COMITÉ SUR L'IMMUNISATION DU QUÉBEC

HPV Immunization of Québec Pre-Adolescents: Two or Three Doses?

INSTITUT NATIONAL
DE SANTÉ PUBLIQUE
DU QUÉBEC

Québec

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Comité sur l'immunisation du Québec

May 2013

Institut national de santé publique Québec

AUTHOR
Comité sur l'immunisation du Québec

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

COLLABORATORS TO THE ADVISORY REPORT
Michel Couillard, Laboratoire de santé publique du Québec, Institut national de santé publique du Québec (deceased at time of publication of this advisory report)
Patricia Goggin, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec
Marie-Hélène Mayrand, Institut national de santé publique du Québec/Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM)

PERSONS CONSULTED
Marc Brisson, Centre de recherche FRSQ du CHA universitaire de Québec, Département de médecine sociale et préventive, Université Laval
François Coutlée, Hôpital Notre-Dame du Centre hospitalier de l'Université de Montréal (CHUM)
Eduardo Franco, McGill University, Department of Oncology and Epidemiology & Biostatics
Philippe Sauthier, Hôpital Notre-Dame/Centre hospitalier de l'Université de Montréal (CHUM)
Marc Steben, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec
Gisèle Trudeau, Agence de la santé et des services sociaux de la Capitale-Nationale, Direction de la santé publique

ORGANIZATIONS CONSULTED
Association des médecins microbiologistes infectiologues du Québec
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Collège québécois des médecins de famille
Table de concertation nationale en maladies infectieuses (TCNMI)
Table de coordination nationale en santé publique (TCNSP)

PROFESSIONALS WHO PROVIDED SUPPORT IN PREPARING THIS DOCUMENT
Mélanie Drolet, Canada Research Chair in Mathematical Modeling and Health Economics of Infectious Diseases, Centre de recherche du CHU de Québec
Carole Dagenais, Laboratoire de santé publique du Québec, Institut national de santé publique du Québec
Jean-François Laprise, Canada Research Chair in Mathematical Modeling and Health Economics of Infectious Diseases, Centre de recherche du CHU de Québec
Manale Ouakki, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec
Andrea Trevisan, Laboratoire de santé publique du Québec (LSPQ), Institut national de santé publique du Québec

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

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LEGAL DEPOSIT – 2nd QUARTER 2014
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ISBN: 978-2-550-70822-3 (PDF)

COMITÉ SUR L'IMMUNISATION DU QUÉBEC (CIQ)

ACTIVE CIQ MEMBERS

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

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

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

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

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

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

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

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

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CIQ EX OFFICIO MEMBERS

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

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

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

ACKNOWLEDGEMENTS

The authors and contributors would like to acknowledge the outstanding work of our dear colleague Michel Couillard, who left us much too soon. With assistance from Andrea Trevisan, Eduardo Franco, Mel Krajden and the team at the Laboratoire de santé publique du Québec, Carole Dagenais in particular, he developed and validated a new platform for conducting HPV serology assays in Québec. The assay developed by Michel and his colleagues enabled the analysis of specimens from 400 girls recruited into the Québec immunogenicity study and contributed significantly to the discussions culminating in the CIQ recommendation set out in this document. Among other things, this platform will enable the continuation of the serological component of independent evaluation of the HPV immunization program. For this, we will always be grateful. Our sincere thanks, Michel.

Note

This document is an English translation of the French Advisory report entitled *La vaccination des pré-adolescents contre les virus du papillome humain (VPH) au Québec: deux ou trois doses.* Institut national de santé publique du Québec. Mai 2013. 71 p.

Section 5 is based on the following report: Brisson, M., Laprise, J.-F. et Drolet, M. Efficacité populationnelle et coût-efficacité de programmes de vaccination contre les VPH à deux ou trois doses. (Population-level effectiveness and cost-effectiveness of HPV vaccination programs after two or three doses). The French version of the report was submitted to the Institut national de santé publique du Québec (INSPQ) in March 2013. The English version has not been reviewed by the authors.

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

EXECUTIVE SUMMARY

In 2007, the Comité sur l'immunisation du Québec (CIQ) recommended an extended schedule exclusively for immunization against the human papilloma virus (HPV) starting in grade 4 (0, 6, 60 months); the committee also stated that the third dose should be administered "if judged necessary." Since the introduction of the Québec HPV immunization program in 2008, similar programs (two doses administered six months apart and a possible third dose if necessary) have been introduced in Mexico and British Columbia. In 2012, the committee of immunization experts in Switzerland recommended for pre-adolescents a schedule comprising two doses administered six months apart. In recent years, a number of studies have been published on the immunogenicity of HPV vaccines administered according to alternative schedules and other studies are presently underway to document the efficacy of one, two, or three doses administered at different intervals.

The present advisory report, which is based on the theoretical framework put forward by Erickson *et al*., summarizes the key data currently available regarding the pertinence of the administration of the third dose of HPV vaccine 60 months after the first dose.

