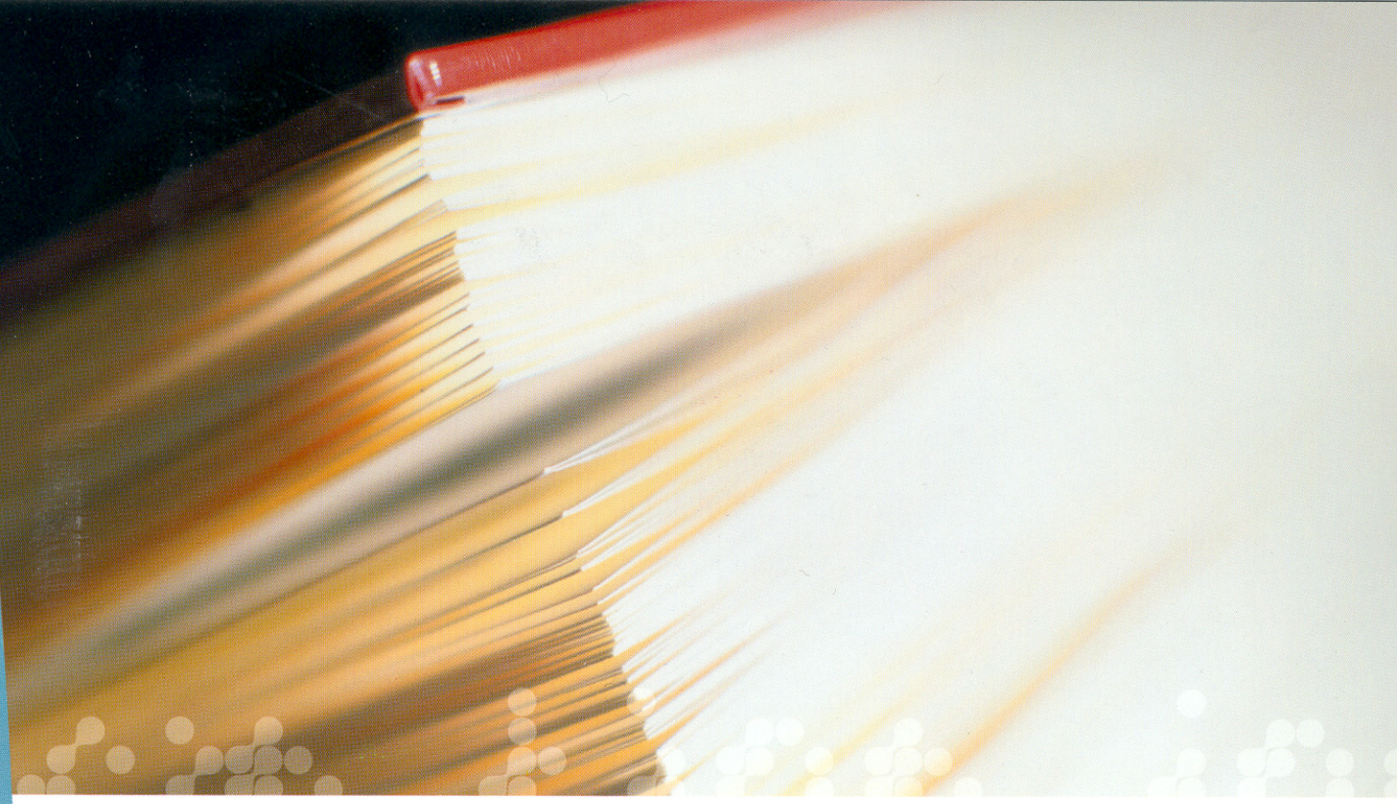

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Prevention by Vaccination of Diseases Attributable to the Human Papilloma Virus in Quebec

INSTITUT NATIONAL DE SANTÉ PUBLIQUE DU QUÉBEC

Québec

SUMMARY, RECOMMENDATIONS AND SYNTHESIS OF FACTS

PREVENTION BY VACCINATION OF DISEASES ATTRIBUTABLE TO THE HUMAN PAPILLOMA VIRUS IN QUEBEC

COMITÉ SUR L'IMMUNISATION DU QUÉBEC (CIQ)

DIRECTION RISQUES BIOLOGIQUES, ENVIRONNEMENTAUX ET OCCUPATIONNELS

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INTRODUCTION

The Comité d'Immunisation du Québec (CIQ) has been advising the Ministère de la Santé et des Services sociaux du Québec (MSSS) since 1990 on the use of new vaccines. This role was maintained upon the creation of the Institut National de Santé Publique du Québec, to which the CIQ is bound. The CIQ is made up of specialists in public health, paediatricians and infectious disease specialists who are the active members with voting power. Ex-officio members and liaison members are also part of the commitee.

The problem of the prevention of diseases attributable to the human papilloma virus (virus du papillome humain) (HPV) extends beyond the field of infectious diseases traditionally prevented by vaccination. This is why the CIQ has followed a different procedure for the preparation of this report by working with a large group of experts, notably from gynaecologists involved with the fight against cancer and from sexually transmitted infectious diseases areas.

The synthesis of facts was done by a writing committee made up of 4 people, following a model developed by Erickson and De Wals (Vaccine, 2005) which is currently the benchmark in this area. This synthesis encompasses all the information available up to August 15, 2007. A broader meeting of the CIQ, with more than 20 experts participating from those areas affected by diseases attributable to HPV, occurred on May 31 and June 1, 2007 in Longueuil. The recommendations outlined in this report, were developed during this meeting. The CIQ then held a special meeting on June 15 to finalize these recommendations. The recommendations were then sent to the organizations interested in this issue, for consultation over the summer. During the meeting on September 27, 2007, the CIQ took account of the commentaries, carried out the appropriate modifications and adopted the final version of the report.

The report is written in two parts: an executive summary which emphasises the main elements of the problem and states the recommendations of the CIQ, followed by a detailed synthesis of facts. Without overshadowing other diseases caused by the HPV, this report focuses on the prevention of cervical cancer. This is the priority reconfirmed during the meeting of the CIQ where the recommendations were worked out. This approach in no way diminishes the goal of also preventing the other diseases caused by the HPV.

The possibility of preventing cervical cancer with vaccination is both an exceptional opportunity and a difficult challenge to undertake. Cervical cancer is a killer despite the considerable efforts invested in screening, and its virtual elimination would be a remarkable step forward. However, the scientific and organizational difficulties of this new program have no common ground with that of other immunization programs, mostly because of the need for co-operative efforts on the part of sectors that have never worked together before and that have very different traditions.

The CIQ thanks all those who have worked in preparing this report. It is available to support those responsible for the Québec immunization program, its implementation and the updating of these recommendations.

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LIST OF ABBREVIATIONS

INITIALS	ABBREVIATIONS
ACIP	Advisory Committee on Immunization Practices
ACQ	*Association des cytologistes du Québec*
ASC-US	Atypical squamous cells of unknown origin
KAP	Knowledge, Attitude and Practice
CIC	Canadian Immunization Committee
NACI	National Advisory Committee on Immunization
CIN	Cervical intraepithelial neoplasia
CIQ	*Comité d'Immunisation du Québec*
LBC	Liquid-based cytology
cLIA	Competitive Luminex based immunoassay
cRIA	Competitive radioimmunoassay
ELISA	Enzyme-linked immunosorbent assay
EMEA	European Medicines Agency
INSPQ	*Institut national de santé publique du Québec*
CHI	Canada Health Infoway
STI	Sexually transmitted infection
LGIL	Low-grade intraepithelial lesion
HGIL	High-grade intraepithelial lesion
LSPQ	*Laboratoire de santé publique du Québec*
GMIT	Geometric mean infectivity titre
MSSS	*Ministère de la Santé et des Services sociaux*
PCR	Polymerase chain reaction
VLP	Virus-like particles
RRP	Recurrent respiratory papillomatosis
QALY	Quality adjusted life year
GMT	Geometric mean titre
HPV	Human Papilloma Virus
URR	Upstream regulation region

1 SUMMARY AND RECOMMENDATIONS

1.1 BURDEN OF DISEASE

There are approximately 40 types of human papilloma virus (HPV) which affect the anogenital area of humans, and about fifteen of those are capable of causing cancer. Cervical cancer was the first type of cancer to be associated with HPV; the virus is present in more than 99% of cases. HPV is also associated with several other types of cancer, notably, cancers of the anus, vulva, vagina, penis and oropharynx. Types 16 and 18 are associated with about 70% of cervical cancers.

The risk of acquiring an HPV infection begins very soon after the onset of sexual relations. In North America, the cumulative life incidence is estimated at more than 70% for all types taken together, which makes HPV the most frequent sexually transmitted infection. The highest prevalence is observed in those 20-24 years of age.

Most of the HPV infections are asymptomatic and disappear within less than 24 months. However, persisting infections can develop into cancer. This development will typically happen over a number of years, sometimes decades. Without treatment, invasive cancers generally result in death, within a more or less short term. Chances of survival vary, depending on the treatment and the stage of the disease when diagnosed.

The standardized incidence rate for the Canadian population for cervical cancer is 6 per 100,000, a marked decrease from what it was in 1978 (14.7 for 100,000). With 1,350 cases in Canada of which 325 are in Québec, cervical cancer is the 13th most common cancer in women and the 2nd most common in female Canadians from 20 to 44 years of age. Annually, there are approximately 240 deaths attributable to cervical cancer, of which 80 are in Québec. This cancer is practically non-existent in those under 20 years of age and rare in those under 30 years of age. Other cancers, (vaginal, vulvar, anal, penile) caused by the HPV total approximately 140 cases yearly in Québec.

There are a lot of screening activities for cervical cancer. In Québec, there is no organized screening approach. The latter is thus opportunistic. Around 1,260,000 cytological screening examinations (Papanicolaou tests) are done annually. The lack of a centralized information system and guidelines in Québec for the follow-up of abnormal cases prevents us from knowing which proportion of women are having an abnormal result and what their clinical course is. We estimate that 9% of the results of the examinations are abnormal or unsatisfactory and would need follow-up. If we were to follow the American standards in matters of follow-up, it would entail 68,000 annual colposcopies.

In Québec, the cost of screening has been estimated at $32.2M for the year 1995. This is the latest estimate. In the United States, it is estimated that the screening for cervical cancer and the follow-up of abnormal cases accounts for 85% of the economic burden related to the fight against this cancer.

The impacts on a psychosocial level of an abnormal result from a screening, and the need to repeat the examination or to receive treatment all create anxiety and entail significant inconvenience for those concerned.

HPV is also associated with non-cancerous lesions such as anogenital condylomas. These lesions are associated with types 6 and 11 in 90% of the cases. We do not have precise epidemiological data on their incidence. If we extrapolate from American data, we would have approximately 20,000 new cases each year in Québec. Recurrent respiratory papillomatosis is also associated with HPV. This condition is much rarer, but can be severe.

1.2 HPV VACCINES

Two vaccines against HPV have been tested in clinical studies: Gardasil™ by Merck Frosst and Cervarix™ by GlaxoSmithKline. The quadrivalent vaccine Gardasil™, which prevents type 6, 11, 16 and 18 HPV virions, was approved in Canada in 2006. The bivalent vaccine Cervarix™, which prevents type 16 and 18 HPV, has been submitted for approval. This latter contains a new adjuvant, AS04. The immunization schedule for both vaccines specifies three doses over a period of 6 months.

The Gardasil™ and Cervarix™ vaccines are sub-unitary vaccines which contain viral pseudo-particles produced by recombinant technologies. These vaccines cannot cause the disease, as they contain no living biological product or DNA and are not infectious. During clinical studies, the vaccines were deemed safe and in general well tolerated.

During these clinical studies, the two vaccines have shown an outstanding efficacy of more than 95% against the development of high-grade intraepithelial lesions associated with HPV 16 and HPV 18 with a follow-up over 5.5 years.

Immunogenicity data is available for women of 9 to 26 years of age and for men of 9 to 15 years of age, vaccinated with Gardasil™ and for women of 10 to 45 years of age vaccinated with Cervarix™. One month after the third dose has been given, almost all the participants (≥ 99%) developed antibodies against HPV types contained in the vaccines. The antibody titres obtained after vaccination are 10 to 100 times higher that those produced by natural infection. Comparative studies have revealed that the geometric mean titre (GMT) of anti-HPV antibodies in pre-adolescents and adolescents of 9 to 14 years of age was two times higher than the GMT in women of 15 to 25 years of age. One month after the second dose of Gardasil™, the GMT observed in young people of 10 to 15 years of age was higher than the GMT observed one month after the third dose on women of 16 to 23 years of age. The seroconversion rate, one month after the second dose, exceeded 97.5% for all types of HPV targeted by the vaccine. The clinical meaning of these results still has to be clarified, as the threshold of antibodies to guarantee protection is not yet established.

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

- the decrease of the number of moderate or severe cervical abnormalities (cervical intraepithelial neoplasia CIN 2/3) and of adenocarcinoma in situ;
- the decrease in incidence of persistent infections with the types of virus targeted by the vaccines.

For ethical reasons and also because of the delay in the emergence of disease, cervical cancer was not used as a primary criterion for the efficacy of anti-HPV vaccines in the clinical studies. It must be mentioned that the evaluation of these efficacy indicators will become essential after the implementation of the program and will require the setting-up of specific information systems.

Other than the prevention of lesions caused by HPV 16 and 18, the Cervarix vaccine had an efficacy of 35 to 60% in the prevention of infections caused by types 31 and 45, which are responsible for 8-10% of cervical cancers. The Gardasil vaccine has shown a protection rate of 99% against anogenital condylomas.

There is no data on the efficacy of the vaccines on men. Women who were already infected by one of the types targeted by the vaccine cannot benefit from the protective effect of the vaccine for that type: hence the need to vaccinate before the onset of sexual contacts.

The three-dose schedule given at 0, 2, 6 or 0, 1, 6 months is currently recommended by the manufacturers of the vaccines. A clinical trial aimed at evaluating the immunogenicity of children 9 to 13 years of age with a schedule of 2 doses, given at a 6-month interval, will begin in the fall of 2007. This clinical trial is financed by the Ministries of Health of British Columbia, Québec and Nova Scotia.

1.3 BENEFITS EXPECTED FROM A UNIVERSAL VACCINATION PROGRAM

Several models were developed to forecast the long-term impact for different strategies of vaccination and to estimate their cost-benefit. The vaccines can prevent 70% of cervical cancer cases. They can also prevent around 55% of high-grade lesions and 25% of low-grade lesions which are caused by HPV 16 and 18. The duration of protection is the element which has the most influence on the impact of the vaccination. A large proportion of the potential benefit could be lost if the efficacy of the vaccine wanes with time and if the cases of cancer are simply postponed. Consequently, measuring the persistence of the efficacy will require the establishment of specific evaluation procedures.

A universal vaccination program which would reach girls of 14 years old or less could cost around $25,000 per QALY (qualified adjusted life year) if the vaccine is effective for the entire lifetime and would cost around $400 per person vaccinated. It is an acceptable threshold for a health intervention. This cost per QALY progressively increases after the age of 14 when the proportion of girls, having been infected by one or another type targeted by the vaccine, increases.

1.4 ACCEPTABILITY AND FEASIBILITY OF VACCINATION

The majority of the studies compiled emphasize a low level of knowledge about HPV in the population, notably on its prevalence and links with cervical cancer.

Despite this lack of knowledge, a notable interest in the vaccines against HPV was noted. The acceptance of vaccination against the HPV is high in adolescents and young women as well as parents of teenagers.

An investigation conducted in the winter of 2006 in the area of the Capitale-Nationale reached 471 respondents between the ages of 18 and 69. Only 15% had heard of HPV. Regardless, 91% of the respondents between the ages of 18 and 25 said that they would accept vaccination against HPV. However, only 65% would still agree if they had to assume the cost. The need to pay for the vaccine was the main barrier, especially with young people between 18 and 25 years of age. The majority of participants (73%) were in favour of providing the vaccine against HPV to adolescents before the beginning of their sexual activities.

