franceschi, S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. Int J Cancer. 2009;124(7):1626-36.

49. Smith, J. S., Backes, D. M., Hoots, B. E., Kurman, R. J., Pimenta, J. M. Human papillomavirus type-distribution in vulvar and vaginal cancers and their associated precursors. Obstet Gynecol. 2009;113(4):917-24.

50. Hoots, B. E., Palefsky, J. M., Pimenta, J. M., Smith, J. S. Human papillomavirus type distribution in anal cancer and anal intraepithelial lesions. Int J Cancer. 2009;124(10):2375-83.

51. Backes, D. M., Kurman, R. J., Pimenta, J. M., Smith, J. S. Systematic review of human papillomavirus prevalence in invasive penile cancer. Cancer Causes Control. 2009;20(4):449-57.

52. Giuliano, A. R., Tortolero-Luna, G., Ferrer, E., Burchell, A. N., de Sanjose, S., Kjaer, S. K., et al. Epidemiology of human papillomavirus infection in men, cancers other than cervical and benign conditions. Vaccine. 2008;26 Suppl 10:K17-28.

53. Patel, P., Hanson, D. L., Sullivan, P. S., Novak, R. M., Moorman, A. C., Tong, T. C., et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. Ann Intern Med. 2008;148(10):728-36.

54. Saleem, A. M., Paulus, J. K., Shapter, A. P., Baxter, N. N., Roberts, P. L., Ricciardi, R. Risk of anal cancer in a cohort with human papillomavirus-related gynecologic neoplasm. Obstet Gynecol. 2011;117(3):643-9.

55. Chaturvedi, A. K., Engels, E. A., Gilbert, E. S., Chen, B. E., Storm, H., Lynch, C. F., et al. Second cancers among 104,760 survivors of cervical cancer: evaluation of long-term risk. J Natl Cancer Inst. 2007;99(21):1634-43.

56. Micali, G., Nasca, M. R., Innocenzi, D., Schwartz, R. A. Penile cancer. J Am Acad Dermatol. 2006;54(3):369-91; quiz 391-4.

57. Parkin, D. M., Bray, F. Chapter 2: The burden of HPV-related cancers. Vaccine. 2006;24 Suppl 3:S11-S25.

58. Herrero, R., Castellsague, X., Pawlita, M., Lissowska, J., Kee, F., Balaram, P., et al. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. J Natl Cancer Inst. 2003;95(23):1772-83.

59. Termine, N., Panzarella, V., Falaschini, S., Russo, A., Matranga, D., Lo Muzio, L., et al. HPV in oral squamous cell carcinoma vs head and neck squamous cell carcinoma biopsies: a meta-analysis (1988-2007). Ann Oncol. 2008;19(10):1681-90.

60. Hobbs, C. G., Sterne, J. A., Bailey, M., Heyderman, R. S., Birchall, M. A., Thomas, S. J. Human papillomavirus and head and neck cancer: a systematic review and meta-analysis. Clin Otolaryngol. 2006;31(4):259-66.

61. Syrjanen, S. The role of human papillomavirus infection in head and neck cancers. Ann Oncol. 2010;21 Suppl 7:vii243-5.

62. Cleveland, J. L., Junger, M. L., Saraiya, M., Markowitz, L. E., Dunne, E. F., Epstein, J. B. The connection between human papillomavirus and oropharyngeal squamous cell carcinomas in the United States: implications for dentistry. J Am Dent Assoc. 2011;142(8):915-24.

63. Chung, C. H., Gillison, M. L. Human papillomavirus in head and neck cancer: its role in pathogenesis and clinical implications. Clin Cancer Res. 2009;15(22):6758-62.

64. Dayyani, F., Etzel, C. J., Liu, M., Ho, C. H., Lippman, S. M., Tsao, A. S. Meta-analysis of the impact of human papillomavirus (HPV) on cancer risk and overall survival in head and neck squamous cell carcinomas (HNSCC). Head Neck Oncol. 2010;2:15.

65. Nasman, A., Attner, P., Hammarstedt, L., Du, J., Eriksson, M., Giraud, G., et al. Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: an epidemic of viral-induced carcinoma? Int J Cancer. 2009;125(2):362-6.

66. Blomberg, M., Nielsen, A., Munk, C., Kjaer, S. K. Trends in head and neck cancer incidence in Denmark, 1978-2007: focus on human papillomavirus associated sites. Int J Cancer. 2011;129(3):733-41.

67. Hocking, J. S., Stein, A., Conway, E. L., Regan, D., Grulich, A., Law, M., et al. Head and neck cancer in Australia between 1982 and 2005 show increasing incidence of potentially HPV-associated oropharyngeal cancers. Br J Cancer. 2011;104(5):886-91.

68. Hammarstedt, L., Dahlstrand, H., Lindquist, D., Onelov, L., Ryott, M., Luo, J., et al. The incidence of tonsillar cancer in Sweden is increasing. Acta Otolaryngol. 2007;127(9):988-92.

69. Auluck, A., Hislop, G., Bajdik, C., Poh, C., Zhang, L., Rosin, M. Trends in oropharyngeal and oral cavity cancer incidence of human papillomavirus (HPV)-related and HPV-unrelated sites in a multicultural population: the British Columbia experience. Cancer. 2010;116(11):2635-44.

70. Chaturvedi, A. K., Engels, E. A., Anderson, W. F., Gillison, M. L. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol. 2008;26(4):612-9.

71. Chaturvedi, A. K., Engels, E. A., Pfeiffer, R. M., Hernandez, B. Y., Xiao, W., Kim, E., et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011;29(32):4294-301.

72. Sturgis, E. M., Cinciripini, P. M. Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? Cancer. 2007;110(7):1429-35.

73. Attner, P., Du, J., Nasman, A., Hammarstedt, L., Ramqvist, T., Lindholm, J., et al. The role of human papillomavirus in the increased incidence of base of tongue cancer. Int J Cancer. 2010;126(12):2879-84.

74. St Guily, J. L., Jacquard, A. C., Pretet, J. L., Haesebaert, J., Beby-Defaux, A., Clavel, C., et al. Human papillomavirus genotype distribution in oropharynx and oral cavity cancer in France–The EDiTH VI study. J Clin Virol. 2011;51(2):100-4.

75. Aubin, F., Pretet, J. L., Jacquard, A. C., Saunier, M., Carcopino, X., Jaroud, F., et al. Human papillomavirus genotype distribution in external acuminata condylomata: a Large French National Study (EDiTH IV). Clin Infect Dis. 2008;47(5):610-5.

76. Garland, S. M., Steben, M., Sings, H. L., James, M., Lu, S., Railkar, R., et al. Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine. J Infect Dis. 2009;199(6):805-14.

77. Drolet, M., Brisson, M., Maunsell, E., Franco, E. L., Coutlee, F., Ferenczy, A., et al. The impact of anogenital warts on health-related quality of life: a 6-month prospective study. Sex Transm Dis. 2011;38(10):949-56.

78. Lacey, C. J., Lowndes, C. M., Shah, K. V. Chapter 4: Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. Vaccine. 2006;24 Suppl 3:S35-41.

79. Dinh, T. H., Sternberg, M., Dunne, E. F., Markowitz, L. E. Genital warts among 18- to 59-year-olds in the United States, national health and nutrition examination survey, 1999--2004. Sex Transm Dis. 2008;35(4):357-60.

80. Kliewer, E. V., Demers, A. A., Elliott, L., Lotocki, R., Butler, J. R., Brisson, M. Twenty-year trends in the incidence and prevalence of diagnosed anogenital warts in Canada. Sex Transm Dis. 2009;36(6):380-6.

81. Marra, F., Ogilvie, G., Colley, L., Kliewer, E., Marra, C. A. Epidemiology and costs associated with genital warts in Canada. Sex Transm Infect. 2009;85(2):111-5.

82. Donne, A. J., Clarke, R. Recurrent respiratory papillomatosis: an uncommon but potentially devastating effect of human papillomavirus in children. Int J STD AIDS. 2010;21(6):381-5.

83. Silverberg, M. J., Thorsen, P., Lindeberg, H., Grant, L. A., Shah, K. V. Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. Obstet Gynecol. 2003;101(4):645-52.

84. Wang, S. S., Sherman, M. E., Hildesheim, A., Lacey, J. V., Jr., Devesa, S. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976-2000. Cancer. 2004;100(5):1035-44.

85. Bray, F., Carstensen, B., Moller, H., Zappa, M., Zakelj, M. P., Lawrence, G., et al. Incidence trends of adenocarcinoma of the cervix in 13 European countries. Cancer Epidemiol Biomarkers Prev. 2005;14(9):2191-9.

86. Louchini, R., Goggin, P., Steben, M. The evolution of HPV-related anogenital cancers reported in Québec – Incidence rates and survival probabilities. Chronic Dis Can. 2008;28(3):99-106.

87. Société canadienne du cancer and Institut national du cancer du Canada. Statistiques canadiennes sur le cancer. Toronto, Canada, 2011.

88. Cress, R. D., Holly, E. A. Incidence of anal cancer in California: increased incidence among men in San Francisco, 1973-1999. Prev Med. 2003;36(5):555-60.

89. Butler, J. R. G., Kliewer, E. V., Demers, A. A. The Cost of Treating Anogenital Warts in Manitoba, Canada. 24th International Papillomavirus Conference and Clinical Workshop, Beijing International Convention Center, China, November 3-10, 2007.

90. Campisi, P., Hawkes, M., Simpson, K. The epidemiology of juvenile onset recurrent respiratory papillomatosis derived from a population level national database. Laryngoscope. 2010;120(6):1233-45.

91. Rodier, C., Lapointe, A., Dal Soglio, D., Mayrand, M. H., Coutlée, F., Roger, M., et al. Juvenile Respiratory Papillomatosis Risk Factors for Severity. 27th International Papillomavirus Conference and Clinical Workshop, Berlin, Germany, September 17-22, 2011.

92. Working group on guidelines for cervical cancer screening in Québec. Guidelines on Cervical Cancer Screening in Québec. Québec: Institut national de santé publique du Québec, 2011, 36 p.

93. Merck Frosst Canada ltée. GARDASIL - Vaccin recombinant quadrivalent contre le virus du papillome humain (types 6, 11, 16 et 18). Québec: Merck Frosst Canada Ltée, 2011. 63 p.

94. GlaxoSmithKline. CERVARIX - Human Papillomavirus vaccine Types 16 and 18 (Recombinant, AS04 adjuvanted). Québec: GlaxoSmithKline, 2011. 52 p.

95. Stanley, M. HPV vaccines. Best Pract Res Clin Obstet Gynaecol. 2006;20(2):279-93.

96. National Advisory Committee on Immunization. Statement on human papillomavirus vaccine. Can Commun Dis Rep. 2007;33(ACS-2):1-32.

97. Plotkin, S. A., Orenstein, W. A., Offit, P. A. Vaccines. Fifth Edition, Stanley, A., Plotkin and Walter A. Orenstein, Philadelphia, 2008, 1725 p.