To our knowledge, there are no good quality efficacy data for the schedules recommended by manufacturers (0, 1, 6 or 0, 2, 6 months) when vaccinating pre-adolescents. Nor efficacy data emerged yet from studies that have used a two-dose schedule with a six-month interval (0, 6 months) or an extended schedule (0, 6, 60 months).

However, some of the results presented at the International Papillomavirus Conference held in San Juan, Puerto Rico in December 2012 are summarized in this advisory report; these include efficacy data (observational studies) that show that there are no vaccine failures (breakthrough*)* for up to almost 10 years in young women who received the vaccine.

Immunogenicity data on available HPV vaccines show that the immune response measured in pre-adolescents (9-13 years) who received two doses six months apart is not inferior (in fact it is generally superior) to that obtained in vaccinated individuals aged 16 years or more, a group for which excellent efficacy data are observed for at least 10 years.

In girls aged 9-13 years, antibody levels one month after the administration of two doses (0, 6 months) or three doses (0, 2, 6 months) are comparable for all four types of HPV. Thirty-six months later, levels are still comparable for types 16 and 11. For types 18 and 6, however, observed antibody levels are lower in girls who received two doses than in girls in the same age group (9-13 years) who received three doses according to a 0-2-6 month schedule (however their antibody levels remain higher than those of women aged 16-23 who received 3 doses).

Preliminary Québec data on girls aged 9-10 years indicate that the first dose of quadrivalent vaccine produces detectable antibodies in 93-100% of girls, depending on the HPV type. These results indicate that a primary immune response occurs after the first dose when administered at this age. These data also indicate that the second dose increases antibody levels considerably. Indeed, a 56-109-fold increase of geometric mean titers (GMTs) was observed one month post-second dose when compared to pre-second dose GMTs. Such an

increase indicates on an anamnestic response. The data also indicate that GMTs are slightly higher one month post-third dose than one month post second dose (from 1.1 to 1.8 fold).

HPV vaccines administered to girls aged 9-11 are well tolerated. However, a two-dose schedule would likely generate fewer adverse events following immunization (AEFI)than a three-dose schedule.

At the current cost of vaccines obtained for the public program, it would cost approximately three million dollars more each year to administer a booster dose to Québec grade 9 girls.

An analysis of the effectiveness and cost-effectiveness of different two- and three-dose immunization strategies, including the immunization of boys, was performed.

According to mathematical modeling predictions produced by the *HPV-ADVISE Québec* model, immunizing girls with a two-dose schedule is a highly cost-effective strategy and of all the strategies examined in this analysis, it is the one that produces the best cost-effectiveness ratio. The model also predictis that the addition of a third dose of vaccine could be a cost-effective strategy if one of the following conditions is met: (1) the period of protection conferred by two doses of vaccine is less than 30 years, or (2) the third dose extends the period of protection when the period of protection conferred by two doses is 30 years or more. According to the model predictions, immunizing both girls and boys using two or three doses is unlikely to be a cost-effective alternative (at the threshold of $40,000 per Quality-Adjusted Life-Year (QALY)) to vaccinating girls only, if the cost of the vaccine is greater than $40 per dose (including administration costs) for boys.

Given that close to 80% of girls are immunized against HPV and that this has an indirect impact on protection for boys, the current immunization program for girls appears to be very efficient (< $15,000 per QALY). At the current cost of the vaccine, extending immunization to all pre-adolescent boys would produce health benefits but, according to economic analyses conducted in Québec and elsewhere, these benefits would not be commensurate with the additional costs incurred at the population level, even with a two-dose schedule. At the vaccine's current cost, introducing a publicly-funded program to immunize all boys could be justified on the basis of political considerations or the principle of ensuring equity, particularly for men who have sex with men (MSM). The feasibility, effectiveness and efficiency of a "targeted" approach that would allow to immunize young men who have or will have sex with men at a point in time when the vaccine is most effective (before they become sexually active) remain to be demonstrated. In terms of protecting men who have sex with men (MSM), the most feasible approach would be to extend vaccination to all pre-adolescent boys.

Schedules comprising fewer doses appear to be generally well accepted by the public and health professionals. However, no Québec study has assessed the acceptability of the two HPV immunization schedules analysed in this advisory report.

In the present immunization context (administration of a Tdap booster and introduction in 2013-2014 of a booster dose of a conjugate meningococcal vaccine in grade 9), negative impacts on acceptability and immunization coverage rates would likely occur if a third

injection (HPV) were to be administered in one vaccination session to 14-year-old girls (Tdap + meningococcus + HPV).

Three-dose HPV vaccine schedules have been introduced in most countries and in other Canadian provinces. Switzerland has retained a two-dose schedule; Québec, if it were to arrive at a similar decision, would not be the first jurisdiction to adopt this scientifically defensible strategy.