Studies also emphasise the favourable attitude of health professionals towards vaccination against HPV. A study carried out amongst 264 obstetrician-gynaecologists, 338 paediatricians and 160 general practitioners from Québec showed that more than 90% intended to recommend the vaccine against HPV to their patients. A similar investigation, done with public health professionals in the province of Québec, indicated that the vaccine against HPV was perceived as useful in a universal vaccination program by 99% of the participants.

1.5 RECOMMENDATIONS

1.5.1 Strategies and immunization programs

Short-term goal: Prevention of precursors of cervical cancer.

Long-term goal: Reduction of incidence and death brought about by cervical cancer.

Principles underlying the recommendations:

- These vaccines are beneficial for all young women between 9 and 26 years of age. However, due to the high cost, the CIQ has prioritized their use by trying to find an optimal efficiency, that is to say, by maximizing the effects of the resources consumed;
- It is preferable to provide the vaccine against HPV before the onset of sexual relations to take advantage of the maximum efficacy of the vaccines;
- It is preferable to provide the vaccine in a primary school environment to obtain a higher immunization coverage, at a lower cost;
- It is possible that a modified schedule of two or three doses of the vaccine would ensure the same protection, or possibly even higher than those schedules recommended by the manufacturers.

Routine vaccination:

The committee recommends a school vaccination program for girls in fourth grade, together with the vaccine against Hepatitis B. It is recommended that the vaccine be used with a longer schedule. The interval between the first two doses would be 6 months. The third dose would be dispensed in third secondary (at the age of 14-15 y-o), together with the vaccination of the DCaT, if this were deemed necessary (see detailed justification in section 1.6).

Catch-up vaccination:

Vaccination for girls in fourth grade should ideally be complemented for a few years with a catch-up vaccination program. This catch-up vaccination will be dependent on available resources. The catch-up vaccination should comprise three doses of the vaccine, in compliance with the manufacturer's recommendations. The CIQ proposes to carry out the catch up vaccination program in the following order of priority:

- all girls in third secondary, until the arrival of cohorts vaccinated in primary four;
- all girls in fourth and fifth secondary, during the first year of the program;
- young girls having left school but of the same age as those being vaccinated in a school environment, should be able to receive free vaccination in designated vaccination centers.

For other women of 26 years of age and less, it would be desirable to offer free vaccine. However, if this strategy is difficult to implement for budgetary reasons, other measures aimed at providing easier access to the vaccine should be developed and implemented (for example: offering the vaccine in family medicine groups at a lower cost, developing vaccination access systems for adults, working out a partial refund for the cost of the vaccine with insurance companies, etc.).

Because of the higher incidence of cervical cancer in native and Inuit women, and the problems in screening and the follow-up of abnormal cases in this population, the committee recommends that the vaccine against HPV be free for all adolescents aged from 9 to 18, living in socio-sanitary areas 17, 18 and in the twenty-eight non treaty First Nation communities whose immunization program is covered by Québec public health.

The program should be implemented as early as the 2008-2009 school year. Until then, we should start training health personnel, informing the public, creating and validating the tools needed to implement the school program, developing and setting up the immunization strategies for adults that are out of school, and creating and setting up evaluation systems.

1.5.2 Impact of vaccination on screening

Screening is a critical tool for the evaluation of an immunization program against HPV. In Québec, there is no centralized management for screening activities, nor is there any information or follow-up system, etc. It is not part of the CIQ mandate to issue recommendations on cervical cancer screening. However, the introduction of immunization will have major impacts on screening. The two activities now have to be planned simultaneously. Because of the direct links between immunization and screening the CIQ has formulated following recommendations:

- An immunization program against HPV will reduce the incidence of cervical cancer, but will not eradicate the disease. All women who are sexually active, whether they have been vaccinated or not, will have to continue to take part in screening for cervical cancer. The CIQ recommends the establishment of a co-ordinated body of interventions, aimed at maintaining and improving compliance with screening: investigations on attitudes and behaviour, various educational interventions, follow-up system, etc;
- Immunization against HPV will have an impact on the screening. A reduction of the prevalence of cervical lesions will bring about a reduction of the positive predictive value of cytological tests. Immunization against HPV will as well have an impact on the use of new screening tests (for example, the tests aimed at detecting viral DNA of different types of HPV). Finally, immunization will reduce the rate of consultations for colposcopy;
- New algorithms must be developed for the screening of vaccinated women. The CIQ recommends that the implementation of an immunization program against HPV be used as an opportunity to set up an organized approach of screening, to establish guidelines and to create a synergy between the various people involved in the prevention of cervical cancer;
- Canada Health Infoway (CHI) supports the development of the pan-Canadian electronic health record, including the Québec health record. CHI supports as well the standardization of laboratory data (i.e. standardization facilitating exchanges between systems), including cytopathology. In Québec, the creation of regional data repository for laboratory results will allow clinicians to have access to standardized results of these tests, regardless of where the consultation of the patients has occurred. As well, there must be a provision made for the creation of a central register, which would facilitate the recruitment and follow-up of women for the screening of cervical cancer and the follow-up of abnormal test results, including colposcopy. The CIQ recommends the establishment of such a register;

- The immunization component of the future public health information system *Panorama* could supply the data on the immunization status against HPV for the residents of Québec which is recorded by vaccinators. The evaluation of the immunization impact against HPV would require phasing in *Panorama*, the future Québec health record and the regional repository for laboratory (which could include the results of HPV detection tests, HPV isolates genotyping and eventually HPV serology) through electronic messaging.

1.5.3 Program evaluation

- Immunization programs must be evaluated. The evaluation of the immunization program against HPV is complex. It is especially critical because of the major impacts on women's health and on the screening activities, the amount of money invested and the need to review the future options according to the knowledge gained. Other information generated in different jurisdictions could be transposed directly to Québec, but there are some specific aspects pertaining to a Québec context. The CIQ recommends that a detailed evaluation plan be developed and financially supported in collaboration with the various authorities involved;
- As the selected immunization strategy moves away from research on the product, it is essential to evaluate the efficacy and duration of the protection afforded by the vaccine. Because of the long latency period of cervical cancers, a reliable indicator will have to be identified (ex. high-grade lesions) to measure the impact of the immunization;
- A follow-up of the immunization coverage obtained will have to be set up. The immunization impact on compliance with screening in vaccinated women must be evaluated, just as periodical studies on knowledge, attitudes and practices of the population and the health professionals are necessary. This is particularly important in the context in which the duration of the protection afforded by the vaccine is unknown;
- The development of a diagnostic platform (serological tests) is essential for the measurement of incidence and prevalence of the different types of HPV, following the introduction of the immunization program. At the moment, these are not available anywhere in the laboratory network in Canada, rendering us totally dependent on the manufacturers for all the evaluation or research work needing serology. The CIQ recommends that a special effort be made to develop this ability in Québec (through the *laboratoire de santé publique du Québec* (LSPQ) of the INSPQ);
- The evaluation of the immunization program will need special tools which are not readily available and which will be difficult to work out on a large scale. The CIQ recommends assessment of the possibility to allocate certain aspects of the evaluation to predetermined geographical areas (for example, one or two of the socio-sanitary areas). The additional data deriving from those areas will facilitate future decisions concerning the prevention of HPV diseases and any abnormalities associated with it.

1.6 JUSTIFICATION FOR THE USE OF A LONGER SCHEDULE

The goal we seek with a longer schedule is to protect as many women as possible appropriately while using the available resources to their best advantage.

Arguments that underlie this proposition are grouped together in two themes: immunological and operational. Finally, mention will be made of the measures to be taken to ensure that the protection afforded by this schedule is appropriate and will effectively help to prevent the disease.

1.6.1 Immunological arguments

- Vaccines against HPV are very immunogenic and stimulate the production of antibody titres far higher than those afforded by the natural infection[1,2];
- The immune response in young people of 9 to 11 years of age is especially good, reaching higher titres after two doses than in young women of 16 to 26 years of age where the clinical efficacy of the vaccine has been proven [3];
- It is well known that the spacing of doses will generally yield higher antibody titres. This has been proven for the Hepatitis B vaccine which is also a recombinant vaccine given to young adults[4]. As well, there is no well articulated justification for schedules of 0, 1, 6 and 0, 2, 6 months, which are suggested by the manufacturers;
- The administration of a booster dose 5 years after the initial immunization yields much higher geometric mean titres than those after the initial immunization. This has been observed as well with the Hepatitis B vaccines (cohort of Québec)[5,6] and with vaccines against HPV[7]. In the context of HPV, where maximum protection is desirable before the onset of sexual activity, the administration of this third dose in third secondary seems amply justified according to today's facts. The lack of data on the length of the protection afforded by the HPV vaccines gives us an additional justification, as this schedule will allow us to obtain the highest possible titres when the last vaccine is given in the school system.

1.6.2 Operational arguments

- Immunization in 4th grade allows us to reach very high immunization coverage at a relatively low administrative cost. This is the best time to administer the vaccination against Hepatitis B, because of the quality of the immune response and the efficiency of the intervention in the school environment. We are seriously thinking of introducing a two-dose schedule against the Hepatitis A and B by using a combined vaccine. The two vaccines could be administered simultaneously, without a third vaccination session;
- Administering two doses instead of three in 4th grade will most likely increase the acceptability, as much with the students as with their parents and the health personnel, while reducing the costs and allowing more vaccinations of young girls with the same resources;
- This schedule takes into account the approved schedule and is consistent with it. The principle of not starting up a new vaccination schedule where the intervals have been extended is well accepted in vaccinology.

1.6.3 Assurance of efficacy

- A clinical trial, in which two doses of vaccine are administered to young girls 9 to 13 years of age, started in 2007, one year before the suggested date for the beginning of the vaccination program. The subjects in the study will be monitored for at least 3 years and probably longer. The data will be available in the next few years and will allow us to make adjustments which may be necessary during the intervention in third secondary;
- The evaluation process which will be implemented to measure the effectiveness of the program will also supply the data allowing us to make adjustments during the program;
- Screening strategies, which will be re-inforced following the introduction of the vaccination program, will provide a safety net for those who are not protected by the vaccine.

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2 SYNTHESIS OF FACTS

2.1 CHAPTER 1 – BURDEN OF DISEASE

2.1.1 Pathogenicity and characteristics of the infectious agent

HPV's are small non-coated viruses (55 nm in diameter), made up of a circular double-stranded DNA which has three regions: early (E) coding non-structural proteins E1 to E7, late (L) coding structural proteins L1 and L2, forming the viral capsid, and a non-coding regulation region (URR for upstream regulation region).

There are more than 100 types of human papilloma virus (HPV) belonging to the family of *Papovaviridae* and of which the genome has been sequenced. Based on their molecular characteristics, they are divided into categories, species and finally into types[8].

About forty genotypes[a] affect, in particular, the anogenital area of humans, of which about fifteen have carcinogenic properties.

Numerous types of HPV cause benign skin infections, like verrucae and plantar warts, or rare forms of skin cancer. This document addresses the category of HPV called "genital".

Cervical cancer is the first type of cancer to have been associated with HPV and some studies have shown it to be present in 99.7% of cases[9]. In relation to their degree of association with cervical cancer, the HPV types are classified in the following categories[10]:

Table 1 Classification of HPV types according to the degree of risk for cervical cancer

Group	Genotypes
Established high-risk	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Probably high-risk	26, 53, 66, 68, 73, 82
Established low risk	6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108

HPV is also associated with numerous other cancer sites, notably the anus, vulva, vagina, penis and oropharynx.

As for types 6 and 11, they would be responsible for 90% of anogenital condylomas.

a. The word "types" will also be used as a short form for the word "genotypes".

For reasons that are unclear, relating to the characteristics of the host and the type, viral DNA can integrate itself to the nucleus of the infected cell, leading to a deregulation of the cell cycle. However, the development of cancer remains a relatively rare event, taking into account the frequency of HPV infections in the population. The infection does not cause a significant inflammatory response in the host and the production of specific antibodies (observed in 40-50% of infected women) is neither constant[11] nor correlated to the severity of the disease[12].

Even though efforts are being made to standardize laboratory testing[13], there are still no validated and commercial serological tests for HPV. At the moment, detection of HPV rests mostly with molecular biology techniques by PCR (polymerase chain reaction). There are also now commercially approved tests for clinical use, such as the Hybrid Capture 2 test, but they are based on an HPV pool, without specification of the type.

2.1.2 Epidemiology of diseases caused by HPV and their natural history

2.1.2.1 Prevalence and incidence of HPV infections

Prevalence

The prevalence of HPV infections at the cervical site varies according to populations, age and the laboratory test used[14,15]. In a large population study on more than 18,000 women from 15 areas and four continents, excluding North America, the average prevalence rate was established at 9.2%. Two-thirds of the infections were caused by high-risk types. The frequency of the different types varied with the continents, with type 16 predominant everywhere. The prevalence was also higher everywhere in young women of less than 25 years of age, followed by a progressive decrease with increase of age. In some countries of South America, another peak of less importance was observed after the age of 45 (Mexico, Chile) or 55 (Colombia).

Until recently, data obtained on prevalence in North America came mostly from convenience samples. Two population-based studies done in the United States were published recently. The first was a study done on 1,921 women of 14 to 59 years of age[16]. The authors estimated a global prevalence of 26.8% for all HPV types and a prevalence of 15.2% for high-risk HPV and 17.8% for low-risk HPV. The prevalence for types 16 and 18 was 1.5% and 0.8%, and for types 6 and 11, 1.3% and 0.1% respectively. As in the aforementioned study, the prevalence was higher in those 20 to 24 years of age and less after. In this study the cervicovaginal samples were obtained by self-sampling.

The second North American study, done on 3,252 young women of 18 to 25 years of age from urine samples, has shown an estimate of global HPV prevalence of 26.9%, of which 20% is of a high-risk type. The prevalence from type 16 was 5.8%[17]. The search for HPV in urine samples is not a well recognized technique and could underestimate the prevalence by some 20 to 25% compared to cervical sampling.

In Canada, the prevalence data available come from convenience samples. The largest series comes from tests done on nearly 5,000 women in a screening program in British

Columbia in 2004[18]. The prevalence was 13.9% for high-risk HPV types and 6.9% for any low-risk type. Type 16 HPV were present in 10.6% of women. The HPV prevalence increased with the severity of lesions in women showing cytological abnormalities.

In Québec, the data available suggest a similar situation. The following table describes the Québec results compiled to date.

Table 2 Québec data on the prevalence of HPV infections

Reference	Context and sample size	Global prevalence	Specific prevalence
Richardson *et al*., 2000[19]	Cross -sectional study done in Montreal, students attending a health university centre 1992-1993; 18-24 of age, mostly (3% > 30 y.o.a.) n = 375 Detection by primer MY9/MY11 and hybridization by dot-blot	All types of HPV: 22.7% High-risk HPV: 11.8% Low-risk HPV: 6.2% Unidentified HPV: 7.1% Mixed infection with at least one high-risk type 2.7%:	The most frequent: High-risk HPV: HPV 16: 4.7% HPV 51: 2.2% Low-risk HPV: HPV 66: 1.6% HPV 6: 1.1% HPV 11: 1.1%
Richardson *et al.*, 2003[20]	Cohort study done in Montreal; women attending a health university centre; 17-42 years of age, average 23 and median 21,1996-1998 n = 621 Detection by primer MY09/MY11 and Line Blot Assay for genotyping	All types of HPV: 29% High-risk HPV: 21.8% Low-risk HPV: 14.8%	The most frequent: High-risk HPV: HPV 16: 7% HPV 18: 3.1% HPV 51: 2.9% HPV 31: 2.6% Low-risk HPV: HPV 53: 4.3% HPV 84: 3.8% HPV 6: 2.7% HPV 11: unavailable

Table 2 Québec data on the prevalence of HPV infections (continued)

Reference	Context and sample size	Global prevalence	Specific prevalence
Mayrand *et al*., 2006[21]	Controlled trial, women attending a screening site in Montreal, 30-69 years of age, 2002-2004, n = 4 184 Detection with HC2 test (pool of 13 high-risk HPV's)	7,7% for high-risk HPV included in the HC2 test, by age group: ▪ 30-39 y..: 12.7% ▪ 40-49 y..: 5.9% ▪ 50-59 y..: 4.8% ▪ 60-69 y..: 3.8%	Unavailable
Brassard *et al.*, 2005[22]	Data from a cohort study done in Nunavik, in the context of primary health care, n = 330, average age 31,4 y.o.a. 2002-2004 Detection by primer PGMY and Line Blot Assay for genotyping	Global prevalence at the beginning of the study: 27% In the positive cases: 49% high-risk types 27% mixed infections (low and high-risk)	HPV 16 is the most frequent

Other data are available in Canada for native populations. In Nunavut and in Winnipeg (Manitoba), the HPV prevalence in native women and non-native women is similar, that is to say 30% for both areas[23,24]. However, surveys have shown that the high-risk HPV prevalence was significantly higher in young women of Nunavut when compared to those of other provinces for the same age groups: the prevalence has been established at 42% for women between 13 and 20 years of age and at 31% for women between 21 and 29 years of age. Among older women, the prevalence was similar to the one observed in other areas of the country[24-26].