98. Paavonen, J., Naud, P., Salmeron, J., Wheeler, C. M., Chow, S. N., Apter, D., et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet. 2009;374(9686):301-14.

99. Chang, Y., Brewer, N. T., Rinas, A. C., Schmitt, K., Smith, J. S. Evaluating the impact of human papillomavirus vaccines. Vaccine. 2009;27(32):4355-62.

100. Lin, K., Doolan, K., Hung, C. F., Wu, T. C. Perspectives for preventive and therapeutic HPV vaccines. J Formos Med Assoc. 2010;109(1):4-24.

101. Campo, M. S., Roden, R. B. Papillomavirus prophylactic vaccines: established successes, new approaches. J Virol. 2010;84(3):1214-20.

102. National Advisory Comittee on Immunization. Update on Human Papillomavirus (HPV) Vaccines. Canada Commun Dis Rep. 2012;38(ACS-1):1-62.

103. Cho, H. J., Oh, Y. K., Kim, Y. B. Advances in human papilloma virus vaccines: a patent review. Expert Opin Ther Pat. 2011;21(3):295-309.

104. Centers for Disease Control and Prevention. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2010;59(20):626-9.

105. Krajden, M., Karunakaran, K., So, S., Palefsky, J. M., Sharma, R., Cook, D., et al. Prevalence of human papillomavirus 16 and 18 neutralizing antibodies in prenatal women in British Columbia. Clin Vaccine Immunol. 2009;16(12):1840-3.

106. Krajden, M., Dobson, S., Cook, D., Chow, R., Yu, A., McNeil, S., et al. Does Merck cLIA Accurately Detect HPV-18 Antibodies in Vaccinated Subjects? Oral presention. 27th International Papillomavirus Conference and Clinical Workshop, Berlin, Germany, September 17-22, 2011.

107. Wideroff, L., Schiffman, M. H., Nonnenmacher, B., Hubbert, N., Kirnbauer, R., Greer, C. E., et al. Evaluation of seroreactivity to human papillomavirus type 16 virus-like particles in an incident case-control study of cervical neoplasia. J Infect Dis. 1995;172(6):1425-30.

108. Ferguson, M., Wilkinson, D. E., Zhou, T. WHO meeting on the standardization of HPV assays and the role of the WHO HPV Laboratory Network in supporting vaccine introduction held on 24-25 January 2008, Geneva, Switzerland. Vaccine. 2009;27(3):337-47.

109. Pastrana, D. V., Buck, C. B., Pang, Y. Y., Thompson, C. D., Castle, P. E., FitzGerald, P. C., et al. Reactivity of human sera in a sensitive, high-throughput pseudovirus-based papillomavirus neutralization assay for HPV16 and HPV18. Virology. 2004;321(2):205-16.

110. Nardelli-Haefliger, D., Roden, R., Balmelli, C., Potts, A., Schiller, J., De Grandi, P. Mucosal but not parenteral immunization with purified human papillomavirus type 16 virus-like particles induces neutralizing titers of antibodies throughout the estrous cycle of mice. J Virol. 1999;73(11):9609-13.

111. Opalka, D., Lachman, C. E., MacMullen, S. A., Jansen, K. U., Smith, J. F., Chirmule, N., et al. Simultaneous quantitation of antibodies to neutralizing epitopes on virus-like particles for human papillomavirus types 6, 11, 16, and 18 by a multiplexed luminex assay. Clin Diagn Lab Immunol. 2003;10(1):108-15.

112. Opalka, D., Matys, K., Bojczuk, P., Green, T., Gesser, R., Saah, A., et al. Multiplexed serologic assay for nine anogenital human papillomavirus types. Clin Vaccine Immunol. 2010;17(5):818-27.

113. Viscidi, R. P., Schiffman, M., Hildesheim, A., Herrero, R., Castle, P. E., Bratti, M. C., et al. Seroreactivity to human papillomavirus (HPV) types 16, 18, or 31 and risk of subsequent HPV infection: results from a population-based study in Costa Rica. Cancer Epidemiol Biomarkers Prev. 2004;13(2):324-7.

114. Stanley, M. A. Immune responses to human papilloma viruses. Indian J Med Res. 2009;130(3):266-76.

115. WHO. Human papillomavirus vaccines. WHO position paper. Wkly Epidemiol Rec. 2009;84(15):118-31.

116. Breitburd, F., Kirnbauer, R., Hubbert, N. L., Nonnenmacher, B., Trin-Dinh-Desmarquet, C., Orth, G., et al. Immunization with viruslike particles from cottontail rabbit papillomavirus (CRPV) can protect against experimental CRPV infection. J Virol. 1995;69(6):3959-63.

117. Suzich, J. A., Ghim, S. J., Palmer-Hill, F. J., White, W. I., Tamura, J. K., Bell, J. A., et al. Systemic immunization with papillomavirus L1 protein completely prevents the development of viral mucosal papillomas. Proc Natl Acad Sci U S A. 1995;92(25):11553-7.

118. Ma, B., Roden, R., Wu, T. C. Current status of human papillomavirus vaccines. J Formos Med Assoc. 2010;109(7):481-3.

119. Garcia-Sicilia, J., Schwarz, T. F., Carmona, A., Peters, K., Malkin, J. E., Tran, P. M., et al. Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine coadministered with combined diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine to girls and young women. J Adolesc Health. 2010;46(2):142-51.

120. Schwarz, T. F., Spaczynski, M., Schneider, A., Wysocki, J., Galaj, A., Perona, P., et al. Immunogenicity and tolerability of an HPV-16/18 AS04-adjuvanted prophylactic cervical cancer vaccine in women aged 15-55 years. Vaccine. 2009;27(4):581-587.

121. Stanley, M., Gissmann, L., Nardelli-Haefliger, D. Immunobiology of human papillomavirus infection and vaccination – implications for second generation vaccines. Vaccine. 2008;26 Suppl 10:K62-7.

122. Einstein, M. H., Baron, M., Levin, M. J., Chatterjee, A., Edwards, R. P., Zepp, F., et al. Comparison of the immunogenicity and safety of Cervarix and Gardasil human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18-45 years. Hum Vaccine. 2009;5(10):705-19.

123. Dobson, S., Dawar, M., Kollmann, T., McNeil, S., Halperin, S., Langley, J., et al. A Two Dose HPV Vaccine Schedule in Girls: Immunogenicity at 24 Months. Poster presentation. 26th International Papillomavirus Conference and Clinical and Public Health Workshops, Montréal, July 3-8, 2010.

124. Krajden, M., Cook, D., Yu, A., Chow, R., Mei, W., McNeil, S., et al. Human papillomavirus 16 (HPV 16) and HPV 18 antibody responses measured by pseudovirus neutralization and competitive Luminex assays in a two- versus three-dose HPV vaccine trial. Clin Vaccine Immunol. 2011;18(3):418-23.

125. Evaluation of the safety and immunogenicity of an investigational vaccination regimen administered in healthy females aged 9 – 25 years as compared to GlaxoSmithKline Biologicals' HPV vaccine 580299 given as a 2-dose or as the standard 3-dose schedule. Available at: http://download.gsk-clinicalstudyregister.com/files/20262.pdf.

126. Kuehn, B. M. Two doses of HPV vaccine may be sufficient. JAMA. 2011;306(15):1643.

127. De Carvalho, N., Teixeira, J., Roteli-Martins, C. M., Naud, P., De Borba, P., Zahaf, T., et al. Sustained efficacy and immunogenicity of HPV-16/18 AS04-adjuvanted vaccine up to 7.3 years in young adult women. Vaccine. 2010;28(38):6247-55.

128. Joura, E. A., Kjaer, S. K., Wheeler, C. M., Sigurdsson, K., Iversen, O. E., Hernandez-Avila, M., et al. HPV antibody levels and clinical efficacy following administration of a prophylactic quadrivalent HPV vaccine. Vaccine. 2008;26(52):6844-51.

129. Frazer, I. H. Measuring serum antibody to human papillomavirus following infection or vaccination. Gynecol Oncol. 2010;118(1 Suppl):S8-11.

130. Stanley, M. Potential mechanisms for HPV vaccine-induced long-term protection. Gynecol Oncol. 2010;118(1 Suppl):S2-7.

131. Fraser, C., Tomassini, J. E., Xi, L., Golm, G., Watson, M., Giuliano, A. R., et al. Modeling the long-term antibody response of a human papillomavirus (HPV) virus-like particle (VLP) type 16 prophylactic vaccine. Vaccine. 2007;25(21):4324-33.

132. David, M. P., Van Herck, K., Hardt, K., Tibaldi, F., Dubin, G., Descamps, D., et al. Long-term persistence of anti-HPV-16 and -18 antibodies induced by vaccination with the AS04-adjuvanted cervical cancer vaccine: modeling of sustained antibody responses. Gynecol Oncol. 2009;115(3 Suppl):S1-6.

133. Petaja, T., Keranen, H., Karppa, T., Kawa, A., Lantela, S., Siitari-Mattila, M., et al. Immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in healthy boys aged 10-18 years. J Adolesc Health. 2009;44(1):33-40.

134. Reisinger, K., Block, S. L., Lazcano-Ponce, E., Samakoses, R., Esser, M. T., Erick, J., et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents. Pediatr Infect Dis J. 2007;26(3):201-09.

135. Einstein, M. H., Baron, M., Levin, M. J., Chatterjee, A., Fox, B., Scholar, S., et al. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 vaccine and HPV-6/11/16/18 vaccine: follow-up from months 12-24 in a Phase III randomized study of healthy women aged 18-45 years. Hum Vaccin. 2011;7(12):1343-58.

136. Olsson, S. E., Villa, L. L., Costa, R. L., Petta, C. A., Andrade, R. P., Malm, C., et al. Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine. Vaccine. 2007;25(26):4931-9.

137. Moscicki, A. B., Wheeler, C. M., Romanowski, B., Hedrick, J., Gall, S., Ferris, D., et al. Anamnestic Response Elicited by a Fourth dose of HPV-16/18 AS04-Adjuvanted Vaccine in Young Women. Abstract presented at Eurogin 2010 congress, Monte Carlo (Monaco), 17-20 February, 2010.

138. Stanley, M. Introduction. The human papillomavirus VLP vaccines. Gynecol Oncol. 2010;118(1 Suppl):S1.

139. Schiller, J. T., Day, P. M., Kines, R. C. Current understanding of the mechanism of HPV infection. Gynecol Oncol. 2010;118(1 Suppl):S12-7.

140. Castellsague, X., Munoz, N., Pitisuttithum, P., Ferris, D., Monsonego, J., Ault, K., et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. Br J Cancer. 2011;105(1):28-37.

141. Wheeler, C. M., Kjaer, S. K., Sigurdsson, K., Iversen, O. E., Hernandez-Avila, M., Perez, G., et al. The Impact of Quadrivalent Human Papillomavirus (HPV; Types 6, 11, 16, and 18) L1 Virus-Like Particle Vaccine on Infection and Disease Due to Oncogenic Nonvaccine HPV Types in Sexually Active Women Aged 16-26 Years. J Infect Dis. 2009;199(7):936-44.