The methods used to measure the prevalence of HPV infections in men are less developed. For populations of similar age, the prevalence of infections in men seems lower to that observed in women, but always with a predominance of type 16[27]. There is no sero-prevalence study on men available in Canada.

Incidence

Numerous studies have shown that the probability of contracting an infection with HPV occurs very early on, after the beginning of sexual relations. In the cohort study of Richardson *et al.,* done with female students in Montreal, the cumulative incidence of the infection in those with a negative test at the start of the study was 18% after one year and 36.4% after two years[20]. In North America, the cumulative incidence for life is estimated at more than 70%[28], which would make it the most frequent sexually transmitted infection (STI)[29]. The data for monitoring the incidence is however limited by the fact that most of

the infections are asymptomatic and that it is not an infection for which there is compulsory notification.

2.1.2.2 Acquisition, transmission and spontaneous evolution of infections caused by HPV

Transmission usually happens by sexual contact but can also occur by cutaneous genital contact. It is therefore not completely avoidable by wearing a condom during sexual relations[30]. The risk of transmission by coital act is much higher than that for other viral STIs, including HIV[31].

Vertical transmission (from mother to child) or transmission from objects is still possible, as these types of genital HPVs can be found in young children, but we still do not know the exact significance of these asymptomatic infections[32, 33].

Most HPV infections will disappear spontaneously in less than 24 months[34] and this disappearance will happen in a shorter time for low-risk HPVs. Persistent infection with a high-risk type increases the cancer risk.

2.1.2.3 Risk factors for acquiring the infection

Because these infections are transmitted for the most part by sexual means, the major risk factor is the number of sexual partners (and the number of their partners)[35]. A young age at the time of sexual debut is also associated with higher risk, probably because of the particular vulnerability of the transformation zone between the endocervix and exocervix in the female adolescent.

2.1.2.4 Pathogenesis of cervical cancer

The evolution of a persistent infection towards a cancer, typically takes many years, sometimes decades. Morphological changes can be seen with a cytological examination of the cervix (Pap test) of which the results are described by the Bethesda terminology. The final histopathological diagnosis, however, relies on the biopsy taken during the colposcopy.

Approximately 85% of cervical cancers are squamous cell carcinomas and 15% are adenocarcinoma. The important stages of the carcinogenesis for squamous cell cancers include low-grade intraepithelial lesion (LSIL at the cytology or CIN1 at the pathology level) and high-grade intraepithelial lesion (HSIL or CIN2/3 at the pathology level).

The following table describes the main stages of carcinogenesis. The reasons that some infections persist and develop into a cancer are not yet clearly understood. Some co-factors may be linked to the host (immune status, HLA, etc.), to the HPV type in question (type 16 in particular, viral load, multiple infections) or to an exogenous factor (infection from *Chlamydia trachomatis*, smoking, prolonged use of oral contraceptives, etc.)[34].

Figure 1 Important stages of the carcinogenesis for cervical cancer

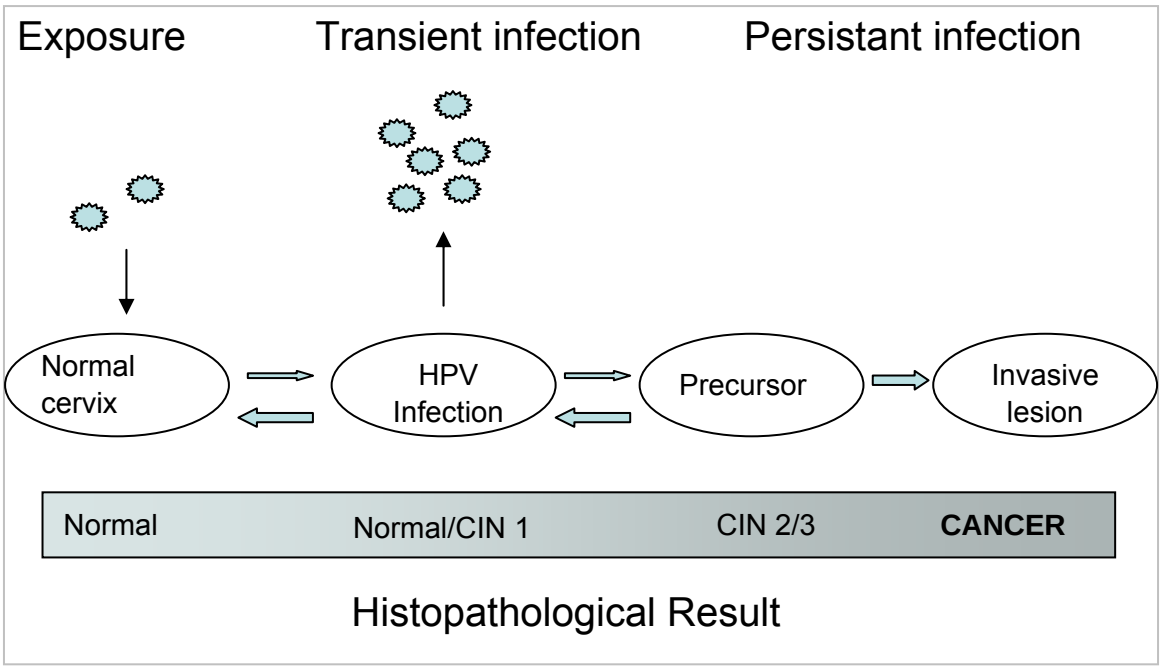


Figure adapted from IARC Handbooks of Cancer Prevention, volume 10, Cervix cancer screening, IARC Press 2005, chapter 1, page 49[36].

The majority of LSIL will regress spontaneously and are not considered as precursors of cancer anymore. In young women in particular, it is estimated that 61% of the lesions disappear in less than a year and 91% in less than three years[37]. These lesions may indicate HPV infection and about 12% of them are caused by low-risk HPV types[38]. A small proportion will develop into more severe lesions.

High-grade lesions (HSIL) can persist, regress or develop into cancer. Cohort studies have shown that the risk of developing into a lesion such as CIN3 or cancer was much higher and faster in the presence of type 16 or 18 than with any other high-risk type[39]. The most recent meta-analysis have shown that types 16 and 18 are responsible, on a global level, for about 65 to 77% of invasive cervical cancers, 41 to 57% of HSIL, 15 to 32% of LSIL and 8 to 19% for equivocal lesions or ASC-US *(atypical squamous cells of unknown origin)*[40]. The majority of adenocarcinomas (86%) are also caused by types 16 or 18.

2.1.2.5 Pathogenesis of other cancers

HPV is also associated with other types of anogenital and oropharyngeal cancers, but the attributable fraction of the risk is lower than that observed in cervical cancer[41] (Table 3). Here again, type 16 is the most predominant, followed by type 18. All these cancers are relatively rare, when compared to cervical cancer, with incidence rates of about or lower than 1-2/100,000.

Table 3 Attributable portion of the risk imputed to HPV for different cancers

Cancer area	Fraction of the risk (%) estimated on a global level
Cervix	100
Anus	90
Penis	40
Vulva, vagina	40
Oropharynx	12 (but higher for some areas like the tonsils and the base of the tongue)[42]

In many countries, it has been noted that the incidence of anal cancer is increasing, especially among young people living in urban areas or among men having sexual relations with other men[43,46]. Infection with HIV appears to be a major risk factor in the latter. With the introduction of highly effective antiretroviral therapies, we could even see paradoxical increase of the incidence of anal cancer due to longer survival of those people[47,48]. The epidemiology of anal cancer in women is not so well known, despite the fact that the incidence of anal cancer is generally higher in women than in men.

Cancers of the vagina are relatively rare and are mostly found in very old women. Cancers of the vulva and in particular the precursors of this cancer (VIN2/3) are increasing in many areas[49,51], where they are found more and more commonly in younger women.

Finally, studies have shown that the risk of developing another anogenital cancer or a precursor of these cancers is higher after a first neoplasia associated with HPV, than in the general population[52].

As for oropharyngeal cancers, the consumption of alcohol and tobacco have long been deemed as the major risk factors in these cancers; we now recognize more and more the role of HPV and the risk associated with orogenital sexual relations[53].

Anogenital condylomas

Condylomas are mostly associated with types 6 and 11. They affect men as much as they do women, with a maximum incidence in the early twenties[54]. As previously mentioned, these types are associated with low risk of cancer.

2.1.3 Clinical manifestations

- Cervical cancer and other anogenital cancers.

Cervical cancers are often found by screening, but they can also show up with non-specific symptoms like pain, post-coital bleeding or fatigue. Manifestations of other cancers vary according to their location. Precursor states are often asymptomatic.

Without treatment, invasive cancers generally end in death within a shorter or longer time frame. Chances of survival vary according to treatment and the stage of the disease when diagnosed (presently, in Québec, the stage is not recorded in the tumour registry).

- External anogenital condylomas.

After an incubation period of 1 to 8 months, condylomas may appear on the vulva, penis, thighs, scrotum or perianal area. They can disappear spontaneously in a few weeks, but a large proportion of people affected by these lesions consult a physician, either because of symptoms (burning, pruritus, bleeding) or for aesthetic reasons. There are several topical treatments available aimed at controlling the symptoms, but not necessarily eradicating the infection[55]. If the disease remains benign, the psychosocial repercussions can be significant because of the social stigma it can create. Low-risk HPV infections can co-exist with high-risk infections and can provoke transient cervical abnormalities, such as LSIL.

- Recurrent respiratory papillomatosis.

Recurrent respiratory papillomatosis (RRP) is a rare condition, affecting young children, following perinatal transmission of HPV infection from a woman with condylomas. Most of these cases would be associated with type 6 or 11 HPV[54]. There is also a rarer form of this condition in adults.

RRP is characterized by a change in the voice or respiratory difficulties. Even though it is rarely fatal, the disease may entail repeated interventions (surgery, tracheotomy). The incidence of these cases has been estimated at 4.3 per 100,000 children in the United States[56] and at 3.6 for 100,000 births in Denmark[57]. There is no registry in Canada or in Québec allowing us to evaluate the incidence of RRP.

- Other pathologies.

Studies are being done to better characterize and evaluate the relation between HPV and other types of cancer like conjunctival cancer, skin cancer and cancer of the superior respiratory and digestive passages.

2.1.4 Epidemiological data

Cervical cancer

At the world level, cervical cancer remains a major health problem and contributes the 2nd highest the number of cancers in women, with some 493,000 cases annually and 274,000 deaths[41]. Most cases occur in developing countries, where there is little or no screening.

The standardized incidence rate in the Canadian population has been estimated for 2007 at 7 per 100,000 in Canada (6 per 100,000 in Québec)[58], a sharp decrease from that of 1978 (14.7 per 100,000). In relation to the number of cases, cervical cancer is 13th among cancers of women in Canada, with 1,350 cases (280 in Québec). It is 2nd after breast cancer, in Canadian women between 20 and 44 years of age[59]. However, because of the slow evolution between the infection and cancer, this cancer is almost non-existent before the age of 20 and even rare, before the age of 30.

The following figures describe the distribution of cervical cancer cases according to age (2a) and the variation of incidence rate (non-standardized) according to age (2b) obtained from the Fichier des tumeurs du Québec, for the years 1997-2001.

Figure 2a Distribution of cervical cancer in Québec according to age group, 1997-2001

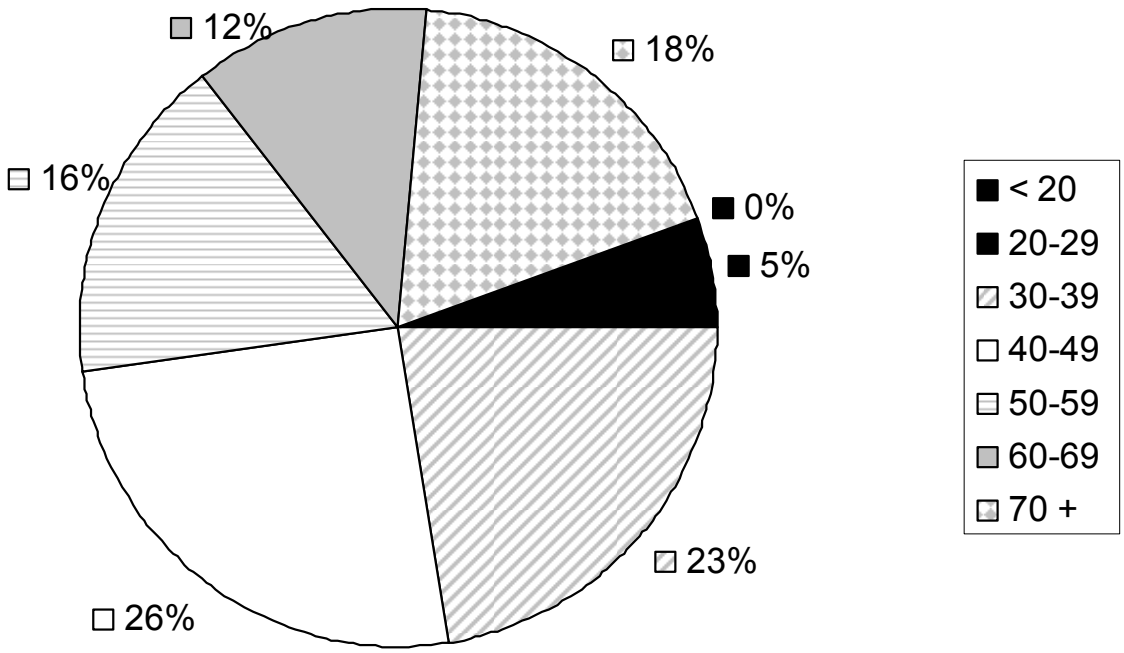
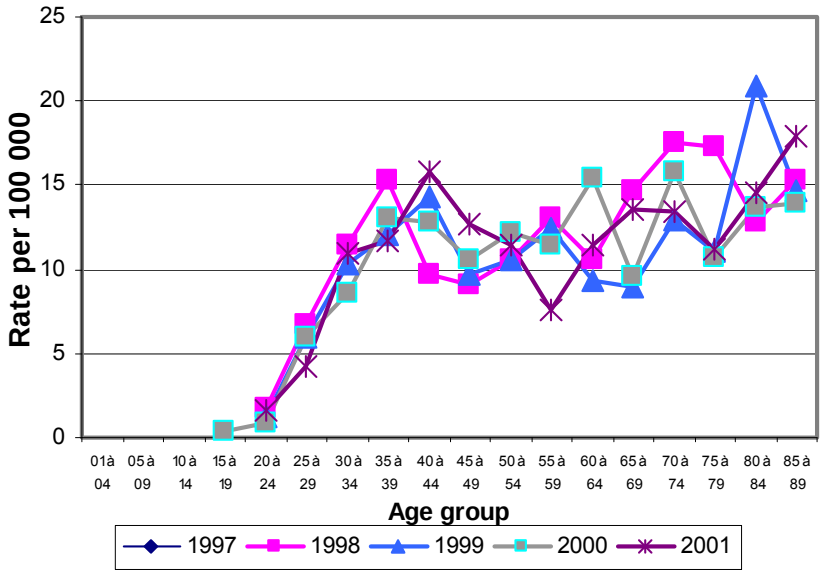


Figure 2b **Incidence rate of cervical cancer in Québec according to age group, 1998-2001**



Other anogenital cancers

There are very few data on a population basis for other types of cancer. In Québec, the annual standardized incidence rate, for the period 1999-2001, appears in table 4[60]. As for cervical cancer (included for purposes of comparison), the majority of cancers are squamous cell carcinomas.