142. Einstein, M. H., Baron, M., Levin, M. J., Chatterjee, A., Fox, B., Scholar, S., et al. Comparison of the immunogenicity of the human papillomavirus (HPV)-16/18 vaccine and the HPV-6/11/16/18 vaccine for oncogenic non-vaccine types HPV-31 and HPV-45 in healthy women aged 18-45 years. Hum Vaccine. 2011;7(12):1359-73.

143. Kemp, T. J., Hildesheim, A., Safaeian, M., Dauner, J. G., Pan, Y., Porras, C., et al. HPV16/18 L1 VLP vaccine induces cross-neutralizing antibodies that may mediate cross-protection. Vaccine. 2011;29(11):2011-4.

144. McKeage, K., Romanowski, B. Spotlight on AS04-adjuvanted human papillomavirus (HPV) types 16 and 18 vaccine (Cervarix(R)). BioDrugs. 2011;25(4):265-9.

145. Neuzil, K. M., Canh do, G., Thiem, V. D., Janmohamed, A., Huong, V. M., Tang, Y., et al. Immunogenicity and reactogenicity of alternative schedules of HPV vaccine in Vietnam: a cluster randomized noninferiority trial. JAMA. 2011;305(14):1424-31.

146. Immunogenicity and safety study of GlaxoSmithKline Biologicals' HPV vaccine GSK580299 administered according to an alternative dosing schedule as compared to the standard dosing schedule in young female subjects aged 15-25 years. Available at: http://download.gsk-clinicalstudyregister.com/files/20262.pdf.

147. Dobson, S., Dawar, M., Money, D., Bettinger, J., Krajden, M., Langley, J., et al. Two Dose Vaccine Trial of Q-HPV: Results at 36 months. Oral presention. 27th International Papillomavirus Conference and Clinical Workshop, Berlin, Germany, September 17-22, 2011.

148. Romanowski, B., Schwarz, T. F., Ferguson, L. M., Peters, K., Dionne, M., Schulze, K., et al. Immunogenicity and safety of HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared to the licensed 3-dose schedule: Results from a randomized study. Hum Vaccine. 2011;7(12):1374-86.

149. Wheeler, C. M., Bautista, O. M., Tomassini, J. E., Nelson, M., Sattler, C. A., Barr, E. Safety and immunogenicity of co-administered quadrivalent human papillomavirus (HPV)-6/11/16/18 L1 virus-like particle (VLP) and hepatitis B (HBV) vaccines. Vaccine. 2008;26(5):686-696.

150. Wheeler, C. M., Harvey, B. M., Pichichero, M. E., Simon, M. W., Combs, S. P., Blatter, M. M., et al. Immunogenicity and safety of human papillomavirus-16/18 as04-adjuvanted vaccine coadministered with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine and/or meningococcal conjugate vaccine to healthy girls 11 to 18 years of age: results from a randomized open trial. Pediatr Infect Dis J. 2011;30(12):e225-34.

151. GlaxoSmithKline. Evaluation of Safety and Immunogenicity of Co-administering Human Papillomavirus Vaccine With Another Vaccine in Healthy Female Subjects. Available at: http://clinicaltrials.gov/ct2/show/NCT00578227?term=HPV+hepatitis+A&rank=8.

152. Gilca, V., Sauvageau, C., Dionne, M., Boulianne, N., Murphy, D., De Serres, G. Preliminary Safety and Immunogenicity Data of Two Doses of Twinrix and Gardasil Co-administered or Administered Separately According to an Extended Schedule. Poster presentation. 4th Vaccine and ISV Global Congress, Vienna, Austria, 3-5 October 2010.

153. Wilkin, T., Lee, J. Y., Lensing, S. Y., Stier, E. A., Goldstone, S. E., Berry, J. M., et al. Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in HIV-1-infected men. J Infect Dis. 2010;202(8):1246-53.

154. Handisurya, A., Schellenbacher, C., Reininger, B., Koszik, F., Vyhnanek, P., Heitger, A., et al. A quadrivalent HPV vaccine induces humoral and cellular immune responses in WHIM immunodeficiency syndrome. Vaccine. 2010;28(30):4837-41.

155. Romanowski, B. Efficacy of the HPV-16/18 AS04-adjuvanted Vaccine against Non-vaccine Oncogenic HPV Types: End-of-Study Results. 26th International Human Papillomavirus Conference and Clinical Workshop, Montréal, July 3-8, 2010.

156. Food and Drug Administration (FDA). Clinical Review Memo – Cervarix, October 15, 2009. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM237976.pdf.

157. Brown, D. R., Kjaer, S. K., Sigurdsson, K., Iversen, O. E., Hernandez-Avila, M., Wheeler, C. M., et al. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16-26 years. J Infect Dis. 2009;199(7):926-35.

158. Munoz, N., Kjaer, S. K., Sigurdsson, K., Iversen, O. E., Hernandez-Avila, M., Wheeler, C. M., et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. J Natl Cancer Inst. 2010;102(5):325-39.

159. Lehtinen, M., Paavonen, J., Wheeler, C. M., Jaisamrarn, U., Garland, S. M., Castellsague, X., et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol. 2011;13(1):89-99.

160. Kjaer, S. K., Sigurdsson, K., Iversen, O. E., Hernandez-Avila, M., Wheeler, C. M., Perez, G., et al. A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (types 6/11/16/18) vaccine against high-grade cervical and external genital lesions. Cancer Prev Res. 2009;2(10):868-78.

161. Malagon, T., Drolet, M., Boily, M., Brisson, M. Issues in Comparing and Interpreting Clinical Trial Measures of Cross-protection. 27th International Papillomavirus Conference and Clinical Workshop, Berlin, Germany, September 17-22, 2011.

162. Wheeler, C. M., Castellsague, X., Garland, S. M., Szarewski, A., Paavonen, J., Naud, P., et al. Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol. 2012;13(1):100-10.

163. GlaxoSmithKline. Results summary for 580299/008. Available at: http://www.gskclinicalstudyregister.com/result_detail.jsp?protocolId=580299%2f008&studyId=063E1C2C-1A99-427D-83F6-525AB3791945&compound=Human+Papillomavirus+Types+16+and+18+Vaccin. Accessed July 2011.

164. Garland, S. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against vulvar/vaginal intraepithelial neoplasia. Oral Poster presention. 27th International Papillomavirus Conference and Clinical Workshop, Berlin, Germany, September 17-22, 2011.

165. Dillner, J., Kjaer, S. K., Wheeler, C. M., Sigurdsson, K., Iversen, O. E., Hernandez-Avila, M., et al. Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial. BMJ. 2010;341:c3493.

166. Munoz, N., Manalastas, R., Jr., Pitisuttithum, P., Tresukosol, D., Monsonego, J., Ault, K., et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomised, double-blind trial. Lancet. 2009;373(9679):1949-57.

167. Descamps, D., Skinner, R., Szarewski, A., Romanowski, B., Garland, S., Lazcano, E., et al. HPV-16/18 AS04-Adjuvanted Vaccine Efficacy in ≥ 26-Year-Old Women After 4-Year Follow-up. Oral presention. 27th International Papillomavirus Conference and Clinical Workshop, Berlin, Germany, September 17-22, 2011.

168. Olsson, S. E., Kjaer, S. K., Sigurdsson, K., Iversen, O. E., Hernandez-Avila, M., Wheeler, C. M., et al. Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection. Hum Vaccin. 2009;5(10):696-704.

169. Szarewski, A., Poppe, W. A., Skinner, S. R., Wheeler, C. M., Paavonen, J., Naud, P., et al. Efficacy of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in women aged 15-25 years with and without serological evidence of previous exposure to HPV-16/18. Int J Cancer. 2012;131(1):106-16.

170. The Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007;356(19):1915-27.

171. Garland, S. Does the HPV-16/18 AS04-Adjuvanted Vaccine Benefit Women with Cervical Disease? Abstract presented at Eurogin 2011 Congress, Lisbon, May 8-11, 2011.

172. Joura, E. A., Garland, S. M., Paavonen, J., Ferris, D. G., Heather, L. S., James, M. K., et al. Impact of Gardasil® in Women Who Have Undergone Definitive Therapy. Abstract presented at Eurogin 2010 congress, Monte Carlo (Monaco), 17-20 february 2010.

173. Hamsikova, E., Smahelova, J., Ludvikova, V., Stasikova, J., Dubova, J., Vydrova, J., et al. Recurrent Respiratory Papillomatosis and HPV Vaccination. Oral poster presention. 27th International Papillomavirus Conference and Clinical Workshop, Berlin, Germany, September 17-22, 2011.

174. Joura, E. A., Garland, S. M., Paavonen, J., Ferris, D. G., Perez, G., Ault, K. A., et al. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. BMJ. 2012;344:e1401.

175. Giuliano, A. R., Palefsky, J. M., Goldstone, S., Moreira, E. D., Jr., Penny, M. E., Aranda, C., et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. N Engl J Med. 2011;364(5):401-11.

176. Giuliano, A. R., Palefsky, J. M., Goldstone, S., Moreira, E. D., Jr., Penny, M. E., Aranda, C., et al. Erratum – Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med. 2011;364(15):1481.

177. Palefsky, J. M., Giuliano, A. R., Goldstone, S., Moreira, E. D., Jr., Aranda, C., Jessen, H., et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med. 2011;365(17):1576-85.

178. Fairley, C. K., Hocking, J. S., Gurrin, L. C., Chen, M. Y., Donovan, B., Bradshaw, C. S. Rapid decline in presentations of genital warts after the implementation of a national quadrivalent human papillomavirus vaccination program for young women. Sex Transm Infect. 2009;85(7):499-502.

179. Donovan, B., Franklin, N., Guy, R., Grulich, A. E., Regan, D. G., Ali, H., et al. Quadrivalent human papillomavirus vaccination and trends in genital warts in Australia: analysis of national sentinel surveillance data. Lancet Infect Dis. 2011;11(1):39-44.

180. Read, T. R., Hocking, J. S., Chen, M. Y., Donovan, B., Bradshaw, C. S., Fairley, C. K. The near disappearance of genital warts in young women 4 years after commencing a national human papillomavirus (HPV) vaccination program. Sex Transm Infect. 2011;87(7):544-7.

181. Kreimer, A. R., Rodriguez, A. C., Hildesheim, A., Herrero, R., Porras, C., Schiffman, M., et al. Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. J Natl Cancer Inst. 2011;103(19):1444-51.

182. Follow-up study to evaluate the long-term efficacy of a HPV vaccine (580299) in healthy young adult women in Brazil. HPV vaccine (580299) (HPV): GlaxoSmithKline (GSK) Biologicals' vaccine against human papillomaviruses 16 and 18. Available at: http://www.google.ca/#hl=en&rlz=1W1ADRA_frCA460&q=HPV-023+EXT+001+Y9&oq=HPV-023+EXT+001+Y9&aq=f&aqi=&aql=&gs_l=serp.12...3078l3078l2l4344l1l1l0l0l0l0l157l157l0j1l1l0.frgbld.&bav=on.2,or.r_gc.r_pw.,cf.osb&fp=6331688d9292f1e8&biw=1024&bih=452. Accessed March 29, 2012.