Table 4 **Incidence of anogenital cancer per 100,000 women-years, Québec, 1999-2001**

Area	Squamous Cell Carcinoma	Adenocarcinoma	Other morphologies
Cervix	5.6	0.5	1.7
Anus (men)	0.4	0.07	0.3
Anus (women)	0.7	0.11	0.22
Vagina	0.2	0.04	0.1
Vulva	1.3	0.2	0.4
Penis	0.8	0.04	0.1

Table 5 describes the relative survival probabilities at 5 years for anogenital cancer cases diagnosed in Québec between 1993 and 1995[60]. Anal cancer in men and vaginal cancer in women have a lower survival rate than do other cancers. The relative survival rate for anal cancer in men deteriorated between 1984-86 (56%) and 1993-95 (45%).

Table 5 Relative survival probability at 5 years, Québec (cancers diagnosed in 1993-1995).

	Cervix	Anus		Vulva	Vagina	Penis
	F	H	F	F	F	H
Relative Survival at 5 years	74%	46%	65%	82%	45%	60%

Anogenital condylomas

There are no epidemiological data available in Québec to determine the prevalence or incidence of anogenital condylomas in the population. This STI is not one of the diseases for which compulsory notification is required and the lesions can be asymptomatic, thus leading to underreporting.

However, we know that the condition is relatively frequent and that it is increasing in many countries, such as Great Britain and the United States, especially in young people[54]. In a study done in Ontario aimed at establishing the prevalence of HPV infections in more than 900 women of 15 to 49 years of age, who had consultations in family medicine clinics, examining doctors documented visible condylomas in 1.1% of the participants[61]. In Manitoba, using billing services data, the prevalence in the population in 2004 was estimated at 0.19% in men and 0.14% in women[62].

2.1.5 Current treatment for the disease and prevention by means other than immunization

Until the arrival of HPV vaccine, the primary prevention of HPV infections was conceivable only by sexual abstinence or by limiting the number of sexual partners, measures that are applicable with great difficulty and that are largely ineffective. Wearing a condom offers only limited protection.

Among all the pathologies associated with HPV, cervical cancer is the only one suitable for screening. Recommendations on what age to start screening and the intervals between tests vary according to the different countries and jurisdictions. In North America, screening generally starts at 18 years of age or at the beginning of sexual relations and the test (the cytological examination or Pap test) is repeated at intervals of one to three years. The need to repeat the test often, so as to ensure some safety, is owing to the poor sensitivity of the Pap test (estimated at around 47% in a meta-analysis[63]).

Numerous new screening and follow-up tools for abnormal cases were introduced or will soon be introduced: liquid-based cytology (LBC), tests aimed at detecting viral DNA and molecular markers[64,66].

LBC improves the clarity of the smear, reduces unsatisfactory results and allows for additional tests on the liquid residue. Benefits gained for sensitivity are minor. Because of the high cost, economic analyses have shown that the cost-effectiveness rate could be unfavourable when the tests are done more often than every three years[67].

There are numerous commercial tests for viral DNA detection of HPV done from liquid sampling, at the cervicovaginal level. The most widely known is the *Hybrid Capture II* ™ test, based on a hybridization technique *in situ*. A second test, using the polymerase chain reaction technique (PCR), the *HPV Amplicor* ™ has been added recently. These two tests are conducted on a pool of 13 high-risk HPV types, without distinction of the type. Their sensitivity in detecting high-grade lesions is in the order of 90% of more. Their specificity is inferior to that of cytology, but the loss of specificity is minimal when the test is done on women of 30 years of age or older, who rarely show new or transitory infections. The existence of these tests allows us to contemplate new screening algorithms.

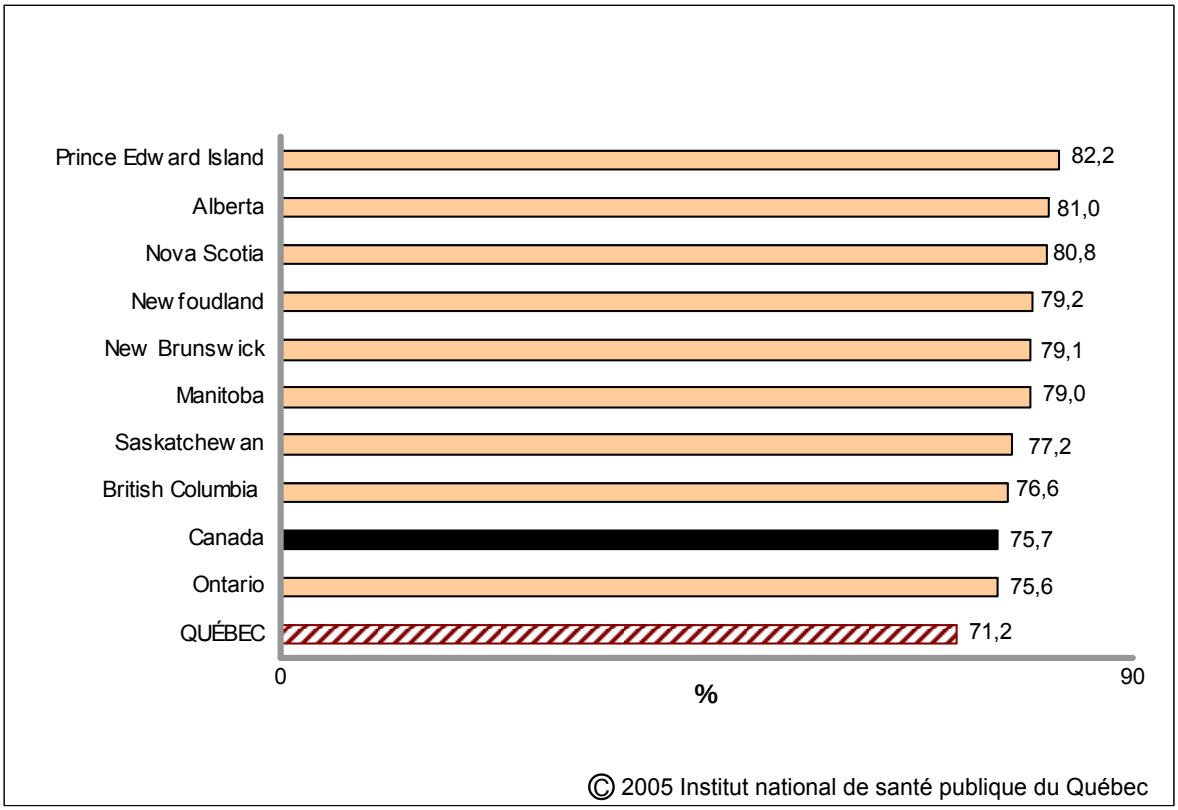
Tests allowing us to distinguish among HPV types should be available soon. These tests would let us identify women with the most high-risk types, so we could offer a more intense follow-up for such cases. Another major evolution comes from the development of molecular markers, allowing us to detect oncogenic proteins associated with the pathological process induced by the viral infection.

Screening technologies for cervical cancer are presently going through a major transformation period, where the morphological paradigm (detection of cellular abnormalities) may gradually be replaced by a viral and molecular paradigm (detection of the infection, expression of oncogenic proteins).

However, it must be noted that the main deficiency in using screening as a strategy for the fight against cervical cancer does not come solely from the performance of the test used, but mostly from the difficulty in reaching women. In Canada, older women, women living alone, women who live in socio-economically underprivileged areas, and women who live in remote areas or face socio-cultural obstacles as is the case with new immigrants, have a higher risk of being under-screened[68,69]. In general, organized approaches to screening are the ones offering the best coverage, more equity and better efficiency[70] but, in North America, screening is more often offered in an opportunist manner, by clinicians.

The following figure illustrates the proportion of women between 18 and 69 years of age in 2003 who had a Pap test in Canada in the last three years[71]. Québec now shows a lower rate of screening than the Canadian average. It is also one of the few provinces without an organized approach to screening.

Figure 3 Proportion of women 18 and 69 years old who had a Pap test within the last three years, Québec, Canadian provinces and Canada, 2003



Anal cancer shows numerous similarities with cervical cancer and screening tests similar to those which exist for cervical cancer could eventually be offered to high-risk groups for this cancer. For now, only people of both sexes infected with HIV and men having anal intercourse are targeted with this measure. There are no valid screening tests for other cancer sites.

2.1.6 Health impact of the disease on the population (clinical burden)

The health impact of infections caused by HPV is quite significant when reviewing the full spectrum of clinical manifestations. It may be shown to be even worse by the ongoing epidemiological studies allowing us to confirm and quantify the aetiological fraction of the risk, for example, contributed by the oropharyngeal cancers. This section describes more specifically the magnitude of the health burden in Québec for the most frequent manifestations.

Cervical cancer certainly ranks first, on the list of anogenital cancers linked to HPV in Québec, and the yearly number of cases is 2.4 times higher than that of all the other sites (325 vs. 140). In all, this represents 400 new cases of cancer annually and more than 100 deaths caused by HPV.

Table 6 Number of cases (adjusted for the fraction attributable to the risk associated to HPV) and number of deaths (not adjusted[b]) for anogenital cancers in Québec

	Cervix	Anus		Vulva	Vagina	Penis
		M	W			
Number of cases (1999 à 2001)	976	82	139	263	57	108
Yearly average	325	27	46	88	19	36
Fraction attributable to HPV (According to scientific literature)	**100%**	**90%**	**90%**	**40%**	**40%**	**40%**
Adjusted yearly average	325	24	41	35	8	32
		140				
Number of deaths (1999 à 2001)	239	21	13	84	29	17
Yearly average (not adjusted)	79	7	4	28	10	6

Apart from the invasive cervical cancers, we must also take into account the screening and follow-up efforts for abnormal cases. In Québec the vast majority of Pap tests are done in the public sector. There is no centralized information system allowing us to describe the clinical course of women with an abnormal result. Table 7 describes the distribution of cases according to the cytology result stemming from data of a survey done by the Association des cytologistes du Québec (ACQ) in 2005, and applied to the total volume of examinations compiled by the MSSS (not taking into account whether it is a screening test or a control test).

b. The attributable fraction of risk cannot be applied automatically in the cases of deaths, as we have no data. The prognosis of cancers linked to HPV could be better than those not linked to HPV, because the former generally respond to radiation therapy.

There are no in Québec for the follow-up of abnormal cases, but, if we apply American standards relating to referrals for colposcopy[72], i.e. all the women with AGC, LGIL or HGIL results and about half of ASC-US cases, we can estimate that about 68,000 women could be referred annually for a colposcopy follow-up and for treatment.

Table 7 Distribution of abnormal cases and estimate of the number of women referred for a colposcopy in Québec in 2005

Result*	Proportion	Number	Estimate: referred for colposcopy
Normal/benign anomaly	87.1%	1,097,889	
Unsatisfactory	1.6%	20,161	
ASC (including ASC-US and ASC-H)	4.6%	57,983	28,992
AGC	0.6%	7,563	7,563
LSIL	2.0%	25,210	25,210
HSIL	0.5%	6,302	6,302
Total		1,215,108	68,067

* According to the results of a survey done by ACQ with the cytology laboratories (n = 36).

There are no data available from Québec on the number of people treated for recurrent respiratory papillomatosis or for anogenital condylomas.

2.1.7 Social impact of the disease

Impacts on a psychosocial level are numerous. An abnormal screening result or the need to receive treatment can generate anxiety and cause significant inconvenience for the people infected, such as having to travel to a special centre to receive the care they need or to take time off from work. Some treatments are painful or cause severe mutilations, especially with invasive cancer. Anogenital condylomas can cause the same stigma as other STI: embarrassment, mistrust of the partner, worry about sexual issues, etc.

Furthermore, screening activities require a lot of resources from the health system. Unfortunately, research allowing us to document these impacts and to validate suitable indicators to measure the quality of life of people infected with a pathology caused by the HPV is still under-developed.

There are no data available in Québec to estimate the social burden associated with infections and pathologies caused by HPV, but, a pan-Canadian study including centres from Québec (PISCES study) is presently underway. It will estimate, in a prospective manner, the psychosocial effects linked to an abnormal cytology result or having anogenital condylomas.

2.1.8 Economic impact

There are no data available in Québec allowing us to estimate the economic burden for all of the conditions linked to HPV. For now, efforts focus mainly on cervical cancer.

A characteristic of this cancer is that the estimate of costs would be very incomplete without taking into account the sizeable screening efforts. American researchers have analyzed data from an HMO, and shown that, in fact, the costs for treating cervical cancer was only 10% of the total costs, where the cost for screening represented 63%, the follow-up of abnormal cases 17% and false positive results 9%[73].

In Québec, screening costs alone were estimated at $32.2M for the year 1995 during the work done to develop a Québec program for the fight against cancer. In 2007, with a cost of $13 for each screening (laboratory part only) and $65 for a first colposcopy, the minimum costs would be more than $16M for those two interventions alone, to which we must add the control tests, medical costs, treatments and indirect costs. A Canadian research project, directed by the INSPQ with partners in three other provinces and a private consulting firm will soon be launched, aimed at establishing patterns of care for a group of women having had an abnormal screening result. This project will allow us to obtain a better estimate of the screening costs, the follow-up costs of abnormal cases and the treatment costs for cervical cancer.

2.2 CHAPTER 2 – VACCINE CHARACTERISTICS

Two vaccines against the human papilloma virus were tested in phase 2 and 3 studies. They are, respectively, Gardasil™ from Merck Frosst and Cervarix™ (also known under the name Silgard™) from GlaxoSmithKline. The quadrivalent vaccine Gardasil™ containing HPV types 6, 11, 16 and 18 was approved in Canada in 2006 and the bivalent vaccine Cervarix™ containing HPV types 16 and 18 was submitted for approval in several countries in March-April 2007[74-78].

2.2.1 Nature and characteristics of the immune agent

Gardasil™ and Cervarix™ vaccines are sub-unitary vaccines that contain virus-like particles (VLP) produced by recombinant technologies. The vaccines are produced by the expression of the L1 protein gene of the virus in the yeast *Saccharomyces cerevisiae* (Gardasil™)[79] or in the cell line *Trichoplusia ni* (Cervarix™)[2].

These vaccines do not contain any living biological product or DNA, which could be infectious and could reproduce itself. The two products are prophylactic vaccines and administration is followed by the production of specific antibodies. Until now the existing vaccines have not shown any therapeutic effect on the disease or modifying effect on the persistence of the HPV infections[80-82].

2.2.2 Nature and characteristics of vaccines

Table 8 Constituents of the HPV vaccines

	Gardasil™	Cervarix™
Antigens : PPV L1	HPV 6 20µg HPV 11 40µg HPV 16 40µg HPV 18 20µg	HPV 16 20µg HPV 18 20µg
Adjuvant	Amorphous aluminum hydroxyphosphate sulphate 225µg	AS04 Aluminium hydroxide 50µg plus 20µg 3-deacylated monophosphoryl lipid A
Others	9,56 mg Sodium chloride 0.78 mg L-histidine 50 mg Polyoxyethylene (20) sorbitan mono-oleate 35 mg Sodium borate	Sodium chloride Dihydrogène phosphate Sodium dehydrated

Gardasil™ et Cervarix™ do not contain any preservative agent or antibiotic.

2.2.3 Manufacturing, production capacity and supply of the vaccine

Merck Frosst and GlaxoSmithKline are international vaccine manufacturers. These companies have been distributing their products for decades in more than 150 countries world wide. However, vaccines against HPV are new products and the relative supply and demand is still unknown. A limited number of countries have defined their vaccination programs against HPV (U.S. Australia, New Zealand, and Germany). The demand for the next months or years is unknown.

The Gardasil™ vaccine is manufactured by Merck Frosst Co. in West Point, Pennsylvania and the Cervarix™ vaccine by GlaxoSmithKline Biologicals in Rixensart, Belgium. The technologies used for the manufacturing of the two vaccines allow a rapid increase in production.

The two companies require a period of six months to satisfy a purchase order for a large public vaccination program.

The vaccine lots for Canada must be tested by Health Canada before their distribution on the market[83].

2.2.4 Administration, number of doses, association with other vaccines

Table 9 Administration of HPV vaccines

	Gardasil™	Cervarix™
Injection	0.5 ml I.M.	0.5ml I.M.
Schedule	0, 2 and 6 months	0, 1 and 6 months
Age groups/efficacy study	Women 16-26 years	Women 15-25 years
Age group/immunogenicity studies (bridging studies)	Women and men 9-15 years	Women 10-55 years; men 10-18 years (in progress)

Both vaccines must be stored in a refrigerator between 2°C and 8°C. The vaccines cannot be frozen and must be kept sheltered from the light. They must be used as they are supplied; no dilution or reconstitution is required[82,83].

The thermostability of the Gardasil™ vaccine has been evaluated as very high. The half-life of the vaccine exposed to 37°C is estimated to be 18 months and 3 months for 42°C. However, small changes in the structure of the amino acids, in the case of a rapid temperature rise, can have a significant impact on the intermolecular contacts that stabilize the L1 protein and the VLP[84] assembly. Such changes can decrease the vaccine's immunogenicity.

Association with other vaccines

There are no anti-HPV vaccines combined with other vaccines.

2.2.5 Nature and characteristics of the immune response

The immune mechanisms of protection against HPV are not well known. It is presumed that the elevated titres of neutralizing antibodies against L1 generated by the administration of repeated doses of VLP containing L1 guarantees protection against HPV. This presumption is based on data from pre-clinical experiments in animals. In these experiments, the passive transfer of the purified immunoglobulin-G originating from donors hyper-immunized with VLP L1 completely protected the unexposed animals against the challenge with the virus[85]. Only the animals vaccinated with VLPs containing intact epitopes generated neutralizing antibodies and only the purified IgG originating from the vaccinated animals protected the recipient animals.

The existing data suggests that the generation of neutralizing antibodies against L1 via VLP L1 would be effective in the prophylaxis of HVP[86] infections. The experimental studies that

demonstrated VLP L1 immunogenicity and efficacy in animal models (rabbits, dogs, cows, monkeys) strongly supports the protective role of the antibodies[81,87-90].

The population studies have demonstrated that the production of type-specific antibodies is common during and after HPV infections in humans[16,91,92]. The vaccination induces the production of neutralizing antibodies directed against the capsid's (protein coat) principle L1 protein. A recently conducted analysis on samples collected from participants in a clinical study demonstrated that vaccination induced the production of T2 cells and IgG1, IgG3 and IgA levels higher than those observed after a naturally[80] occurring infection.

The presence of antibodies on the mucous membrane is probably not a determinant for protection. In fact, only 5 to 52% of women vaccinated with VLP L1 develop mucous antibodies against the different HPV types contained in the vaccines[93], but all were protected against the high-grade lesions, for at least ten months or so. Anti-IgA antibodies were also detected in the cervical secretions after vaccination, but at a much lower level than the IgG[86].

The humoral immunity induced by the VLP L1 vaccines appears to be type-specific. However, we observe a significant homology in the L1 amino acid sequence among several types of viruses. This fact allows us to assume that there are cross-neutralizing antibodies[81, 94]. The adjuvants included in the HPV vaccines are different. The Gardasil™ vaccine contains amorphous aluminum hydroxyphosphate sulphate while the AS04 adjuvant is used in the Cervarix™ vaccine. The latter contains aluminum hydroxide and 3-deacyled monophosphoryle A lipids which enable the production of a highly elevated antibody titre[78].

2.2.6 Immunogenicity in different population groups

The vaccines that contain the VLPs are highly immunogenic in different population groups. During the clinical studies, the subjects having received the VLP L1 produced anti-VLP L1 antibody titres that were much more elevated than the titres observed after natural infections[78,95,96]. Immunogenicity is measured via a specific titre of antibodies for each type of VLP.

There are no international standards for HPV[1, 97] serology. The two vaccine manufacturers developed their own serological tests. Consequently, comparing results that come from studies with different vaccines is not possible. Furthermore, the correlation between the antibody titre and the protection against HPVs remains undefined. The manufacturers have defined the seropositivity threshold for their tests by taking into account the difference between the serum from individuals who are HPV PCR positive, and the serum from individuals who are HPV PCR negative and low-risk candidates for the HVP infection. In the studies with Gardasil™, the cRIA tests (competitive radioimmunoassay; *this test is no longer available*) and cLIA (competitive Luminex based immunoassay) were used. In the studies with Cervarix™, the ELISA test (enzyme-linked immunosorbent assay) was used.

The results obtained from the different studies conducted with the same tests after vaccination with the same vaccine are concordant for the same type of virus, but cannot be compared with different types[13,98]. However, we can measure and compare the geometric mean titre (GMT) in vaccinated persons versus GMT after a natural infection.

Immunogenicity data are available for women aged 9-26 and men aged 7-15 vaccinated with Gardasil™ and for women aged 10-55 vaccinated with Cervarix™.

One month after the third dose of the series, almost all participants (≥ 99%) in the phase II and III studies (partial data available) developed antibodies against the VLPs contained in the vaccines. The antibody titres obtained after vaccination were 10 to 100 times more elevated than the titres produced by a natural infection. The comparative studies revealed that the GMTs of the HPV antibodies in preadolescents and adolescents aged 9-14 were two times more elevated than the GMTs in women aged 15-25. In a study in which Cervarix™ was used, the GMT of anti-HPV 16 and anti-HPV 18 observed in women aged 10-14 were respectively 2, 4 and 6 times more elevated than in girls aged 15-25, 26-45 and 46-55 (Dubin G; ICAAC, 2005, Washington). In another study using Gardasil™, the anti-HPV GMTs observed in girls and boys aged 10-15 were approximately 2 times more elevated than the GMTs observed in women aged 16-23[3]. This observation was consistent in all geographic regions (Europe, Asia, Australia, South America and North America) at all times during the study.

In clinical studies, the GMTs were affected by hormonal cycles and were more elevated if the vaccine was administered during the proliferative phase and lower if it was administered during the ovulation phase[86].

In the clinical studies using Gardasil™, 58% of participants (aged 16-26) were taking oral contraceptives. The use of oral contraceptives did not affect the immune response.

In general, following the culmination of antibody formation, at one month after the third dose, we observe a significant decline until month 18, after which the titres stabilize for a period of at least 18 months. The threshold observed after vaccination with the Gardasil™ vaccine is above the titres observed in women who have had natural HPV 11 or 16 infections, and they are almost the same as the titres observed in women who have had natural HPV 6 and 18[83] infections. The anti-HPV titres 16 and 18 observed after the administration of the Cervarix™ vaccine were always well above the titres observed in women that had natural HPV 16 and 18[2,99,100] infections.

2.2.7 Short-term and long-term efficacy of vaccines

The main criteria used in the clinical trials to determine the efficacy of the vaccines were:

- the reduction of incidence of persistent infections (from 4 to 12 months, depending on the definition used) with the types of viruses targeted by the vaccines;
- the reduction of moderate and high-grade dysplasia (CIN2/3) and of *in-situ* carcinoma.

It must also be mentioned that the use of cervical cancer as a primary criterion to measure the efficacy of the anti-HPV vaccines in the clinical studies would not be ethical since the screening can prevent the majority of cancers through identification and treatment of precancerous pathologies. Furthermore, the usual interval between the infection and the development of the cancer takes more than 10 years[101,102].

The efficacy of both vaccines was studied in double-blind placebo-controlled clinical trials. Over 30,000 women participated in the clinical trials with each of the vaccines (a significant number of these women are still being followed). The populations studied were geographically spread out over several continents, including North America. The subjects identified as already being infected with a type of HPV targeted by the vaccine were not eligible for the efficacy evaluations "*per protocol"*. The evaluation of parameters began seven months after the administration of the first dose (this being one month after the completion of the series). This method enables the simulation of adolescents or adults who receive a complete series of vaccines before being exposed to the types of viruses contained in the vaccines[75,103].

In women with no evidence of prior exposure to the types of virus targeted by the vaccine, the efficacy was very high for both vaccines. A reduction of more than 90% of persistent infection (HPV DNA detected sequentially twice at 4-12 month intervals in women who were initially HPV DNA negative) and in the number of high-grade lesions caused by the HPV types targeted by the vaccine was observed for 4.5-5.5 years after vaccination[2,103-107].

In all evaluations of efficacy conducted according to protocol, the Gardasil™ vaccine was >95% effective against the development of high-grade lesions associated with HPVs 16 and 18, precancerous lesions of the vulva and the vagina and anogenital condylomas.

In general, in the trials with the Gardasil™ vaccine, 27% of women presented with evidence of prior exposure or a current infection with one or more types of HPV targeted by the vaccine. We did not observe any protective effects from the vaccine against CIN 2/3 type lesions in women who were HVP 16 or18 positive. A moderate reduction was observed in women who were HPV DNA positive, but seronegative before vaccination.[104]. The efficacy of the Gardasil™ vaccine against anogenital condylomas associated with HPVs 6 and 11 was 99%.

In the FUTURE I[108] study, the efficacy of the Gardasil™ vaccine against CINs 1-3 and *in- situ* adenocarcinoma was evaluated independently from the causal virus type. The rates per 100 person-year of CIN 1-3 and *in-situ* adenocarcinoma in this study was 4.7 among vaccinated women and 5.9 among non-vaccinated women, which translates into an efficacy of 20%. In a larger scale study, FUTURE II, the CIN 2-3 and *in-situ* adenocarcinoma rates were 1.3 among vaccinated women and 1.5 among non-vaccinated women, a reduction of 17-18%[106,109]. It appears that one of the factors that explains this low efficacy is the vaccination of women previously exposed to the types of viruses targeted by the vaccine[110]. Consequently, the authors conclude that it is preferable to administer the vaccine before subjects become sexually active[107].

Five and a half years after administration, the efficacy of Cervarix™ was 98% against incident infections and 100% against persistent infections, ASCUS, CIN1 and CIN2 related to HPV 16 and HPV 18. The efficacy of the vaccine against CIN2 independent of HPV type was 68%. The authors conclude that significant cross protection against infections with HPV 45 and 31 was observed[111]. In a recent publication[105], the efficacy of the bivalent vaccine against CIN2 containing HPV 16 and 18 DNA was 90.4%. It is important to mention that in

all cases of CIN2 observed in vaccinated women, the DNA of other oncogenic viruses was also detected.

We do not have data available regarding the efficacy of the vaccines against HPVs for longer periods of time. However, the clinical trial results demonstrate that antibodies remain detectable in the majority of vaccinated women for at least 54-60 months. This finding is encouraging because long-term protection has been demonstrated in pre-clinical studies despite the low levels of antibodies[85,112].

In the clinical trials, the efficacy of the vaccines against HPVs, defined as the absence of clinical infection due to immunity, was demonstrated over a period of two-five years[2,104-106].

The role of the natural exposure (natural booster) in long-term protection was not demonstrated in the clinical trials. However, the fact that 50% of women remain seropositive 10 years after a natural infection (after the last detection of HPV DNA) suggests a possible protective effect of the natural boosters[81].

The GMTs observed after vaccination of seropositive women for the types targeted by the vaccine before immunization were significantly higher than in naive women[3]. This suggests the presence of a type-specific anamnestic response.

The persistency of antibodies after vaccination was estimated by using two mathematical models. The antibody titre kinetics against HPV 16 observed over a period of 48 months was used in a conventional model. The second model was modified to take immunologic memory into consideration. It was estimated that after the administration of three doses of the vaccine given to women aged 16-23, the level of antibodies remains above the titres observed after a natural infection over a period of 12 years and at a detectable level over 32 years in 50% of vaccinated women. With the modified model, the authors estimate that 76% of vaccinated women will have a titre higher than the one associated with the reduction of HPV 16 infections and more than 99% will retain a detectable level of antibodies throughout their entire lives[113].

Long-term follow-up studies are currently in progress in Scandinavian countries to evaluate the long-term safety, efficacy and immunogenicity of Gardasil™.

In the mathematical modelling, the duration of post-vaccine protection is highlighted as a very important factor in the cumulative reduction of cases of cervical cancer[76,114]. The vaccination of girls aged 12 years can prevent 61% of cervical cancers if the protection is for life and only 6% if the protection is for 30 years. The second scenario could be improved if booster doses are administered[114,115].

2.2.8 Effect of vaccines on transmission of pathogenic organisms

There is no field experience (post-marketing studies) regarding the effect of the vaccination on the transmission of HPVs.

The results from the clinical trials using Cervarix™ demonstrated an efficacy of over 80% against infections with HPVs 16 and 18 in women who had received at least one dose of the vaccine.

Over a period of 4-5 years, efficacy against persistent infections after the administration of Gardasil™ or Cervarix™ was over 92% in women who received at least one dose of the vaccine[2,104]. With such a decrease in the incidence and persistence of the HPVs targeted by the vaccines, we can expect, over the long run, a significant decrease in the transmission and circulation of these types of viruses. However, due to the fact that HPV infections are very common among the general population (over 70% of the population being infected at least once in a lifetime) and the fact that the proportion of vaccinated among sexually active individuals will more than likely be low, on a medium-term basis, we can not expect a significant reduction in the transmission of HPVs in the general population.

The results from the FUTURE II study demonstrate that a significant proportion of CIN 2, CIN 3 and in-situ adenocarcinoma are caused by HPVs that are not targeted by the vaccine. In this study, we observed a threshold in the incidence of illnesses caused by HPV 16 and 18 among vaccinated women. However, the incidence of the same illnesses caused by virus types not included in the vaccine kept increasing. This observation demonstrates the possibility of replacing HPVs 16 and 18 by other carcinogenic types of HPV [110].

The mathematical modelling demonstrated that in a heterosexual population, the transmission of HPVs can be completely stopped by protecting just one sex[116]. The simulations in the dynamic models show that, if a high vaccination coverage is obtained among women, the vaccination of men brings very little additional benefit to the reduction of numbers in cervical cancer[117]. However, if the anogenital condylomas are taken into account, the arguments above lose their significance[80,81].

2.2.9 Short-term and long-term effectiveness in the population

The immune response in men and women is similar, but the protection of men by vaccination is unknown[77].

However, even if many questions don't have clear answers, it is possible to make estimates by assuming a given effectiveness of the vaccine. For example, if we assume that the immunization is 90% effective against the types of virus targeted by the vaccines, (with or without booster doses to assure long-term protection) the major impact in developed countries would be the reduction of 50 to 60% of CIN2/3 incidence among vaccinated women compared to unvaccinated women, given that the HPVs 16 and 18 account for 60-70% of all CIN2/3 lesions. This protection will considerably reduce negative medical and psychological consequences for women as well as the need for treatment and the costs related to those treatments. We anticipate that the effect of the vaccine on the incidence of cervical cancers will be at least as significant as on the CIN2/3s. If the vaccines are widely administered, including to women who are or will be irregularly screened, the positive impact of the vaccination could be even greater[77].

The phase 3 clinical trials and the population studies in progress should answer more clearly the questions regarding the effectiveness of the vaccines against HPVs on a short and long-term basis[118,119].

2.2.10 Safety of the vaccines

In the clinical trials, the VLP L1 vaccines proved to be safe and well tolerated, although we do not have long-term data available[1,120-122]. The most common side effect after vaccination with the Gardasil™ and Cervarix™ vaccines is a local reaction at the injection site, with the majority of subjects from the vaccinated group (71-93%) and placebo (73-87%) reporting localized pain. Erythema at the site of injection is the reaction most often associated with the vaccine (34-36% vs. 21-24% in the placebo group). In general, the number of localized reactions after the administration of Gardasil™ or Cervarix™ was 6-8% higher than in the placebo group.

The systemic side effect most often reported is headache (38-62% vs. 33-61% in the placebo group). In general, the frequency of systemic reactions in the experimental groups and placebo groups were the same.