183. Woodman, C. B., Collins, S., Winter, H., Bailey, A., Ellis, J., Prior, P., et al. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. Lancet. 2001;357(9271):1831-6.

184. Brown, D. R., Shew, M. L., Qadadri, B., Neptune, N., Vargas, M., Tu, W., et al. A longitudinal study of genital human papillomavirus infection in a cohort of closely followed adolescent women. J Infect Dis. 2005;191(2):182-92.

185. Gilca, V., Dionne, M., Sauvageau, C., De Serres, G., Boulianne, N., Deceuninck, G. Gardasil and Twinrix Co-administration: Preliminary Safety Data. Poster presentation. 25th International Papillomavirus Conference, May 8-14, Malmö, Sweden. 2009.

186. Agorastos, T., Chatzigeorgiou, K., Brotherton, J. M., Garland, S. M. Safety of human papillomavirus (HPV) vaccines: a review of the international experience so far. Vaccine. 2009;27(52):7270-81.

187. Allen, J. D., Coronado, G. D., Williams, R. S., Glenn, B., Escoffery, C., Fernandez, M., et al. A systematic review of measures used in studies of human papillomavirus (HPV) vaccine acceptability. Vaccine. 2010;28(24):4027-37.

188. Das, A., Madhwapathi, V., Davies, P., Brown, G., Dearnley, E., Spencer, A., et al. Knowledge and acceptability of the HPV vaccine by school children and their parents in Birmingham. Vaccine. 2010;28(6):1440-6.

189. Cooper Robbins, S. C., Bernard, D., McCaffery, K., Brotherton, J., Garland, S., Skinner, S. R. "Is cancer contagious?": Australian adolescent girls and their parents: making the most of limited information about HPV and HPV vaccination. Vaccine. 2010;28(19):3398-408.

190. Conroy, K., Rosenthal, S. L., Zimet, G. D., Jin, Y., Bernstein, D. I., Glynn, S., et al. Human papillomavirus vaccine uptake, predictors of vaccination, and self-reported barriers to vaccination. J Womens Health. 2009;18(10):1679-86.

191. Trim, K., Nagji, N., Elit, L., Roy, K. Parental knowledge, attitudes, and behaviours towards human papillomavirus vaccination for their children: a systematic review from 2001 to 2011. Obstet Gynecol Int. 2012;2012:921236.

192. Ogilvie, G., Remple, V., Marra, F., McNeil, S., Naus, M., Pielak, K., et al. Parental intention to have daughters receive the human papillomavirus vaccine. CMAJ. 2007;177(12):1506-12.

193. Guay, M., Clément, P., Sauvageau, C., Dubé, E., Boulianne, N., Hamid, A., et al. Évaluation de l'implantation du programme de vaccination VPH des adolescentes du Québec. Flash Vigie. 2012;7(6):1-4.

194. Cerigo, H., Macdonald, M. E., Franco, E. L., Brassard, P. Inuit women's attitudes and experiences towards cervical cancer and prevention strategies in Nunavik, Québec. Int J Circumpolar Health. 2011 Oct 26:0.

195. Cerigo, H., Macdonald, M. E., Franco, E. L., Brassard, P. Awareness and knowledge about human papillomavirus among Inuit women in Nunavik, Québec. J Community Health. 2011;36(1):56-62.

196. Ministère de la Santé et des Services sociaux. Vigie - Interventions - Couverture vaccinale en milieu scolaire. Flash Vigie : Bulletin québécois de vigie et d'intervention en maladies infectieuses. 2010;5(3):1-2.

197. Lenehan, J. G., Leonard, K. C., Nandra, S., Isaacs, C. R., Mathew, A., Fisher, W. A. Women's knowledge, attitudes, and intentions concerning human papillomavirus vaccination: findings of a waiting room survey of obstetrics-gynaecology outpatients. J Obstet Gynecol Can. 2008;30(6):489-99.

198. Giede, C., McFadden, L. L., Komonoski, P., Agrawal, A., Stauffer, A., Pierson, R. The acceptability of HPV vaccination among women attending the University of Saskatchewan Student Health Services. J Obstet Gynaecol Can. 2010;32(7):679-86.

199. Kiely, M., De Wals, P., Sauvageau, C., Dubé, E., Deceuninck, G. Human Papillomavirus: Vaccination, Screening and Sexual Behaviors of Women in Québec. 26th International Papillomavirus Conference, Montréal, 2010.

200. Lavoie, F., Goggin, P., Sauvageau, C., Dubé, E., Gilca, V., Deceuninck, G. What Do Young Women Know, Think and Do About HPV Prevention in Québec (Canada)? 26th International Papillomavirus Conference, Montréal, 2010.

201. Krawczyk, A. L., Perez, S., Lau, E., Holcroft, C. A., Amsel, R., Knauper, B., et al. Human papillomavirus vaccination intentions and uptake in college women. Health Psychol. 2012;31(5):685-93.

202. Centers for Disease Control and Prevention. Recommendations on the use of quadrivalent human papillomavirus vaccine in males — Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2011;60(50):1705-8.

203. Liddon, N., Hood, J., Wynn, B. A., Markowitz, L. E. Acceptability of human papillomavirus vaccine for males: a review of the literature. J Adolesc Health. 2010;46(2):113-23.

204. Brabin, L., Roberts, S. A., Farzaneh, F., Kitchener, H. C. Future acceptance of adolescent human papillomavirus vaccination: a survey of parental attitudes. Vaccine. 2006;24(16):3087-94.

205. Olshen, E., Woods, E. R., Austin, S. B., Luskin, M., Bauchner, H. Parental acceptance of the human papillomavirus vaccine. J Adolesc Health. 2005;37(3):248-51.

206. Slomovitz, B. M., Sun, C. C., Frumovitz, M., Soliman, P. T., Schmeler, K. M., Pearson, H. C., et al. Are women ready for the HPV vaccine? Gynecol Oncol. 2006;103(1):151-4.

207. Sauvageau, C., Duval, B., Gilca, V., Lavoie, F., Ouakki, M. Human papilloma virus vaccine and cervical cancer screening acceptability among adults in Québec, Canada. BMC Public Health. 2007;7(1):304.

208. Ogilvie, G. S., Remple, V. P., Marra, F., McNeil, S. A., Naus, M., Pielak, K., et al. Intention of parents to have male children vaccinated with the human papillomavirus vaccine. Sex Transm Infect. 2008;84(4):318-23.

209. Watts, L. A., Joseph, N., Wallace, M., Rauh-Hain, J. A., Muzikansky, A., Growdon, W. B., et al. HPV vaccine: a comparison of attitudes and behavioral perspectives between Latino and non-Latino women. Gynecol Oncol. 2009;112(3):577-82.

210. Dursun, P., Altuntas, B., Kuscu, E., Ayhan, A. Women's knowledge about human papillomavirus and their acceptance of HPV vaccine. Aust N Z J Obstet Gynaecol. 2009;49(2):202-6.

211. Lenselink, C. H., Gerrits, M. M., Melchers, W. J., Massuger, L. F., van Hamont, D., Bekkers, R. L. Parental acceptance of human papillomavirus vaccines. Eur J Obstet Gynecol Reprod Biol. 2008;137(1):103-7.

212. Noakes, K., Yarwood, J., Salisbury, D. Parental response to the introduction of a vaccine against human papilloma virus. Hum Vaccine. 2006;2(6):243-8.

213. de Visser, R., McDonnell, E. Correlates of parents' reports of acceptability of human papilloma virus vaccination for their school-aged children. Sexual Health. 2008;5(4):331-8.

214. Boehner, C. W., Howe, S. R., Bernstein, D. I., Rosenthal, S. L. Viral sexually transmitted disease vaccine acceptability among college students. Sex Transm Dis. 2003;30(10):774-8.

215. Jones, M., Cook, R. Intent to receive an HPV vaccine among university men and women and implications for vaccine administration. J Am Coll Health. 2008;57(1):23-32.

216. Ferris, D. G., Waller, J. L., Miller, J., Patel, P., Price, G. A., Jackson, L., et al. Variables associated with human papillomavirus (HPV) vaccine acceptance by men. J Am Board Fam Med. 2009;22(1):34-42.

217. Gerend, M. A., Barley, J. Human papillomavirus vaccine acceptability among young adult men. Sex Transm Dis. 2009;36(1):58-62.

218. Lenselink, C. H., Schmeink, C. E., Melchers, W. J., Massuger, L. F., Hendriks, J. C., van Hamont, D., et al. Young adults and acceptance of the human papillomavirus vaccine. Public Health. 2008;122(12):1295-301.

219. Simatherai, D., Bradshaw, C. S., Fairley, C. K., Bush, M., Heley, S., Chen, M. Y. What men who have sex with men think about the human papillomavirus vaccine. Sex Transm Infect. 2009;85(2):148-9.

220. Reiter, P. L., Brewer, N. T., Smith, J. S. Human papillomavirus knowledge and vaccine acceptability among a national sample of heterosexual men. Sex Transm Infect. 2010;86(3):241-6.

221. Gilbert, P., Brewer, N., Reiter, P., Ng, T., Smith, J. HPV vaccine acceptability in heterosexual, gay, and bisexual men. Am J Mens Health. 2011;5(4):297-305.

222. Reiter, P. L., Brewer, N. T., McRee, A. L., Gilbert, P., Smith, J. S. Acceptability of HPV vaccine among a national sample of gay and bisexual men. Sex Transm Dis. 2010;37(3):197-203.

223. Thomas, E. A., Goldstone, S. E. Should I or shouldn't I: decision making, knowledge and behavioral effects of quadrivalent HPV vaccination in men who have sex with men. Vaccine. 2011;29(3):570-6.

224. Daley, E. M., Marhefka, S. L., Buhi, E. R., Vamos, C. A., Hernandez, N. D., Giuliano, A. R. Human papillomavirus vaccine intentions among men participating in a human papillomavirus natural history study versus a comparison sample. Sex Transm Dis. 2010;37(10):644-52.

225. Katz, M. L., Krieger, J. L., Roberto, A. J. Human papillomavirus (HPV): college male's knowledge, perceived risk, sources of information, vaccine barriers and communication. J Mens health. 2011;8(3):175-184.

226. Wheldon, C. W., Daley, E. M., Buhi, E. R., Nyitray, A. G., Giuliano, A. R. Health beliefs and attitudes associated with HPV vaccine intention among young gay and bisexual men in the southeastern United States. Vaccine. 2011;29(45):8060-5.

227. Petrovic, K., Burney, S., Fletcher, J. The relationship of knowledge, health value and health self-efficacy with men's intentions to receive the human papillomavirus (HPV) vaccine. J Health Psychol. 2011;16(8):1198-207.