The proportion of vaccinated individuals that reported a localized or general reaction after the first dose of the vaccine was slightly higher than that observed after the second and third doses throughout various age groups. A smaller proportion of girls and boys aged 10-15 than women aged 16-23 reported local reactions after the administration of the vaccine. However, the women aged 16-23 reported less often fever of ≥ 37.8°C[3].

Vaccination against HPVs and pregnancy: The Gardasil™ vaccine is not recommended during pregnancy. Despite the fact that no causal relationship has been determined between the vaccine and pregnancy or adverse effects on the developing foetus, the data regarding the vaccination during pregnancy are limited. If a woman becomes pregnant after the start of vaccination, any remaining vaccine doses should be delayed until after the pregnancy. If one or more doses have been administered during pregnancy, there are no indications that any type of intervention is needed[83,123].

Contraindications: Vaccines against HPVs are contraindicated in patients who have demonstrated hypersensitivity to one or more of the vaccine's components.

2.2.11 Possible interaction with other vaccines

In general, the recombinant vaccines do not interact or interact very little with other vaccines[124-127].

The available data regarding the combined administration of anti-HPV vaccines and other vaccines remain limited. It has been shown that the concomitant administration (at different injection sites) of three doses of anti-HPV and Hepatitis B vaccines (recombinant) does not diminish either the seroconversion, the seroprotection or the GMTs for either of the two vaccines[83]. The frequency of undesirable side effects observed was similar during the co-administration of the two vaccines and during the administration of the Gardasil™ vaccine

alone. Studies are planned to assess the concomitant administration of Gardasil™, the conjugate vaccine against meningococcus and acellular pertussis vaccine. Three other studies are in progress with Cervarix™ and Boostrix, Boostrix-IPV, and Menactra.

2.2.12 Conclusions of chapter 2

The two vaccines, Gardasil™ and Cervarix™, are effective and safe, at least on a short-term basis. Both vaccines protect against oncogenic types HPV 16 and 18 that are responsible for approximately 70% of cases of cervical cancer. Gardasil™ also protects against HPV 6 and 11 which are responsible for approximately 90% of condyloma cases. However, in clinical trials, Cervarix™ demonstrated a somewhat stronger immune response (after 5 years of monitoring) and partial cross protection against three oncogenic HPV types responsible for an additional 7-10% of cervical cancers. The studies in progress will allow identification of any significant clinical differences between the two vaccines.

Studies on the duration of protection, the efficacy of the vaccination in different population groups, the efficacy of various vaccination schedules and the impact of the vaccination on screening as well as on the transmission of HPVs are needed.

2.3 CHAPTER 3 – STRATEGIES AND IMMUNIZATION PROGRAM

2.3.1 Existing recommendations for the use of the vaccine

In Canada, the National Committee on Immunization (NACI) has published its statement regarding the use of the Gardasil[83] vaccine. NACI recommends the vaccine for all women aged 9 to 26. They specify that women aged 14 to 26 may have been infected by any of the virus types contained in the vaccine, which would diminish the benefits of the vaccination. They could nevertheless benefit from the vaccination since it is highly unlikely that they have been infected by all the types of viruses contained in the vaccine. This is true for women who have cervical lesions associated to HPVs. Vaccination of men and women over the age of 26 is not recommended due to the lack of data on the efficacy of the vaccine. Studies are in progress.

In the United States, the *Advisory Committee on Immunization Practices* (ACIP) recommends that the vaccination be routine for girls aged 11-12 years with the possibility of starting as young as 9 years of age. They also recommend the catch-up vaccination for all women aged 13-26.

The Canadian Immunization Committee (CIC) plans on filing its recommendations in December 2007.

2.3.2 Objectives of immunization

The objective proposed for the HPV immunisation program in Canada is the reduction of incidence and mortality from cervical cancer. Reaching this goal will take several years.

It is impossible to foresee eliminating the illness completely with the current vaccines.

Other possible objectives would be the reduction of incidence and mortality from other cancers caused by HPV.

It is also possible to foresee, as an objective, diminishing the incidence of diseases caused by low-risk HPV types, mainly condylomas.

2.3.3 Different strategies and potential vaccination programs to reduce the incidence of cervical cancer

The vaccine has been available for purchase with prescription since its approval. Here we are interested in the strategies of a publicly funded immunization program.

We can consider the following options:

- Only at-risk groups;
- 1 age cohort;
- 2 or more cohorts;
- All women for whom the vaccine is recommended (9 to 26 years).

The option of vaccinating all at-risk groups free of charge was not considered for several reasons, the main one being that at a population level, the effectiveness of this strategy is probably limited. The pros and cons of the other options are summarized in Table 10.

Table 10 Expected effects of different vaccination strategies

Criteria	1 cohort	2 + cohorts	9-26 years
Efficacy	+	++	+++
Delay	+++	++	+
Cost	+	++	+++
Feasibility	+++	++	+
Fairness	-	+	+++

- minimum, +++ maximum

2.3.4 Implementation modalities

Implementation of an HPV vaccination program raises several difficulties for public health. Only the school-based Hepatitis B vaccination program of preadolescents is comparable.

2.3.4.1 School-based vaccination program

It is possible to vaccinate one or more cohorts in the school environment. It would be relatively simple for the cohort vaccinated against Hepatitis B to be immunized, since this vaccination program is already in place and is given in 3 doses. It is conducted during the 4th grade of elementary school in Québec, when the children are aged 9-10 years.

We could also consider combining HPV vaccination with DCaT booster vaccination which is administered in Secondary 3, when the children are approximately 14 years of age. Only one routine visit is made at this time. Sometimes a second visit is conducted for catch-up vaccinations that have been previously omitted. HPV vaccination would thus require at least one, but in most cases, two additional visits to the one already being conducted. The pilot project conducted before the implementation of Hepatitis B vaccination had highlighted the additional difficulties associated with vaccination in high school[128], which led to the decision to offer the vaccination against Hepatitis B in elementary school. Another difficulty with this option is that some youths have already left school before Secondary 3.

2.3.4.2 Absence of a vaccination system for adolescents and adults

The vaccine is recommended for several age groups, up to the age of 26 and possibly higher in the future. These are adolescents and young adults who don't regularly receive vaccinations, who rarely consult the health system and who often do not have their own assigned doctor. The majority have left the school system. This is also a clientele whose financial means are limited when it comes to purchasing the vaccine and paying for its administration.

In Québec, there is not an organized vaccination system, comparable to what is in place for children, that would take into account the specific needs of an adult clientele.

Vaccination against influenza is seasonal and is mainly geared towards the elderly or workers vaccinated at work. It requires, in most cases, only one dose and can easily be administered in the setting of an annual follow-up visit. HPV vaccination requires 3 doses and is not normally given during a medical visit or in a work environment.

No study has described the organization of adults' vaccination or documented the modalities that would facilitate it. The need to maintain the cold chain adds an element of complexity for vaccines purchased at the pharmacy. Generally, the CLSCs refuse to administer a vaccine without being certain of its biological integrity. Doctors are not paid specifically for the vaccination alone. There are no vaccination clinics other than traveller's clinics who are only interested in the clientele of travellers.

2.3.5 Objectives of the program, in terms of reducing the pathologies caused by HPV

This issue will be discussed in chapter 4.3 with the modelling that has been used to predict the impact of a possible HPV vaccination program.

2.3.6 Operational objectives

Objectives of vaccine coverage will vary depending on the vaccination strategy. The school-based Hepatitis B vaccination program attains a coverage rate of 90% for three doses, varying slightly depending on the region. For DCaT given in high school, vaccination coverage data are incomplete and vary between 70 and 90%. The vaccination coverage of adolescents and adults outside of the school environment will clearly be lower. It will definitely be determined by the usual parameters of access to vaccination (cost, opening hours, wait times, etc.) and vaccination promotion (see chapters 5 and 6 on acceptability and feasibility of the HPV vaccination).

2.4 CHAPTER 4 – COST EFFECTIVENESS OF A VACCINATION PROGRAM AGAINST HPV

2.4.1 Cost of the vaccine

The quadrivalent Gardasil vaccine by Merck Frosst is sold for $135 for one dose or $405 for a complete vaccination series. This amount is usually increased by a variable percentage during its sale at the pharmacy or clinic.

A bivalent vaccine manufactured by GlaxoSmithKline has not yet been approved in Canada. In Australia, the cost for three doses of Cervarix is $362 USD. We do not know what price will be fixed by the Canadian manufacturer.

2.4.2 Ultimate cost of the program

The cost of a possible program will depend on the number of vaccine doses distributed and administrative costs.

The number of youth per age cohort in schools varies from one year to the next. At the current rate, school-based vaccination for one age cohort of girls, approximately 40,000 girls, would cost approximately $16M. This amount would be decreased by those girls who would refuse the vaccination and those who have already left school. We would need to add the administrative cost, which will greatly vary, depending on whether or not we use already scheduled vaccination visits or introduce new visits. The total cost for the purchase of vaccines in Québec for 2007 would be approximately $45M.

The federal government has promised, in its latest budget, financing of $300M for the purchase of HPV vaccines. This would translate into approximately $75M for Québec or the equivalent of four cohorts of young girls.

2.4.3 Effectiveness of the program in terms of reduction of the disease

The estimate of the impact on the disease from a possible HPV vaccination program is substantially more complex than vaccination against childhood diseases. This is due to several factors: the multiplicity of morbid manifestations, the long latency period between infection and cancer, the unknowns regarding the disease's natural history and in terms of replacement of HPV types following vaccination, the assumptions surrounding the vaccine itself and notably the duration of protection, the existence of cervical cancer screening activities and their future evolution.

One additional issue pertains to the large number of clinical manifestations of interest. The modelisation can be based on persistent infections (prevalence), low and high-grade lesions (CIN1 and CIN2-3) or the two types of cervical cancer. The modelisation can also have as the main objective condylomas and other HPV-associated cancers.

Mathematical modelling is currently the only way of predicting the impacts of a vaccination program in relation to different implementation strategies and different unknowns regarding natural history, vaccine efficacy and vaccination coverage. There are two major types of modeling: the cohort models and the dynamic models. The dynamic models are more complex because they consider infection transmission probability between individuals. This allows them to document the impact of herd immunity.

Several models have been published to date, especially in the United States and in Scandinavian countries[116,117,129-134]. Work is in progress in Canada[135,115,136] and articles are submitted for publication from teams in British Columbia and Québec. The available data will therefore evolve rapidly following these studies and, afterwards, as other observational data on the disease or on the impact of the vaccination become available.

- Importance of the main unknown factors:
  - Duration of protection of the vaccine: clinical trials have demonstrated, to date, that the vaccination's protection persists up to five years after vaccination. We must therefore consider scenarios in which the duration of protection will vary between 10 years and an entire lifetime. Short duration of protection could simply mean delaying the acquisition of the infection and the subsequent occurrence of cancer;
  - Duration of protection conferred by the disease and the time of infection acquisition that will eventually lead to cancer. Because of a highly variable delay between the infection and the cancer, we are currently unaware of whether or not the cancers are all caused by infections contracted in the first years of sexually active life, resulting in the occurrence of cancer spread out in the different age groups. The other hypothesis is that the interval between the infection and the cancer is comparatively constant and that cancers in older women are therefore caused by infections that occurred later in life. The duration of protection conferred by the vaccine will have a much greater impact if the first hypothesis is correct;
  - Replacement of HPV types targeted by the vaccine with other high-risk types: in the hypothesis in which the decrease in infections caused by the types targeted by the

vaccine facilitated the increase of other types, we could see a gradual reduction of positive impacts from the vaccination;

- The rate of vaccination coverage: according to the vaccination coverage rates attained, herd immunity will be more or less significant and the vaccination program's impact will be altered accordingly.

Brisson and collaborators have recently published on the impact of these uncertainties[115]. They use a cohort model and available Canadian data, in the context of cervical cancer screening in Canada. Their basic model assumes the vaccination of all 12 year-old girls with a quadrivalent vaccine at 95% efficacy and a lifelong duration. Such a program would result in a decrease of 61% of cervical cancer in this cohort. However, if the duration of protection of the vaccine is 30 years and no booster is administered, the decrease in cancers will only be 6%. The basic model predicts a decrease of 21% in infections, 24% for the CIN1 and 49% for the CIN2/3. Their model also allowed them to estimate that among 12 year-old girls, the number needed to vaccinate to prevent an episode of genital warts would be 8, and to prevent a case of cervical cancer, 324[136].

The table below demonstrates certain published results based on mathematical models.

Table 11 Impact of vaccination against HPV on the disease, on the basis of the different vaccine characteristics[c]

Assumptions	Sanders *et al.* 2003	Kulasingam *et al*. 2003	Goldie *et al*. 2004	Brisson *et al*. 2007	Taira *et al.* 2004	Elbasha *et al.* 2007	Marra *et al.* 2007
Model	Cohort	Cohort	Cohort	Cohort	Hybrid (cohort and dynamic)	Dynamic	Dynamic
Vaccine target HPV types	13 types of high risk HPVs	70% of high-risk type HPVs	HPV 16/18	HPV 16/18 HPV 6/11/16/18	HPV 16/18	HPV 6/11/16/18	HPV 16/18
Vaccination age group	Girls aged 12 years	Girls aged 12 years	Girls aged 12 years	Girls aged 12 years	Girls aged 12 years ± boys	Girls aged 12 years ± boys	Girls aged 11 years and 14 years
Vaccination coverage	70%	100%	100%	100%	70%	70% (linear for the first 5 years)	F11: 85% F14: 80%
Vaccination efficacy	75%	90%	90%	95%	90%	90%	100%
Duration of protection	10 years	10 years	Permanent	Permanent	10 years	Permanent	Permanent
Booster administration	Every 10 years	None	None	None	At the age of 22	None	None
Vaccine cost (3 doses administration)	$300 (2001 US$)	$200 (2001 US$)	$377 (2002 US$)	$400	$300 (2001 US$)	$360 (2005 US$)	$400
Booster cost	$100 (2001 US$)	–	–	–	$100 (2001 US$)	–	–
Reduction in cervical cancer cases	20% (21% mortality reduction)	15%	60%	62%	62% ♀ 64% ♀&♂	78% ♀ 91% ♀&♂	41% ♀F14
Reduction in precancer lesions **CIN 1** **CIN 2/3**	 ---- 21%	 ---- ----	 ---- ----	 24% 47%	 ---- ----	 ---- ----	 ---- ----
Reduction in HPV infections	13%	----	----	----	95% ♀ 99% ♀&♂	----	75% ♀F14
Reduction in condyloma cases	----	----	----	86%	----	83% ♀ 97% ♀&♂	----

c. Fawziah Marra, Pharm.D, University of British Columbia, BC Centre for Disease control, *Cost-effectiveness of the Human Papillomavirus Vaccine*, Personal communication.

Overall, the models predict 15 to 78% reduction in the risk of cancer for women vaccinated at the age of 12. The dynamic models produce more favourable estimates. The decrease in cancer rates occurs more rapidly with the introduction of a booster for women of a more advanced age.

Vaccinating girls at the age of 9 rather than 12 would produce the following impacts:

- A delay of 3 years for the appearance of clinical impacts. This delay only has a moderate influence on the incidence of cancer that is nonetheless much delayed;
- The duration of vaccine protection has a major impact. If protection lasts a lifetime, there is no impact. If it last only for 10 years, the girls gradually become more vulnerable once again at the age of maximum prevalence of the infection and the health benefit will have been very modest.

In addition to its impact on HPV-associated diseases, the vaccination program will have significant repercussions on cervical cancer screening activities. Besides the reduction of low and high-grade cases caused by HPV types included in the vaccines, it is possible to modify the algorithms currently used for monitoring positive cases during screening, re-evaluating the selection of tests and the follow-up procedures.

2.4.4 Economic and social benefits

The economic benefit for Québec from the reductions addressed in 2.4.3 is difficult to measure for several reasons. We currently do not have the cost of treating the diseases (cervical cancer, benign lesions). We also do not have the cost of screening activities. This cost can vary significantly between areas due to variations of the screening modalities. Québec, having an opportunistic approach to screening, doesn't have a screening registry or other information sources regarding the overall screening activities; we are thus unaware of the global cost. We are also not aware to what degree the recommendations from different professional associations are respected by clinicians. Once the results from the Pan-Canadian research project (described in section 1.1.8) are made available, the economic and social benefits of the vaccination will be able to be more accurately evaluated.

In United States, the direct cost of prevention and treatment of HPV-related diseases has been estimated to be $4 billion, with $200M for the treatment of condylomas and $400M for cervical cancer. The remainder, 85% of the total, is used for screening and following up abnormal Pap tests[82]. The cost of other HPV-related diseases is not known.

2.4.5 Other associated benefits

Introduction of HPV vaccination could be an opportunity to determine modalities for organizing cervical cancer screening activities in Québec. This could possibly increase its efficiency.

Several models have been developed to estimate the cost per year gained and by QALY by assuming different vaccination strategies.

As opposed to current screening practices, the cost per year gained for vaccination of girls aged 12 with a bivalent HPV vaccine was estimated between $32,000 and $93,000 in the studies using a cohort model[114,116,130,132] while the cost per QALY varied from $23,000 to $31,000. The dynamic models[129,134,135] demonstrated an inferior cost-effectiveness ratio, from $15,000 to $25,000 for a girls-only program. The cost per QALY varied between $3,000 and $37,000 depending on the model used, the duration of protection of the vaccine and other assumptions[114,134].

This is a threshold that can be considered as acceptable for a health intervention. The cost per QALY gradually increases after the age of 14 dependent on the proportion of girls having been infected by any of the types targeted by the vaccine.

HPV vaccination of girls and boys has been estimated at $170,000-$400,000[135,129] per QALY.

2.5 CHAPTER 5 – ACCEPTABILITY OF A POSSIBLE IMMUNIZATION PROGRAM AGAINST HPV

2.5.1 Public perception of the risks, the severity and the need to control HPV

Several studies have described the negative psychological consequences arising from abnormal test results of cervical cancer screening[137-140]. Others have documented social, psychological and sexual difficulties experienced by the women who receive a diagnosis of HPV infection[140-144]. However, common findings across the studies reveal a poor level of knowledge about HPV in studied populations[145-154], notably regarding its prevalence and its link with cervical cancer.

Despite this lack of knowledge, there is significant public interest in HPV vaccines. The intention to be vaccinated against HPV is high in female adolescents and young women[150,151,155-163] and there is also support for the vaccine among parents of adolescents daughters[146,147,153,155,158,159,161,163-168] and in general population[148]. For example, the results from a survey conducted in the United States indicated that 44 of the 52 women surveyed, aged between 18 and 30, would be ¨extremely¨ or ¨very¨ interested in receiving the vaccine against HPV[157]. One study indicated that 68% of 60 women aged between 15 and 28 stated that they were extremely or somewhat inclined to pay for the vaccine against HPV, even if this vaccine was not covered by their insurance[150]. Studies on parental attitudes illustrated that 81% of parents of 7 year-old children would agree to have their children vaccinated[152] and that 67% of women having a daughter would give their consent to have their children vaccinated against HPVs[159].

Several factors influenced attitudes about HPV vaccination, mainly:

- HPV vaccine endorsement by health professionals[146,147,151,156,158,164];
- Social support[152,157,166,168];
- Belief in the vaccine's safety and efficacy[148,149,152,155,156,158,166];
- Perceived risk and severity of the disease[148,149, 152,155,156,158,166,168];
- Positive attitude towards vaccination in general[153,157,159,164,165];
- Low cost of the vaccines[157];
- For parents, having a preadolescent or adolescent daughter[146,152,165].

Many researchers had concerns about parental attitudes and beliefs towards sexually transmitted infection (STI) vaccines. However, published data does not show clear evidence that the sexual transmissibility of HPV is a significant obstacle to vaccine acceptance[149,153,167,169]. The socio-demographic characteristics, such as race, sex, income and religious belief were not associated with the acceptability of the vaccination either[152,153,159,161,164,166,167,169].

Finally, there is no clear evidence regarding the impact of the level of knowledge about HPV on vaccine acceptance. Some studies have indicated that educational interventions could increase the acceptability of the HPV vaccination[148,161], especially in those who are undecided[164], while others believed that the knowledge level surrounding HPV was not related to the acceptability of the vaccines[146,166].

Data from Québec

The results of published studies are comparable to the only currently available Québec population data. During winter 2006, in Capitale-Nationale area, a telephone survey assessed knowledge, attitudes and practices related to the HPV vaccination from 471 respondents aged between 18 and 69 (317 women and 154 men). From this number, only 15% had heard of HPV before the survey. Regardless, 91% of participants aged between 18 and 25 would agree to be vaccination against HPVs. However, only 72% would still want it if they had to bear the cost. Furthermore, 89% of respondents were in favour of men receiving the HPV vaccine if the vaccination would protect women against cervical cancer. As documented in the literature, the recommendation by a doctor to take the vaccine was the main factor associated with the acceptability of the vaccine. The requirement of having to pay for the vaccine was the main obstacle, especially for the younger participants (18-25 years). The majority of participants (72%) were in favour of the vaccine being administered to adolescents before the onset of sexual activity. Lastly, 85% would recommend the HPV vaccine to their daughter or niece.

2.5.2 Demand for and acceptability of HPV immunization program among health professionals

Studies conducted before 2004 with American paediatricians[170], general practitioners[171], obstetrician-gynecologists[172] and nurses[173] reported low levels of knowledge about HPV. However, existing data on the acceptance of HPV vaccine among health professionals suggest that the majority of healthcare providers are willing to recommend the vaccine[170-173].

The endorsement of HPV vaccines by professional organizations and advisory committees[170-173], the safety of the vaccines and long-lasting immunity[170-172], higher HPV knowledge[170,171] as well as fewer perceived barriers to vaccination[170, 171] were associated with health professional's intention to recommend HPV vaccine.

Empirical studies also suggested that health professionals will be more likely to recommend the HPV vaccine to girls than boys[170,171] and to older adolescents rather than younger ones[170-173]. The apprehension health professionals felt towards discussing sexuality with their patients[170,171,173] and the fears related to negative reactions from parents[170, 171] represented the main barriers to the intention to recommend the HPV vaccines.

Data from Québec*:*

In a large-scale study conducted with health professionals from four Canadian provinces in spring 2006[d], a questionnaire was completed by 264 obstetrician-gynaecologists, 338 paediatricians and 160 general practitioners from Québec. Results indicated a low level of knowledge surrounding HPV: the obstetricians-gynaecologists obtained a medium score of 5.8 out of 9 while the scores of the paediatricians and general practitioners were 3.3 and 4.0 respectively. Despite these findings, over 90% of respondents would recommend the HPV vaccines depending on the type of financing, vaccination schedule and vaccine characteristics.

d. Duval B., Dobson S., Gemmill I., McNeil S., *et al*., 2006. Health Professionals Survey: Knowledge, Attitudes, and Practices about HPV Vaccines Use and Their Potential Impact on Cervical Cancer Screening Interventions. Institut national de santé publique du Québec, University of British Columbia, Kingston, Frontenac and Lennox & Addington Public Health, Canadian center for vaccinology, Unité de recherche en santé publique – CHUQ, Direction régionale de santé publique de la Capitale-Nationale, Québec. Submitted for publication.

Table 12 Proportion of Québec clinicians intending to recommend HPV vaccine to their patients

	Obstetricians-gynaecologists	Paediatricians	General practitioners
I would recommend the HPV vaccine to my patients if it is publicly funded			
Somewhat agree	24%	23%	29%
Completely agree	61%	63%	54%
Total	85%	86%	83%
I would recommend the vaccines even if the patients had to pay for it (estimated cost: $100 per dose x 3 doses)			
Somewhat agree	40%	48%	54%
Completely agree	39%	35%	25%
Total	79%	85%	79%
I would recommend the HPV vaccines if they were administered in 2 doses			
Somewhat agree	47%	51%	56%
Completely agree	41%	40%	29%
Total	88%	91%	85%
I would recommend the HPV vaccines if they were administered in 3 doses			
Somewhat agree	40%	44%	44%
Completely agree	35%	31%	20%
Total	75%	75%	64%
I would recommend the HPV vaccines if they protect against both cervical cancer and condylomas			
Somewhat agree	33%	37%	35%
Completely agree	60%	57%	55%
Total	93%	94%	90%
I would recommend the HPV vaccines if they protect (only) against cervical cancer			
Somewhat agree	39%	39%	50%
Completely agree	39%	46%	30%
Total	78%	85%	80%

Over 92% of obstetricians-gynaecologists, paediatricians and general practitioners believed that the HPV vaccines should be given prior to onset of sexual activity and between 69% and 80%, before the age of 14. Only between 5 and 25% of participants felt they had received sufficient information regarding HPV vaccines.

Table 13 illustrates the opinion of Québec clinicians regarding the impact of HPV vaccination on cervical cancer screening.

Table 13 Opinion of Québec clinicians on screening and vaccination

	Obstetricians-gynaecologists	Paediatricians	General practitioners
The HPV vaccination will allow screening to begin later in life			
Somewhat agree	26%	22%	17%
Completely agree	5%	5%	6%
Total	31%	27%	23%
The HPV vaccination will allow reducing the frequency of screening interventions in vaccinated women			
Somewhat agree	51%	42%	47%
Completely agree	17%	7%	9%
Total	68%	49%	56%
The HPV vaccination will allow reducing the number of post-screening interventions			
Somewhat agree	49%	49%	49%
Completely agree	32%	21%	23%
Total	81%	70%	72%

In the spring of 2006, a similar survey was conducted with public health professionals (PHPs) in 18 Québec regions before and after an information workshop on HPV infection, screening and vaccination[e]. This study indicated that the knowledge of professionals was insufficient, but that significant improvements could be achieved after a brief training workshop. For example, before the training workshop, 47% of respondents agreed with the fact that HPV is an essential cause of cervical cancer versus 87% after the training workshop; 30% versus 85% that condylomas do not lead to cervical cancer and 47% versus 98% that HPV 16 and 18 are responsible for more than 60% of cervical cancer cases. Most of the Québec PHPs support universal HPV immunization of girls before sexual debut (91% pre- and 100% post-workshop) and almost all thought that it will be well accepted by the public and by vaccinators. PHPs believed that the majority of clinicians would recommend HPV vaccination if vaccines are publicly funded. The majority of PHPs would recommend HPV vaccine if it reduces by at least 50% the number of abnormal Pap tests, screening related interventions, and cervical cancer cases.

e. Duval B., Gilca V., Sauvageau C., Lavoie F., Goggin P., Steben M., 2006. Impact of one day workshop on public health professional's knowledge, attitudes and beliefs on HPV infection, screening and vaccination. Data presented at the *Journées annuelles de santé publique* 2006.

2.5.3 Priority of approval for immunization programs when compared with other programs

Data from Québec

One of the objectives of the survey conducted with Québec public health professionals in 2006 was to assess the professional's perceptions regarding the usefulness of seven new vaccines[f]. On a scale of 1 (strongly disagree) to 4 (strongly agree), the participants were invited to express their information needs and their position regarding the usefulness of the seven following new vaccines: MMRV, DTPa-IPV-HBV-Hib heptavalent vaccine, HPV, Hepatitis A (HAV), conjugated meningococcus ACYW-135, herpes-zoster and rotavirus. Overall, the vaccines against HPVs were classified as the most appropriate by the public health professionals for a universal immunization program and among the four safest and most effective vaccines. The professionals also believed that vaccines against HPVs would be accepted by vaccinators and the public. Table 14 presents the perceptions of participants before and after the information workshop.

f. Gilca V., Duval B., Sauvageau C., Lavoie F., Goggin P., Steben M., 2006. Québec public health professionals' perception of the usefulness of new vaccines for a universal immunization program: pre- and post-workshop result. Submitted for publication.

Table 14 Percentage of public health professionals in agreement with various assertions about HPV and HPV vaccine

	Before training N=34 **In agreement[g]**	After training N=41 **In agreement[g]**
This vaccine should be included in a universal immunization program		
HPV	100%	97.6%
MMRV	100%	97.4%
DTaP-IPV-HBV-Hib	100%	89.7%
Hepatitis A (HAV)	82.4%	89.5%
Herpes-zoster	63.6%	82.9%
Meningococcus ACYW-135	84.4%	65.8%
Rotavirus	54.6%	39.0%
This vaccine is safe		
Hepatitis A (HAV)	82.4%	97.5%
MMRV	61.8%	100%
DTaP-IPV-HBV-Hib	67.6%	97.6%
HPV	47.1%	100%
Meningococcus ACYW-135	73.5%	95.0%
Herpes-zoster	38.2%	92.7%
Rotavirus	29.4%	78.1%
This vaccine is effective		
MMRV	76.5%	100%
Hepatitis A (HAV)	85.3%	97.5%
DTaP-IPV-HBV-Hib	76.5%	97.6%
HPV	55.9%	100%
Meningococcus ACYW-135	70.6%	95.0%
Herpes-zoster	32.4%	92.7%
Rotavirus	26.5%	85.4%
This vaccine will be accepted by the public		
MMRV	100%	100%
DTaP-IPV-HBV-Hib	100%	97.5%
Hepatitis A (HAV)	91.2%	94.9%
HPV	87.9%	100%
Meningococcus ACYW-135	91.2%	85.4%
Herpes-zoster	63.6%	87.8%
Rotavirus	59.4%	53.7%
This vaccine will be accepted by vaccinators		
MMRV	100%	100%
DTaP-IPV-HBV-Hib	100%	100%
Hepatitis A (HAV)	94.1%	89.7%
HPV	84.9%	100%
Meningococcus ACYW-135	94.1%	82.9%
Herpes-zoster	60.6%	85.0%
Rotavirus	53.1%	51.2%

g. The “completely in agreement” and “somewhat in agreement” responses are grouped together.

2.6 CHAPTER 6 – FEASIBILITY OF IMPLEMENTING AN HPV IMMUNIZATION PROGRAM

2.6.1 Impacts on immunization programs and health care sectors

HPV vaccines are not publicly funded yet, and individuals have to purchase the vaccine and find a place to get vaccinated.

School based HPV immunization programs could be combined with hepatitis B (HBV) vaccination or with the DTaP. In those instances, two injections in the same visit would be administered. This situation could create negative consequences on acceptability and feasibility of HPV vaccination. However, a vaccination within the school environment allows reaching significant coverage at a lower cost[174].

An HPV immunization program will decrease the number of cervical cancer cases, but will not eradicate the disease. Cervical cancer screening will have to be maintained for several reasons. Immunization with existing vaccines will not protect against all types of high-risk HPV[83,175] and will not treat prevalent HPV infections[83].

Appropriate health-care messages should follow the introduction of HPV vaccination to ensure that women will continue to be screened for cervical cancer. Vaccination and screening must remain complementary in the prevention of cervical cancer[176]. A false sense of security in women could lead to negative consequences in the prevention of cervical cancer.

The implementation of HPV vaccination could have a positive impact on the health care sector. Cervical cancer screening interventions could be modified due to HPV vaccination, for example by decreasing the frequency of interventions or by initiating screening at a later age for vaccinated women[130,175,177]. HPV vaccination might as well decrease the rate of colposcopy referral[178-180]. Lastly, HPV vaccination could have a positive impact on the number of STI consultations[181].

Data from Québec

The majority of Québec clinicians surveyed estimated that HPV vaccination would decrease the number of post-screening interventions. However, not as many of them could foresee a decrease in the frequency of screening interventions or their initiation at a later age for vaccinated women (see Table 13, section 2.5.2).

2.6.2 Accessibility of target population/estimated level of coverage

HPV vaccines are designed to prevent infection with HPV genotypes targeted by the vaccines but are not designed to treat women who have already been infected with these genotypes. Indeed, HPV vaccination would best be implemented before the onset of sexual activity[83]. Although this should be interpreted with caution, the results from the different surveys reported that an average of approximately 20% of Canadians at 15 years old had already had sexual intercourse[83,182]. The following tables illustrate some of the results of two studies on Canadian adolescent's sexual health[83].