228. Hernandez, B. Y., Wilkens, L. R., Thompson, P. J., Shvetsov, Y. B., Goodman, M. T., Ning, L., et al. Acceptability of prophylactic human papillomavirus vaccination among adult men. Hum Vaccine. 2010;6(6):467-75.

229. Crosby, R. A., DiClemente, R. J., Salazar, L. F., Nash, R., Younge, S., Head, S. Human papillomavirus vaccine intention among college men: what's oral sex got to do with it? J Am Coll Health. 2012;60(1):8-12.

230. Kahn, J. A., Zimet, G. D., Bernstein, D. I., Riedesel, J. M., Lan, D., Huang, B., et al. Pediatricians' intention to administer human papillomavirus vaccine: the role of practice characteristics, knowledge, and attitudes. J Adolesc Health. 2005;37(6):502-10.

231. Daley, M. F., Liddon, N., Crane, L. A., Beaty, B. L., Barrow, J., Babbel, C., et al. A national survey of pediatrician knowledge and attitudes regarding human papillomavirus vaccination. Pediatrics. 2006;118(6):2280-9.

232. Kahn, J. A., Rosenthal, S. L., Tissot, A. M., Bernstein, D. I., Wetzel, C., Zimet, G. D. Factors influencing pediatricians' intention to recommend human papillomavirus vaccines. Ambul Pediatr. 2007;7(5):367-73.

233. Riedesel, J. M., Rosenthal, S. L., Zimet, G. D., Bernstein, D. I., Huang, B., Lan, D., et al. Attitudes about human papillomavirus vaccine among family physicians. J Pediatr Adolesc Gynecol. 2005;18(6):391-398.

234. Esposito, S., Bosis, S., Pelucchi, C., Begliatti, E., Rognoni, A., Bellasio, M., et al. Pediatrician knowledge and attitudes regarding human papillomavirus disease and its prevention. Vaccine. 2007;25(35):6437-46.

235. Duval, B., Gilca, V., Boulianne, N., Pielak, K., Halperin, B., Simpson, M. A., et al. Cervical cancer prevention by vaccination: nurses' knowledge, attitudes and intentions. J Adv Nurs. 2009;65(3):499-508.

236. Duval, B., Gilca, V., McNeil, S., Dobson, S., Money, D., Gemmill, I. M., et al. Vaccination against human papillomavirus: a baseline survey of Canadian clinicians' knowledge, attitudes and beliefs. Vaccine. 2007;25(45):7841-7.

237. Tan, J., Farrell, L., Allen, D. G. The attitudes of Australian gynaecologists to HPV vaccination: an ASCCP survey. Aust N Z J Obstet Gynaecol. 2010;50(5):472-7.

238. Weiss, T. W., Zimet, G. D., Rosenthal, S. L., Brenneman, S. K., Klein, J. D. Human papillomavirus vaccination of males: attitudes and perceptions of physicians who vaccinate females. J Adolesc Health. 2010;47(1):3-11.

239. Zimet, G. D., Stupiansky, N. W., Weiss, T. W., Rosenthal, S. L., Good, M. B., Vichnin, M. D. Influence of patient's relationship status and HPV history on physicians' decisions to recommend HPV vaccination. Vaccine. 2011;29(3):378-81.

240. Markowitz, L. E., Dunne, E. F., Saraiya, M., Lawson, H. W., Chesson, H., Unger, E. R. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2007;56(RR-2):1-24.

241. Mailllard, R. Le gardasil, un vaccin pour rien? Available at: http://www.protegez-vous.ca/sante-et-alimentation/gardasil.html. Accessed 18 January, 2012.

242. Maréchal, I. L'épidemie inventée. Le Journal de Montréal. 3 octobre 2011.

243. Le Réseau canadien pour la santé des femmes. Campagne de vaccination contre le VPH est trompeuse et contraire à l'éthique. Available at: http://www.cwhn.ca/fr/print/fr/node/43781. Accessed 18 January, 2012.

244. Chouinard, M.-A. Virus du papillome humain - Québec rate la cible. Le Devoir. 1er septembre 2011.

245. Gagnon, L. Vaccins et médicaments. La Presse. 6 octobre 2011.

246. Tomljenovic, L., Shaw, C. A. Human papillomavirus (HPV) vaccine policy and evidence-based medicine: Are they at odds? Annals Med. 2011.

247. Lippman, A., Melnychuk, R., Shimmin, C., Boscoe, M. Human papillomavirus, vaccines and women's health: questions and cautions. CMAJ. 2007;177(5):484-7.

248. Sauvageau, C., Dubé, E., Bradet, R., Mondor, M., Moisan, J. Les services de vaccination dans les pharmacies du Québec. Québec: Institut national de santé publique du Québec, 2011. 55 pages + annexes.

249. Ministère de la Santé et des Services sociaux. Vaccination en milieu scolaire - Hépatite B. Flash Vigie. 2011;6(8):1-2.

250. Leask, J., Jackson, C., Trevena, L., McCaffery, K., Brotherton, J. Implementation of the Australian HPV vaccination program for adult women: qualitative key informant interviews. Vaccine. 2009;27(40):5505-12.

251. Dubé, E., Duval, B., Gilca, V., Goggin, P. Prevention by vaccination of diseases attribuable to the human papilloma virus in Québec. Québec: Institut national de santé publique du Québec, 2007, 73 p.

252. Zimmerman, R. K. Ethical analysis of HPV vaccine policy options. Vaccine. 2006;24(22):4812-20.

253. Lo, B. HPV vaccine and adolescents' sexual activity. BMJ. 2006;332(7550):1106-7.

254. de Melo-Martin, I. The promise of the human papillomavirus vaccine does not confer immunity against ethical reflection. Oncologist. 2006;11(4):393-6.

255. Massé, R. Éthique et santé publique, Enjeux, valeurs et normativité. Québec. 2003;Les Presses de l'Université Laval.

256. National Advisory Committee on Immunization. Update on human papillomavirus (HPV) vaccines. Can Commun Dis Control. 2012;37(ASC-7):1-69.

257. Van de Velde, N., Brisson, M., Boily, M. C. Understanding differences in predictions of HPV vaccine effectiveness: a comparative model-based analysis. Vaccine. 2010;28(33):5473-84.

258. Van de Velde, N., Drolet, M., Boily, M. C., Malagon, T., Brisson, M. Population-level impact of the bivalent, quadrivalent and candidate nonavalent HPV vaccines: a model-based analysis. J Natl Cancer Inst.104(22):1712-23.

259. Brisson, M., Van de Velde, N., De Wals, P., Boily, M. C. The potential cost-effectiveness of prophylactic human papillomavirus vaccines in Canada. Vaccine. 2007;25(29):5399-408.

260. Hu, D., Goldie, S. The economic burden of noncervical human papillomavirus disease in the United States. Am J Obstet Gynecol. 2008;198(5):500 e1-7.

261. Tully, S. P., Anonychuk, A. M., Sanchez, D. M., Galvani, A. P., Bauch, C. T. Time for change? An economic evaluation of integrated cervical screening and HPV immunization programs in Canada. Vaccine. 2012;30(2):425-35.

262. Kulasingam, S. L., Rajan, R., St Pierre, Y., Atwood, C. V., Myers, E. R., Franco, E. L. Human papillomavirus testing with Pap triage for cervical cancer prevention in Canada: a cost-effectiveness analysis. BMC Med. 2009;7:69.

263. Vijayaraghavan, A., Efrusy, M. B., Mayrand, M. H., Santas, C. C., Goggin, P. Cost-effectiveness of high-risk human papillomavirus testing for cervical cancer screening in Québec, Canada. Can J Public Health. 2010;101(3):220-5.

264. Drolet, M., Brisson, M., Maunsell, E., Franco, E. L., Coutlee, F., Ferenczy, A., et al. The psychosocial impact of an abnormal cervical smear result. Psycho-oncology. 2011;21(10):1071-81.

265. Kim, J. J., Goldie, S. J. Cost effectiveness analysis of including boys in a human papillomavirus vaccination program in the United States. BMJ. 2009;339:b3884.

266. Jit, M., Chapman, R., Hughes, O., Choi, Y. H. Comparing bivalent and quadrivalent human papillomavirus vaccines: economic evaluation based on transmission model. BMJ. 2011;343:d5775.

267. National Cancer Institute. Base de données SEER : Surveillance Epidemiology and End Results. National Institutes of Health: National Cancer Institute (NCI) Bethesda, USA 2006. Available at: http://seer.cancer.gov.

268. Villa, L. L., Costa, R. L., Petta, C. A., Andrade, R. P., Ault, K. A., Giuliano, A. R., et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol. 2005;6(5):271-8.

269. Food and Drug Administration (FDA). Clinical Review of Biologics License Application Supplement for Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant (Gardasil®) to extend indication for prevention of vaginal and vulvar cancers related to HPV types 16 and 18 [Accessed May 2011]. Available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm111274.pdf.

270. Statistics Canada. Canadian Community Health Survey (CCHS- Cycle 3.1) [Accessed January 2011]. Available at: www.statcan.gc.ca.

271. Demers, A. A., Kliewer, E. V., Musto, G., Butler, J., Lawrence, E., Shearer, B., et al. Epidemiology of cervical abnormalities and utilization of related health care resources. Winnipeg: Cancer Care Manitoba, 2009. 49 p.

272. McLachlin, C. M., Mai, V., Murphy, J., Fung-Kee-Fung, M., Chambers, A., Oliver, T. K. Ontario cervical cancer screening clinical practice guidelines. J Obstet Gynaecol Can. 2007;29(4):344-53.

273. Manitoba Cervical Cancer Screening Program (Cancer Care Manitoba). Screening Guidelines [Accessed in 2011]. Available at: http://www.cancercare.mb.ca/resource/File/MCCSP/HealthCareProfessional/MCCSP_Guideline_Chart_Jan10.pdf.

274. BC Cancer Agency. Screening for the Cancer of the Cervix: An office manual for health professionals. 9e ed. Vancouver: BC: Cervical Cancer Screening Program, 2010. 15 p.

275. Daling, J. R., Madeleine, M. M., Johnson, L. G., Schwartz, S. M., Shera, K. A., Wurscher, M. A., et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. Cancer. 2004;101(2):270-80.

276. Liu, S., Semenciw, R., Probert, A., Mao, Y. Cervical cancer in Canada: changing patterns in incidence and mortality. Int J Gynecol Cancer. 2001;11(1):24-31.

277. Ades, S., Koushik, A., Duarte-Franco, E., Mansour, N., Arseneau, J., Provencher, D., et al. Selected class I and class II HLA alleles and haplotypes and risk of high-grade cervical intraepithelial neoplasia. Int J Cancer. 2008;122(12):2820-6.

278. Public Health Agency of Canada. Cancer surveillance On-line. Available at: http://dsol-smed.phac-aspc.gc.ca/dsol-smed/cancer/index-eng.php. Accessed January 2011.

279. BC Cancer Agency. Cervical cancer screening program. 2009 Annual report [Accessed January 2011]. Available at http://www.bccancer.bc.ca, Vancouver, BC.

280. Clifford, G. Personals communications (International Agency for Research on Cancer, CliffordG@iarc.fr).

281. Marra, F., Cloutier, K., Oteng, B., Marra, C., Ogilvie, G. Effectiveness and cost effectiveness of human papillomavirus vaccine: a systematic review. PharmacoEconomics. 2009;27(2):127-47.

282. Anonychuk, A. M., Bauch, C. T., Merid, M. F., Van Kriekinge, G., Demarteau, N. A cost-utility analysis of cervical cancer vaccination in preadolescent Canadian females. BMC Public Health. 2009;9:401.

283. Goldie, S. J., Kohli, M., Grima, D., Weinstein, M. C., Wright, T. C., Bosch, F. X., et al. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. J Natl Cancer Inst. 2004;96(8):604-15.

284. Sanders, G. D., Taira, A. V. Cost-effectiveness of a potential vaccine for human papillomavirus. Emerg Infect Dis. 2003;9(1):37-48.

285. Elbasha, E. H., Dasbach, E. J., Insinga, R. P. Model for assessing human papillomavirus vaccination strategies. Emerg Infect Dis. 2007;13(1):28-41.

286. Chesson, H. W., Ekwueme, D. U., Saraiya, M., Markowitz, L. E. Cost-effectiveness of human papillomavirus vaccination in the United States. Emerg Infect Dis. 2008;14(2):244-51.

287. Chesson, H. W., Ekwueme, D. U., Saraiya, M., Dunne, E. F., Markowitz, L. E. The cost-effectiveness of male HPV vaccination in the United States. Vaccine. 2011;29(46):8443-50.

288. Kim, J. J., Goldie, S. J. Health and economic implications of HPV vaccination in the United States. N Engl J Med. 2008;359(8):821-32.

289. Dasbach, E. J., Insinga, R. P., Elbasha, E. H. The epidemiological and economic impact of a quadrivalent human papillomavirus vaccine (6/11/16/18) in the UK. BJOG. 2008;115(8):947-56.

290. Kulasingam, S. L., Benard, S., Barnabas, R. V., Largeron, N., Myers, E. R. Adding a quadrivalent human papillomavirus vaccine to the UK cervical cancer screening program: A cost-effectiveness analysis. Cost Eff Resour Alloc. 2008;6:4.

291. Jit, M., Choi, Y. H., Edmunds, W. J. Economic evaluation of human papillomavirus vaccination in the United Kingdom. BMJ. 2008;337:a769.

292. Kulasingam, S., Connelly, L., Conway, E., Hocking, J. S., Myers, E., Regan, D. G., et al. A cost-effectiveness analysis of adding a human papillomavirus vaccine to the Australian National Cervical Cancer Screening Program. Sex Health. 2007;4(3):165-75.

293. Kim, J. J., Ortendahl, J., Goldie, S. J. Cost-effectiveness of human papillomavirus vaccination and cervical cancer screening in women older than 30 years in the United States. Ann Intern Med. 2009;151(8):538-45.

294. Taira, A. V., Neukermans, C. P., Sanders, G. D. Evaluating human papillomavirus vaccination programs. Emerg Infect Dis. 2004;10(11):1915-23.

295. Elbasha, E. H., Dasbach, E. J. Impact of vaccinating boys and men against HPV in the United States. Vaccine. 2010;28(42):6858-67.

296. Kim, J. J. Targeted human papillomavirus vaccination of men who have sex with men in the USA: a cost-effectiveness modelling analysis. Lancet Infect Dis. 2010;10(12):845-52.

297. Rosenthal, S. L., Weiss, T. W., Zimet, G. D., Ma, L., Good, M. B., Vichnin, M. D. Predictors of HPV vaccine uptake among women aged 19-26: importance of a physician's recommendation. Vaccine. 2011;29(5):890-5.

298. Zimet, G. D., Weiss, T. W., Rosenthal, S. L., Good, M. B., Vichnin, M. D. Reasons for non-vaccination against HPV and future vaccination intentions among 19-26 year-old women. BMC Women's Health. 2010;10:27.

299. Caskey, R., Lindau, S. T., Alexander, G. C. Knowledge and early adoption of HPV vaccine among girls and young women: results of a national survey. J Adolesc Health. 2009;45(5):453-62.

300. Roberts, M. E., Gerrard, M., Reimer, R., Gibbons, F. X. Mother-daughter communication and human papillomavirus vaccine uptake by college students. Pediatrics. 2010;125(5):982-9.

301. Allen, J. D., Mohllajee, A. P., Shelton, R. C., Othus, M. K., Fontenot, H. B., Hanna, R. Stage of adoption of the human papillomavirus vaccine among college women. Prev Med. 2009;48(5):420-5.

302. Licht, A. S., Murphy, J. M., Hyland, A. J., Fix, B. V., Hawk, L. W., Mahoney, M. C. Is use of the human papillomavirus vaccine among female college students related to human papillomavirus knowledge and risk perception? Sex Transm Infect. 2010;86(1):74-8.

303. Kahn, J. A., Ding, L., Huang, B., Zimet, G. D., Rosenthal, S. L., Frazier, A. L. Mothers' intention for their daughters and themselves to receive the human papillomavirus vaccine: a national study of nurses. Pediatrics. 2009;123(6):1439-45.

304. Kahn, J. A., Rosenthal, S. L., Jin, Y., Huang, B., Namakydoust, A., Zimet, G. D. Rates of human papillomavirus vaccination, attitudes about vaccination, and human papillomavirus prevalence in young women. Obstet Gynecol. 2008;111(5):1103-10.

305. Cui, Y., Baldwin, S. B., Wiley, D. J., Fielding, J. E. Human papillomavirus vaccine among adult women: disparities in awareness and acceptance. Am J Prev Med. 2010;39(6):559-63.

306. Bendik, M. K., Mayo, R. M., Parker, V. G. Knowledge, perceptions, and motivations related to HPV vaccination among college women. J Cancer Educ. 2011;26(3):459-64.

307. Bednarczyk, R. A., Birkhead, G. S., Morse, D. L., Doleyres, H., McNutt, L. A. Human papillomavirus vaccine uptake and barriers: association with perceived risk, actual risk and race/ethnicity among female students at a New York State university, 2010. Vaccine. 2011;29(17):3138-43.

308. Juraskova, I., Bari, R. A., O'Brien, M. T., McCaffery, K. J. HPV vaccine promotion: does referring to both cervical cancer and genital warts affect intended and actual vaccination behavior? Womens Health Issues. 2011;21(1):71-9.

309. Forster, A. S., Marlow, L. A., Wardle, J., Stephenson, J., Waller, J. Understanding adolescents' intentions to have the HPV vaccine. Vaccine. 2010;28(7):1673-6.

310. Mortensen, G. L. Drivers and barriers to acceptance of human-papillomavirus vaccination among young women: a qualitative and quantitative study. BMC Public Health. 2010;10:68.

311. Mehu-Parant, F., Rouzier, R., Soulat, J. M., Parant, O. Eligibility and willingness of first-year students entering university to participate in a HPV vaccination catch-up program. Eur J Obstet Gynecol Reprod Biol. 2010;148(2):186-90.

312. Sundstrom, K., Tran, T. N., Lundholm, C., Young, C., Sparen, P., Dahlstrom, L. A. Acceptability of HPV vaccination among young adults aged 18-30 years–a population based survey in Sweden. Vaccine. 2010;28(47):7492-500.

313. Blodt, S., Holmberg, C., Muller-Nordhorn, J., Rieckmann, N. Human papillomavirus awareness, knowledge and vaccine acceptance: a survey among 18-25 year old male and female vocational school students in Berlin, Germany. Eur J Public Health. 2011.

314. Reiter, P. L., McRee, A. L., Gottlieb, S. L., Brewer, N. T. HPV vaccine for adolescent males: acceptability to parents post-vaccine licensure. Vaccine. 2010;28(38):6292-7.

315. Dempsey, A. F., Butchart, A., Singer, D., Clark, S., Davis, M. Factors aassociated with parental intentions for male human papillomavirus vaccination: results of a national survey. Sex Transm Dis. 2011;38(8):769-76.

316. Rand, C. M., Schaffer, S. J., Humiston, S. G., Albertin, C. S., Shone, L. P., Heintz, E. V., et al. Patient-provider communication and human papillomavirus vaccine acceptance. Clin Pediatr (Phila). 2011;50(2):106-13.

317. Dahlstrom, L. A., Tran, T. N., Lundholm, C., Young, C., Sundstrom, K., Sparen, P. Attitudes to HPV vaccination among parents of children aged 12-15 years–a population-based survey in Sweden. Int J Cancer. 2010;126(2):500-7.

318. Mortensen, G. L. Parental attitudes towards vaccinating sons with human papillomavirus vaccine. Dan Med Bull. 2010;57(12):A4230.

319. Medeiros, R., Ramada, D. Knowledge differences between male and female university students about human papillomavirus (HPV) and cervical cancer: implications for health strategies and vaccination. Vaccine. 2010;29(2):153-160.

320. Gottlieb, S. L., Brewer, N. T., Smith, J. S., Keating, K. M., Markowitz, L. E. Availability of human papillomavirus vaccine at medical practices in an area with elevated rates of cervical cancer. J Adolesc Health. 2009;45(5):438-44.

321. Ko, E. M., Missmer, S., Johnson, N. R. Physician attitudes and practice toward human papillomavirus vaccination. J Low Genit Tract Dis. 2010;14(4):339-45.

322. Daley, M. F., Crane, L. A., Markowitz, L. E., Black, S. R., Beaty, B. L., Barrow, J., et al. Human papillomavirus vaccination practices: a survey of US physicians 18 months after licensure. Pediatrics. 2010;126(3):425-33.

323. Hopkins, T. G., Wood, N. J., West, R. M., Darling, J. C. UK health professionals' attitudes and knowledge regarding human papillomavirus (HPV) vaccination: a West Yorkshire Study. J Paediatr Child Health. 2009;45(11):652-5.

APPENDIX 1

MANAGEMENT OF CONFLICTS OF INTEREST

MANAGEMENT OF CONFLICTS OF INTEREST

SUMMARY OF DECLARATIONS OF INTEREST

of the members of the INSPQ Ad Hoc Scientific Committee on HPV Vaccination, which includes the members of the Comité sur l'immunisation du Québec (CIQ)

JULY 2012

The Institut national de santé publique du Québec (INSPQ) asked the members of the INSPQ Ad Hoc Scientific Committee on HPV Vaccination, which includes the members of the Comité sur l'immunisation du Québec (CIQ), to declare any situations in the past three years that might constitute a conflict of interest with respect to the subject of study. The Committee members were therefore required to complete a declaration of interest (DI) form in order to disclose any direct or indirect ties with private companies or public institutions whose products or activities are related to the field of HPV vaccination.

This document provides a summary of the interests reported by the Committee members. A summary was distributed to all the participants present at the start of the working session of January 26, 2012. The members not present at that meeting also received a copy.