Table 15 Sexual behaviour of Canadian adolescents by age group, CAAH 2005[h]

	14 years	15 years	16 years	17 years
Canadians teens report being sexually active	7%	20%	34%	45%

Table 16 Age at first sexual contact reported by Canadian girls aged 15-19 years, cycle 2.1 CCHS 2003[i]

	12 years	13 years	14 years
Age at first sexual contact	1.1%	3.3%	9.0%

A school vaccination program remains an effective way to reach young girls and to ensure that all required doses are administered[182]. A large majority of Canadians aged 14 years attend school full time[j].

2.6.3 Availability of resources for marketing and communication to the public and information for and training of health professionals

Since the approval of HPV vaccine by Health Canada in July 2006, a lot of information regarding HPV has been circulating in the mass media. Health Canada, the Canadian Cancer Society, the Public Health Agency of Canada, The Canadian Women's Health Network, and the Ministry of Health and Social Services, among others, have made HPV information available online. Merck Frosst, the manufacturer of Gardasil™, has also created an Internet website for HPV information, www.tellsomeone.ca.

However, content analysis of media's coverage of HPV vaccine from the United States have shown that many stories on television or newspapers had incomplete information about the link between HPV and cervical cancer and about HPV prevention, transmission, symptoms,

h. Canadian Association of Adolescent Health. *Sexual behaviours and attitudes of Canadian teenagers and mothers*. Available online at: http://www.acsa-caah.ca/ang/pdf/misc/research.pdf
i. Statistics Canada. Division of health inquiries. *Canadian Community Health Survey (CCHS) 2003*. Available online at: http://www.statcan.ca
j. In 1998-99, 97.1% of Canadians aged between 7 and 14 years were attending school full time (Statistics Canada, http://www.statcan.ca/anglais/freepub/81-229-XIB/0000081-229-XIB.pdf).

and prevalence. Thus, this could lead to an inadequate picture or lack of understanding of the complexity of HPV infection and cervical cancer[183-185].

Data from Québec

In Québec, a survey to identify the training needs of public health professionals, for new vaccines and for basic immunization training, has been undertaken. The data that will be generated will support the implementation of regional immunization programs by setting up training sessions and tools corresponding to the identified needs.

Also, various research projects looking at the organization of immunization services for adults and adolescents are in progress[k]. The objective of these projects is to document both the offer and accessibility of vaccination services and the demand in the community.

2.7 CHAPTER 7 – ABILITY TO EVALUATE THE IMMUNIZATION PROGRAM AGAINST HPV

Universal vaccination program brings about significant costs, touches millions of healthy people and has a vast number of unknowns. Recent meningococcus and pneumococcus vaccination programs introduced in Québec have been subjected to prior monitoring over several years. Extensive evaluation programs were introduced, covering a period of more than 10 years. The MSSS is financing a 15-year study to document the duration of the protection conferred by the vaccine against Hepatitis B in preadolescents.

In comparison, there has been very little work done to date in Québec and Canada to prepare for the evaluation of the future HPV immunization program. Taking into account the costs predicted, the importance and impact of the unknowns, the scientific and organizational complexity of the program, the ability to evaluate the program is extremely important.

The list of elements to compile for the evaluation of this program is long and costs for collecting them are often very high. We will need to find certain information produced in other contexts that can be transposed directly onto the Québec situation.. We will also have to rank the elements that can be more easily collected in Québec due to our expertise and favourable circumstances. Lastly, aspects more specific to a Québec context must also be identified and documented onsite.

k. Sauvageau, C., Duval, B., *et al.*, 2007. Les services de vaccination offerts à la population adulte dans la région de la Capitale-Nationale : état de la situation et orientations futures, Les services de vaccination offerts à la population adulte : État de la situation et orientations futures dans quatre régions du Québec, Les services de vaccination offerts aux adultes : le point de vue de la population. Direction régionale de santé publique de la Capitale-Nationale, Institut national de santé publique du Québec.

2.7.1 Desirability of the evaluation for the public, health professionals and decision makers

As for all universal immunization programs, the MSSS insists that we submit an evaluation plan to them. This is especially true for HPV vaccination, considering the large number of unknowns listed in the previous chapters and the very significant costs of future immunization program and screening activities.

Knowledge, attitudes and behaviours of the public and health professionals have been partially documented in Québec (see chapter 5). We have ascertained that the knowledge was generally low. Attitudes toward the vaccination were generally favourable but several factors (cost, accessibility, etc.) influenced intentions. We are not aware of the impact the vaccination will have on screening compliance of vaccinated women. We must also be prepared to address negative reactions from vaccinated women who will still have positive screening tests.

It will therefore be necessary to plan periodic surveys of public and professionals to measure the evolution of knowledge and attitudes towards the program that will be proposed and follow-up behaviours for screening recommendations. Data collected elsewhere on this subject cannot be considered beforehand as representative of Québec. Québec has good expertise in this field that is well known at the Canadian level and even internationally.

2.7.2 Information systems to measure vaccine coverage and the quality of the immunization services

HPV vaccination will most likely take place in the schools, administered by the public health system, with catch-up in the private and public systems. There is currently no vaccination registry except in the regions of Québec and Estrie. However, the *Panorama* project, which aims to create such a registry, will be gradually implemented, probably beginning in 2008. In the meantime, the only way to document the vaccination coverage for Québec is the execution of postal or telephone surveys.

The vaccination coverage against HPVs can be partially monitored in the Capitale-Nationale and Estrie areas to the extent that the vaccinators agree to forward the information to the existing registries.

HPV vaccination targeting adolescents and adults requires different services than those that exist for infants. Vaccination services for adults and adolescents are almost non-existent outside of school-based programs (Hepatitis B and DTaP boosters). They are limited to vaccinations in travel-health clinics, which are not covered by insurance and therefore chargeable, and to influenza vaccine, which is a seasonal vaccination. In Québec, there is no specific remuneration for the administration of a vaccine. The vaccines that are not publicly funded are not subject to monitoring by public health.

Therefore, there is currently no vaccination system for adults and adolescents in Québec. Also, there is no possible evaluation method. Projects are underway in the Capitale-Nationale area, with expansion possibilities to other Québec areas, to document the offer of

vaccination services to adolescents and adults, the expectations of the public and innovative strategies for offering vaccination services (pharmacies, nursing groups, family medicine groups, etc.). This approach will also be useful for other adult vaccines, approved or on the verge of being approved (shingles, pertussis booster, hepatitis, etc.).

2.7.3 Information system to measure the decrease of diseases caused by HPV and the impacts on screening for cervical cancer

Normally, we evaluate the impact of a vaccination program by measuring the frequency of cases, hospitalizations and deaths. In the case of the HPV vaccination, we run into two major types of problems for measuring our success in reducing cervical cancers. Cancers are produced after a very long latency period. In Québec, we possess good cancer registries but we will not be able to use them for several years to measure the impact of the vaccination. The clinical trials have bypassed this problem by using other impact measurements: high-grade lesions, low-grade lesions, persistent infections and the incidence of infections. The high and low-grade lesions are identified by screening tests. Unfortunately, there is not a centralized registry for these lesions. Also, there are no commercial tests available to specifically measure the presence of infections by HPV types targeted by the vaccines. The existing virology tests measure, in a general manner, the presence of one of the high-risk HPVs, without specifying the type. The use of these tests is still not very common in Québec. We are also interested in measuring the impact of the vaccination on screening practices, the algorithms followed, the frequency of colposcopy referrals, etc. There is currently no description of practices or a registry allowing us to document them. Also, there are no commercial serological tests enabling the measurement of the presence of antibodies against one or any of the HPV types. In Québec, we have no data regarding the frequency of anogenital condylomas and there is no data bank enabling their measurement.

Therefore, we ascertain that measuring impacts on the disease and screening will be difficult to achieve.

Efforts are in progress to create a baseline. We have compiled the existing data into the cancer registry. Studies are being developed to document HPV prevalence in the population, the screening practices and their costs, by possibly using the RAMQ registry.

We will need to elaborate an evaluation plan of the impact by specifying the priority indicators and by implementing appropriate mechanisms to collect the information. We must also test new screening algorithms in a response to the introduction of the vaccination. These should also be subjected to an evaluation.

2.7.4 Information system for side effects of the vaccine

As with all vaccines, it would be justified to seek to document the frequency of rare side effects or ones that are specific to a certain population group (immunocompromised, allergic people, etc.) that have not been identified in the clinical trials. Specific to HPV vaccination is the fact that they are administered mainly to young women who are of childbearing age. The manufacturers intend to create registries of pregnant women who have been vaccinated to document the impact on the pregnancy.

The usual monitoring mechanisms for clinical manifestations occurring after an immunization (ESPRI) could also be used for the HPV vaccines.

2.7.5 System to connect the different data banks and the concept of evaluation zones

It is possible to link population data banks in Québec, especially for research purposes. The absence of vaccination and screening registries in Québec significantly limits these possibilities. The arrival of the *Panorama* system could possibly change this state of things in the future. For the time being, only the regions equipped with a vaccination registry could link this information with the screening data collected from the regional hospitals and laboratories to document impacts.

This difficulty in linking existing data banks, in addition to the lack of specific documentation tools for infections caused by the types targeted by the vaccine, is a severe handicap in the evaluation of the program's impacts. One hypothesis is to support the creation of evaluation zones where we could concentrate activities by creating data banks or by linking existing banks. After having measured the initial situation, we could realize, in priority, the studies likely to document the impacts of the vaccination.

2.7.6 Conclusions of chapter 7

Evaluation of the HPV vaccination program will be crucial and complex. Evaluation requires the development of a comprehensive plan and will demand significant resources.

2.8 CHAPTER 8 – EQUITY OF THE NEW PROGRAMS, INCLUDING UNIVERSALITY, ACCESSIBILITY AND FREE SERVICES FOR THE POPULATION GROUPS WHICH ARE MOST VULNERABLE

If the cost of the vaccine and its administration are to be paid by individuals themselves and not publicly funded, access to HPV vaccination will be problematic. Currently in Canada, social disparities exist in the use of screening services[l] and cervical cancer affects mainly women of lower socio-economic status or those who live in certain geographic zones[186]. Absence of a publicly funded HPV immunization program might introduce an inequity in HPV and cancer prevention. A school-based immunization program could reduce these disparities by reaching all girls who go to school, without respect in their socio-demographic characteristics. However, if no catch-up is implemented, such a program will remain inequitable for the teenagers outside the targeted school level and for the women from 16 to 26 years old who are not going to school, but for whom HPV vaccine is recommended. It could also be unfair not to offer the HPV vaccines to women who live in regions where access to screening services is limited.

Lastly, many men feel concerned and worried about HPV and its possible effect on their health[m]. Although uncommon, anal and penile cancers are frequently associated with HPV 16 and 18[187]. HPV vaccination of men could also prevent condylomas and reduce the transmission to women of high-risk HPVs targeted by the vaccines. If the clinical studies demonstrate the efficacy of the vaccine against HPVs in men, it could be unfair to not offer the HPV vaccination to them.

2.9 CHAPTER 9 – ETHICAL FACTORS, INCLUDING INFORMED CONSENT AND PROTECTION OF CONFIDENTIAL MEDICAL DATA

Because it's a sexually transmitted disease, HPV is different from many others vaccine preventable diseases like measles, rubella, varicella or whooping cough. This difference could engender ethical dilemmas.

Many of these ethical dilemmas originate in the preoccupation about sending a morally wrong message, such as endorsement of sexual promiscuity. Will HPV vaccination promote sexuality in the youth? Is administration of the vaccine to a child an encouragement of earlier sexual activity? Even if similar concerns were raised, implementation in 1994 of hepatitis B, (an infection also sexually transmitted) immunization programs has not engendered major opposition in Canada. In fact, even after some fears were voiced, the establishment of the vaccination program in fourth grade did not produce any major parental opposition. Furthermore, studies reviewed indicated that only between 6% and 12% of parents were worried about the impact of the HPV vaccination on the sexual life of their children[155,164,167,188]. Finally, according to some ethicists[189,190], vaccination against HPV, as opposed to abortion, cannot be considered morally wrong per se, because its long term goal is cancer prevention.

l. http://www.phac-aspc.gc.ca/publicat/ccsic-dccuac/pdf/cervical-e3.pdf.
m. http://www.hpvnews.ashastd.org/article.asp?qid=233&sid=4&.

From an ethical point of view, false expectations are as well problematic. Public discussion needs to be nuanced to ensure that potential recipients appreciate both the benefits and limitations of vaccine[191].

If, for epidemiological or logistic reasons, the HPV vaccines are offered free of charge to some sub-groups of the population, for example Native and Inuit populations, then it may lead to problems of stigmatization.

Health professionals who will recommend HPV vaccine while knowing that a number of individuals cannot buy it will be confronted with an ethical dilemma. Besides, because HPV is sexually transmitted and because HPV vaccine will probably be targeted to 11- or 12-year-old girls, health practitioner's values may be confronted by official recommendations.

Finally, vaccination will require informed consent. Parental consent for HPV immunization of an adolescent might be problematic; the most controversial issue will arise when a young girl under 14 years of age wants the vaccination without her parents' permission[189-191].

2.10 CHAPTER 10 – CONFORMITY OF A POSSIBLE VACCINATION PROGRAM AGAINST HPV WITH THAT OF FUTURE OR EXISTING PROGRAMS IN OTHER JURISDICTIONS/COUNTRIES

The Gardasil™ vaccine, manufactured by Merck Frosst, is approved in more than 60 countries[192].

In the United States, the Advisory Committee on Immunization Practices (ACIP) voted on June 29, 2006 to recommend routine vaccination with three doses of quadrivalent HPV vaccine for females 11-12 years of age. The ACIP recommendation also allows for vaccination of girls beginning at nine-years-old as well as catch-up vaccination of girls and women 13-26 years old[n].

In Australia, since 2007, HPV vaccination of girls and women aged 12 to 26 has been publicly funded. HPV vaccine is put on the National Immunisation Program on an ongoing basis for 12 and 13 year old girls to be delivered through schools. The Australian government will also fund a two year catch-up program for 13 to 18 year old girls in school and for 18 to 26 year old women, to be delivered through GPs [o].

In Europe, in September 2006, the European Medicines Agency (EMEA) approved the HPV vaccine Gardasil™ for use in girls and women between 9 and 26 years of age, in 25 countries of the European Union[p].

In Canada, the National Advisory Committee on Immunization (NACI) formulated recommendations about utilization of HPV vaccine in February of 2007. The vaccine has been approved for use and is now recommended to girls aged 9-13 years. NACI also

n. www.cdc.gov/od/oc/media/pressrel/r060629.htm.
o. http://www.health.gov.au/internet/ministers/publishing.nsf/content/487014123B6EBBA1CA257234008126EC/$File/abb155.pdf.
p. http://www.jci.org/cgi/content/full/116/12/3087.

supports vaccination of adolescent and young women aged 9-26 years who could benefit from the vaccine, even if they are sexually active. Vaccination of girls younger than 9 years of age and of pregnant women is not recommended[79].

2.11 CHAPTER 11 – RESEARCH QUESTIONS

Acceptability of HPV vaccination:

The knowledge, attitudes and practices (KAP) about HPV vaccination are related to a specific socio-cultural and historical context and are apt to change. Periodic surveys will have to be done to follow and analyze the evolution of:

- The acceptability of HPV vaccination, and the values that are linked to it, for women and young girls;
- Attitudes of Québec parents regarding vaccination of girls against a STI;
- The impact of HPV vaccination on the KAP of women regarding screening for cervical cancer.
- Effective and ethically worthy information tools and promotional strategies must be developed that will not create false hopes or false feelings of security in the population.

As well, following the official recommendations and the establishment of a possible immunization program, some surveys will have to follow the evolution of:

- The KAP and values about HPV vaccination for health professionals;
- The KAP of health professionals in regards to the vaccination of young girls against a STI;
- The needs and preferences of Québec health professionals for training tools and information on HPV.

Organization of vaccination services for HPV :

The effects of HPV vaccination on the incidence of cervical cancer will be hard to measure for a number of years after the introduction of an immunization program. Studies will have to be done to establish:

- The most efficient strategies for combining HPV vaccination and screening interventions for cervical cancer and guidelines for screening of HPV immunized women;
- Efficient strategies for HPV vaccination of young adults and girls outside school-based programs.

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