1. *No interests reported for the following members:*

   Lucie Bédard, Dominique Biron, François Boucher, Marjolaine Brideau, Réjean Dion, Charles Frenette, Monique Landry, Bruno Leclerc, Céline Rousseau, Jocelyne Sauvé, Bruno Turmel and Louise Valiquette.

2. *The following members held research grants as principal investigator or co-investigator from public institutions[(1)] or private companies[(2)] whose products or activities are related to the field of HPV vaccination:*

   Nicole Boulianne,[(1-2)] Paul Brassard,[(1-2)] Marc Brisson,[(1-2)] Michel Couillard,[(1-2)] François Coutlée,[(1-2)] Gaston de Serres,[(2)] Philippe de Wals,[(1-2)] Marc Dionne,[(2)] Ève Dubé,[(1-2)] Eduardo Franco,[(1-2)] Vladimir Gilca,[(1-2)] Patricia Goggin,[(1)] Maryse Guay,[(1)] Marc Lebel,[(2)] Marie-Hélène Mayrand,[(1-2)] Lina Noël,[(1)] Caroline Quach,[(2)] Zeev Rosberger,[(1)] Chantal Sauvageau[(1-2)] and Bruce Tapiéro.[(2)]

3. *The following members have received consulting fees, presentation fees or reimbursement of travel expenses for conventions from private companies whose products or activities are related to the field of HPV vaccination:*

   Marc Brisson, Yen-Giang Bui, Alex Carignan, François Coutlée, Philippe de Wals, Marc Dionne, Eduardo Franco. Vladimir Gilca, Patricia Goggin, Anne-Marie Grenier, Maryse Guay, Marc Lebel, Marie-Hélène Mayrand, Michel Roy, Philippe Sauthier, Chantal Sauvageau and Dominique Tessier.

4. *The following members hold Investments (shares) of less than $25,000 in the capital of a private company whose products or activities are related to the field of HPV vaccination:*

   Michel Couillard

5. *The following members received funding for an organization for which they are or were responsible from private companies whose products or activities are related to the field of HPV vaccination:*

   Nicole Boulianne (immunization unit, DRBST, INSPQ and vaccination research team, CR-CHUQ), Michel Couillard (LSPQ/INSPQ), Marc Dionne (DRBST/INSPQ), Caroline Quach (Health Outcomes Research Axis of the RI-MUHC) and Dominique Tessier (Dominique Tessier Communications and Bleu, Réseau d'experts).

6. Public position statements

No significant public position statements in connection with HPV vaccination were reported.

All the declared interests were evaluated by a committee that included the Committee chair, the head of the immunization unit and the director of the Direction des risques biologiques et de la santé au travail (DRBST) of the INSPQ. They reviewed the declarations of interest on the basis of their connection with HPV vaccination (specific interest) and the circumstances (type and extent of the interest, period and duration of the interest, etc.). They concluded that all the individuals who completed a DI summarized above were eligible to serve on the INSPQ Ad Hoc Scientific Committee on HPV Vaccination, subject to disclosure of the interests of all the members.

Three individuals were consulted concerning the present advice on HPV vaccination but did not participate in decision making. These individuals did not complete a DI. They were Horacio Arruda, Marc Steben and Sylvie Venne.

Finally, three members of the CIQ did not participate in the development of the present advice, but approved the final version. They were Marc Lebel, Dominique Tessier and Marjolaine Brideau.

APPENDIX 2

SURVEYS OF WOMEN AGED 18-26 YEARS ON THE ACCEPTABILITY OF HPV VACCINATION

Table A1 Surveys of women aged 18-26 years on the acceptability of HPV vaccination

Author, year, country	Method, population, age	Results
Rosenthal 2009 United States[297]	Postal survey (2008), HPV-vaccinated females aged 9-26	• Response rate: 25%, n = 345 • Factor influencing vaccination decision: physician's recommendation
Zimet 2010 United States[298]	Postal survey (2008), females aged 9-26 not vaccinated against HPV (Same survey as the previous article)	• Response rate: 16%, n = 185 • 32% considered the vaccine very important for them, 30% had discussed the vaccine with a physician, 15% had received a strong recommendation • 48% did not intend to make a special effort to be vaccinated • Reasons for non-vaccination: married or in a monogamous relationship, questions about the vaccine, cost of the vaccine
Caskey 2009 United States[299]	Internet survey (2007), females aged 13-26, participating in a panel	• Response rate: 54%, n = 1,011 • 18% had received ≥ 1 dose of the HPV vaccine (30% of 13- to 17-year-olds and 9% of 18- to 26-year-olds) • Factors influencing vaccination decision: physician's recommendation, support of the family, more knowledgeable about HPV
Roberts 2010 United States[300]	Written or on-line questionnaire as part of a credit course Conducted from 2007 to 2009 993 female students aged 18-25	• Response rate: 97%, n = 972 • 49% vaccinated against HPV (≥ 1 dose) • Mother's approval was associated with vaccination, even among adults
Allen 2008 United States[301]	2007 Internet survey of 4,774 female university students aged 18-22	• Response rate: 40%, n = 1,401 • 53% intended to be vaccinated, 12% had been vaccinated • Not well informed about HPV • Social norms associated with vaccination
Licht 2010 United States[302]	Questionnaire distributed in class or via the Internet, year not specified, female university students aged 18-26	• Response rate not specified, n = 406 • 44% had received at least one dose of HPV vaccine • 18-year-olds were four times more likely to be vaccinated than 19- to 26-year-olds • Some correlation between level of knowledge and vaccination; risk perception was not a factor
Khan 2009 United States[303]	Postal questionnaire sent in 2006-07, mothers of girls (Nurses Health Survey)	• Response rate: 84%, n = 7,207 • Intention increased with suggested age of vaccination: 48% if 9-12 years, 68% if 13-15 years and 86% if 16-18 years • 48% of mothers would agree to be vaccinated if recommended

Table A1 Surveys of women aged 18-26 years on the acceptability of HPV vaccination (cont'd)

Author, year, country	Method, population, age	Results
Khan 2008 United States[304]	HPV tests and questionnaire, 2006-2007, sexually active females aged 13-26 recruited in clinics	• Response rate: 98% • Average age: 18.7 • 5% had received ≥ 1 dose and 66% intended to be vaccinated • 68% were HPV-infected, but the majority were negative for the vaccine types
Conroy 2009 United States[190]	Longitudinal study conducted in 2006-2007, females aged 13-26 recruited in clinics	• 72% completed the two study phases, n = 189 • Average age: 17 • 36% had received ≥ 1 dose • Young age, free vaccine and social norms were associated with vaccination
Cui 2010 United States[305]	Telephone survey conducted in 2007 Women aged 18-55 Random sample (random digit dialing)	• Response rate: 18%, n = 2,295 • 311 women aged 18-26, 5% of whom had received ≥ 1 dose of HPV vaccine • 61% of 18- to 55-year-old females would agree to be vaccinated, 27- to 49-year-olds had higher intention than 18- to 26-year-olds • Higher intention was associated with lower level of education
Bendik 2011 United States[306]	Electronic survey, year not specified. Female university students aged 18-24. Health Belief Model	• Response rate: 31%, n = 1,975 • Average age: 20 • 37% had received ≥ 1 dose of HPV vaccine • Recommendation of parent and physician, perception of severity and susceptibility were associated with vaccination
Bednarczyk 2010 United States[307]	Questionnaires completed in waiting rooms of university clinics or in class by women aged 18-22 in New York in 2010	• Response rate: 75% in clinics (n = 207) and 59% in class (n = 381) • 56% had received ≥ 1 dose of HPV vaccine • Factors associated with vaccination: had specific discussion with a health care professional, have had sexual relations and have received the meningococcal vaccine • Barriers: concerns about vaccine side effects, no medical recommendation
Juraskova 2011 Australia[308]	Electronic questionnaire (2007) completed by non-vaccinated female university students under 27. Compares two fact-sheets: 1: prevention of cervical cancer only 2: prevention of cervical cancer and genital warts	• Response rate: 95%, n = 159 • Average age: 19 • 79% intended to receive the vaccine, not influenced by the content of the fact-sheet • 95% would prefer the quadrivalent vaccine • At 2-month follow-up, 37% had been vaccinated, without significant difference between the groups

Table A1 Surveys of women aged 18-26 years on the acceptability of HPV vaccination (cont'd)

Author, year, country	Method, population, age	Results
Forster 2009 England[309]	Questionnaire completed in class in 2009 by female students aged 16-18 targeted for HPV vaccination the following year	• Response rate: 94%, n = 617 • 70% intended to receive the vaccine • Christian religion and white race were associated with vaccine acceptability
Mortensen 2010 Denmark[310]	Telephone interviews and focus groups in 2009, low-income women aged 16-26 (qualitative)	• Response rate: 95%, n = 794 • 24% had been vaccinated • 29% refused vaccination • Low level of knowledge in both groups • Vaccinees had more often discussed the vaccine with parents and physician • Main barrier: cost
Mehu-Parant 2009 France[311]	Anonymous questionnaire completed by female university students during medical visits in 2008	• Response rate: 93%, n = 606 • Average age: 19 • 8% had been vaccinated, 64% intended to receive the vaccine • Lack of knowledge and concerns about side effects were associated with vaccination refusal
Sundstrom 2010 Sweden[312]	Multi-method survey (Internet, telephone, postal) Conducted in 2007, men and women aged 18-30	• Response rate: ♀ 55%, n = 8,855 • 34% intended to receive the vaccine only if free, 40% even if not free, 25% no intention or uncertain
Blodt 2011 Germany[313] (also mentioned in Table A3)	Questionnaire completed in class by students aged 18-25 in 2010	• Response rate not indicated, n = 504, 259 women and 245 men • 67% of the women eligible for reimbursement of the vaccine (aged 18-20) had been vaccinated • 38% of the non-vaccinated women intended to receive the vaccine, 33% were uncertain
Lenehan 2008 Canada[197]	Written questionnaire completed during medical visits in 2007 Adult women Average age: 33	• Response rate: 91%, n = 98 • 13 respondents were < 26 years of age • A significant percentage were in favour of vaccinating girls (78%) and boys (71%), but only a few would seek vaccination for themselves (12%) • Medical recommendation was the factor most influencing vaccination decision
Giede 2010 Canada[198]	Questionnaire completed by female university students during medical visits in 2008	• Response rate: 93%, n = 371 • Average age: 22 • 60% intended to be vaccinated, 31% were uncertain, 8% did not intend to receive the vaccine • Main barriers: cost, concerns about side effects, low level of knowledge

Table A1 Surveys of women aged 18-26 years on the acceptability of HPV vaccination (cont'd)

Author, year, county	Method, population, age	Results
Kiely 2010 Canada[199]	Postal survey of 2,400 women aged 24 conducted in 2009, RAMQ sample	• Response rate: 56%, n = 1,347 • 5% had received the HPV vaccine • Low perception of their vulnerability to HPV
Lavoie 2010 Canada[200]	Internet survey of women aged 18-30 living in two regions of Québec, conducted in 2009	• Response rate: 18% (5,446 e-mails sent), n = 1,005 • Of the total, 5% had been vaccinated, 28% intended to receive the vaccine and 35% did not intend to receive the vaccine; 12% were undecided, 20% had not heard about HPV or the HPV vaccine • Low perception of vulnerability and older age associated with low intention

APPENDIX 3

ARTICLES ON THE ACCEPTABILITY OF HPV VACCINATION OF BOYS NOT MENTIONED IN LIDDON'S REVIEW OF THE LITERATURE

Table A2 Articles on the acceptability of HPV vaccination of boys not mentioned in Liddon's review of the literature[203]

Author, year, country	Method, population, age	Results
Reiter 2010 United States[314]	Internet survey (panel), 2009, parents of boys aged 9-18	• Response rate: 66%, n = 414 • 47% would agree to have their sons vaccinated if free, 11% if not free ($400)
Dempsey 2011 United States[315]	Internet survey, on-line panel (2009), parents of children aged 0-17	• Response rate: 62%, n = 1,178 • 90% considered vaccinating boys an important priority • But only 51% intended to have their sons vaccinated
Rand 2011 United States[316]	Telephone interviews of parents of adolescents (aged 11-17) and adolescents aged 15-17, conducted in 2007-2008, recruited from medical clinic patients	• Parents: n = 430, adolescents: n = 208 • 85% of the parents of boys and 93% of the parents of girls believed that the vaccine should also be given to boys • 97% of the girls and 94% of the boys questioned believed that the vaccine should also be given to boys
Dahlstrom 2009 Sweden[317]	Internet survey (with postal and telephone reminder) conducted in 2007 Random sample of 20,000 parents of children aged 12-15 years (16,000 girls, 4,000 boys)	• Participation rate: 70% n = 13,946 (11,187 parents of girls, 2,759 parents of boys) • 65% of the parents of girls would have their daughter vaccinated even if the vaccine was not free vs 57% of the parents of boys • Preferred age for vaccination: 15-17
Mortensen 2010 Denmark[318]	Telephone survey (2010) of parents of boys aged 12-15. Random sample (random digit dialing)	• Response rate: 4% (450 parents out of 10,445 calls) • n = 450 • 80% would like to have their sons aged 12-15 vaccinated (34% only if free, 45% even if not free) • Reasons for refusal: lack of knowledge about the vaccine, concerns about side effects

APPENDIX 4

ARTICLES ON THE ACCEPTABILITY OF HPV VACCINATION OF MEN ≥ 18 YEARS NOT MENTIONED IN LIDDON'S REVIEW OF THE LITERATURE

Table A3 Articles on the acceptability of HPV vaccination of men ≥ 18 years not mentioned in Liddon's review of the literature[203]

Author, year, country	Method population, age	Results
Reiter 2010 United States*[220]	Internet survey in 2009, panel members: 296 heterosexual men aged 18-59	• Response rate: 70%, n = 296 • Low level of knowledge about HPV • 63% had heard about the vaccine and 37% would agree to receive it • Acceptability higher in urban areas and if respondents believed that a physician would recommend it
Gilbert 2010 United States*[221]	Internet survey in 2009, panel members: 312 homosexuals or bisexuals compared with 296 heterosexuals aged 18-59	• Response rate: 70%, n = 312 • Homosexuals and bisexuals were better informed about HPV than heterosexuals, and 73% would agree to receive the vaccine • Higher perception of their risk (susceptibility)
Reiter 2010 United States*[222]	Internet survey in 2009, panel members: 236 homosexuals and 70 bisexuals aged 18-59	• Response rate: 70%, n = 306 • 74% would agree to receive the vaccine • High intention associated with physician's recommendation, having ≥ 5 sexual partners and perception of severity of HPV
Daley 2010 United States[224]	Questionnaire completed in 2007-2009 by 296 men (heterosexuals) participating in a study on HPV prevention (HIM Study); compared with 198 university students constituting a control group (questionnaire completed in class) Methodological problems: intention measured differently	• Response rate: 98% • n = 296 compared with 198 students • Intention to receive the vaccine very high among study participants (94%) • Intention among university students: 5% would agree to receive the vaccine, 24% would agree if they knew more about the vaccine, 33% did not know, and 38% would refuse • Respondents who answered "uncertain" or "agree" were grouped together under the heading "open to vaccination" (62%)
Thomas 2011 United States[223]	Written or telephone questionnaire (2009) completed by gay men recruited in clinics. They had been offered the HPV vaccine the previous year.	• Response rate not mentioned • n = 191 men, average age: 37 • 68 (36%) refused the vaccine, 123 were vaccinated (64%) • High level of knowledge among all respondents • Cost of the vaccine and lack of approval by the Food and Drug Administration (FDA) associated with non-vaccination
Katz 2011 United States[225]	Questionnaire completed in class, year not specified (before FDA approval of the vaccine for boys)	• n = 165 men aged 16-26 • 12% considered themselves at risk of HPV infection • 79% would agree to receive the vaccine if recommended by a physician

* These three articles describe different aspects of the same study.

Table A3 Articles on the acceptability of HPV vaccination of men ≥ 18 years not mentioned in Liddon's review of the literature[203] (cont'd)

Author, year, country	Method population, age	Results
Wheldon 2011 United States[226]	Electronic survey of gay and bisexual students, conducted in 2010, based on the Health Belief Model and the Theory of Planned Behaviour	• n = 179 men aged 18-29 • 93% had heard about HPV • 26% knew that the vaccine is available for men • 36% intended to receive the vaccine
Hernandez 2010 United States[228]	Interviews of participants in a cohort study on HPV infection, conducted in Hawaii between 2004 and 2007	• n = 445 men ≥ 18 years (62% between 18 and 26 years), 80% heterosexuals, 20% homosexuals • 16% had heard about the HPV vaccine • 69% intended to receive the vaccine
Crosby 2012 United States[229]	Electronic survey, year not specified (2 months after FDA approval of Gardasil® for men) Based on (Rogers') Protection Motivation Theory	• n = 150 men aged 18-24, majority Blacks, 90% heterosexuals • Participants who engaged in oral sex perceived themselves at higher risk of oral cancer and were more inclined to have high intention to be vaccinated against HPV • % or number of those who intended to receive the vaccine not indicated
Blodt 2011 Germany[313] (also mentioned in Table A1)	Questionnaire completed in class by students aged 18-25, conducted in 2010	• n = 504, 259 women and 245 men Response rate not indicated • 8% of men intended to receive the vaccine, 55% were undecided
Sundstrom 2010 Sweden[312]	Multi-method survey (Internet, telephone, postal) of men and women aged 18-30, conducted in 2007	• Response rate: 43%, n = 1,712 men (and 8,855 women) • 37% ♂ (34% ♀) would agree to be vaccinated only if free, 32% ♂ (40% ♀) would agree to be vaccinated even if they had to pay for the vaccine, 32% ♂ (25% ♀) would refuse or were uncertain • Higher intention when respondents had several sexual partners
Medeiros 2011 Portugal[319]	Questionnaire completed in class by university students, 2007-2008 Age: 17-35 (median: 20)	• Response rate: 89%, n = 1,706 • 55% had heard about HPV (40% of men and 64% of women) • 89% would agree to be vaccinated against HPV (76% of men and 94% of women)
Petrovic 2011 Australia[227]	Electronic survey, conducted in 2009, men aged 18-26, recruited through ads distributed on a university campus, in community and sports centres, and hospitals	• n = 121, response rate not specified. Number of those who intended to receive the vaccine not indicated • Knowledge about HPV and health self-efficacy predicted vaccine acceptability

APPENDIX 5

ARTICLES ON THE ACCEPTABILITY OF HPV VACCINATION AMONG HEALTH CARE PROFESSIONALS NOT MENTIONED IN LIDDON'S REVIEW OF THE LITERATURE

Table A4 Articles on the acceptability of HPV vaccination among health care professionals not mentioned in Liddon's review of the literature[203]

Author, year, country	Method population, age	Results
Tan 2010 Australia[237]	Internet and postal survey of all gynecologists in Australia and New Zealand conducted by the Australian Society of Colposcopy in 2009	• Response rate: 49%, n = 836 • 91% recommended the vaccine for females aged 12-26 (94% for those aged 19-26), 67% for those aged 27-45 • Low level of knowledge associated with lower recommendation
Gottlieb 2009 United States[320]	Telephone survey (2007) of private and public medical clinics with ♀ patients aged 9-26	• Response rate: 74%, n = 71 • 62% have the HPV vaccine available • Barriers: high cost of the vaccine, insufficient reimbursement, complexity of ordering and storing the vaccines
Weiss 2010 United States[238]	Postal survey (2008) of family physicians and pediatricians who have already vaccinated ♀ against HPV Compensation for survey participation	• Response rate: 45%, n = 1,094 • Recommendation by age: 9-10 years: 18% ♀, 24% ♂ 11-12 years: 70% ♀, 64% ♂ 13-18 years: 98♀, 93 ♂ 19-26 years: 93♀, 93 ♂
Zimet 2011 United States[239]	Fax survey (2008) of family physicians, general practitioners and gynecologists who have already vaccinated ♀ against HPV Compensation for survey participation	• Response rate: 34%, n = 271 • The respondents considered vaccination of married women or those living with a stable partner a lower priority
Ko 2010 United States[321]	Internet survey (2007) of gynecologists, internists and pediatricians	• Response rate: 29%, n = 424 • 80% offer the HPV vaccine, including 90% to women aged 19-26 and 61% to those aged 14-18 • Reimbursement is a major barrier • Attitudes or beliefs not a factor in decision concerning vaccination of patients
Daley 2010 United States[322]	Internet survey (or postal survey, depending on the respondent's preference) of a panel of pediatricians and family physicians (famMD) in 2008	• Response rate: 81% pediatricians, 79% famMD • n = 340 pediatricians + 331 famMD • 98% pediatricians and 88% famMD have vaccinated ♀ against HPV • More recommend the vaccine to older women • 94% of pediatricians and 85% of famMD strongly recommend vaccinating ♀ aged 19-26

Table A4 Articles on the acceptability of HPV vaccination among health care professionals not mentioned in Liddon's review of the literature[203] (cont'd)

Author, year, country	Method population, age	Results
Hopkins 2009 United Kingdom[323]	Internet survey (2007) of pediatricians, general practitioners and obstetricians/gynecologists	• Response rate: 23%, n = 222 • 88% were in favour of vaccinating girls aged 11-13, but only 68% felt at ease in recommending the vaccine to girls under 16 • 69% considered the quadrivalent vaccine to be superior

N° de publication : 1705

EXPERTISE
CONSEIL

INFORMATION

FORMATION

www.**inspq**.qc.ca

RECHERCHE
ÉVALUATION
ET INNOVATION

COLLABORATION
INTERNATIONALE

LABORATOIRES
ET DÉPISTAGE

Institut national de santé publique Québec