Moreover, Australian studies have shown that only a few years after the introduction of the HPV immunization program for girls and women (vaccine provided for free until age 26 during the first two years of the program and to age 18 thereafter), herd immunity had developed, gradually conferring protection to the vast majority of vaccinated and unvaccinated boys and girls. The high vaccination coverage achieved in Québec in routine and catch up programs where the vaccine is offered free of charge to girls up to the age of 18 since 2008 is also contributing to create a herd immunity. If a minority of vaccinated individuals were to lose their immunity over time, they would remain protected indirectly, owing to the lower probability of exposure to the virus. Cervical cancer screening activities also provide an additional safety net, at least in terms of preventing this health problem.

Recommendations

After evaluating the available scientific data and consulting with experts, the members of the Comité sur l'immunisation du Québec have recommended by consensus not to provide a booster dose to grade 9 girls who received two doses of vaccine in the grade 4.

This recommendation is conditional upon the implementation of effective mechanisms to monitor the epidemiology of HPV and to timely detect any sign that might make questionable the reasons for this decision. The key measures that will need to be put in place are as follows:

1. Maintain scientific vigilance with respect to the results of alternative HPV immunization schedules, particularly those that comprise two doses. At present, we cannot rule out the possibility that a later booster dose may be required in the future with either two-dose or three-dose initial schedules.
2. Monitor antibody levels among the first cohorts of girls who received two doses at age 9 and compare the antibody levels in girls who received a booster dose with those who did not.
3. Measure the comparative efficacy of the two schedules (0, 6 months and 0, 6, 60 months) by implementing and carrying out the ICI-VPH study, which will measure persistent HPV infections in women immunized according to one or the other of these schedules.
4. It will also be important to monitor the prevalence of HPV infection (through cross-sectional studies) in successive cohorts of young women (those not vaccinated; those who received three doses on a catch-up basis; those who received three doses in grade 9; and those who received two doses in grade 4). Initial measures could be made in the context of a start-up study and then repeated over time.

5. Monitoring the types of HPV detected in precursors and cervical cancers constitutes another important aspect to be evaluated. This could be achieved using the demonstration zones put in place in 2008 in the Estrie and Capitale-Nationale regions. The types of HPV identified in cancers that occurred in these regions in 2006-2009 constitute a pre-immunization baseline. Repeating these measures over time would make it possible to monitor the evolution of the different types of HPV detected in cancers as the cohorts of vaccinated girls advance in age.
6. The future inclusion of cervical cancer precursors in the cancer registry will also make it possible to monitor the frequency of these lesions over time.
7. Measuring and monitoring the trends in incidence of lesions detected in the context of screening tests, diagnostic and follow-up examinations is another important component. However, the implementation of the Québec demonstration zones revealed how complex and difficult (manual collection, imprecise denominators, impossibility of knowing how many women in demonstration zones venture outside their region to access services, problems following the care trajectory when different facilities use different identifiers) it can be, in the absence of a provincial registry, to gather reliable information on screening, diagnosis and follow up activities and to measure the incidence of cancer precursors.

Immunization data gathered in schools are entered into the local systems (I-CLSC) of health and social service centres (CSSS) or in regional databases (VAXIN and LOGIVAC) that identify vaccinated individuals and the number of doses they received. The legislation governing the implementation of the provincial immunization registry provides the opportunity for the recovery of all historical immunization data housed in the various local and regional systems. For example, the data pertaining to girls vaccinated since the program was implemented in 2008 will be entered into the registry, which will facilitate monitoring.

It will also be important to pursue efforts to achieve and maintain levels of vaccine coverage that meet provincial objectives (90% in grade 4). Particular attention should be paid to verifying immunization status in grade 9 and offering the HPV vaccine (ideally in a school setting) to all girls who have no proof of immunization.

In the short term, a communication plan will be needed so that the various stakeholder groups for the Québec HPV immunization program can be informed about the reasons behind the recommendation not to administer the third dose of the extended schedule, as initially planned. It will also be important to emphasize that this recommendation applies only to the immunization of pre-adolescents and that the three-dose schedule (0, 2, 6 months) should be offered to all other age groups.

The CIQ also wishes to reiterate that HPV vaccines do not confer protection against all types of HPV and recommends that cervical cancer screening continue for all women, whether vaccinated or not. Furthermore, since HPV vaccines do not confer protection against all sexually transmitted infections, safe sex practices are recommended for everyone, regardless of their HPV immunization status.

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LIST OF ACRONYMS AND ABBREVIATIONS

95% CI	95% confidence interval
AEFI	Adverse event following immunization
APC	Antigen-presenting cell
ASCUS +	Atypical squamous cells of undetermined significance
CIN	Cervical intraepithelial neoplasia
CIQ	Comité sur l'immunisation du Québec
cLIA	Competitive Luminex-based immunoassay
GMTs	Geometric mean titres
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HPV-ADVISE	Agent-based Dynamic model for VaccInation and Screening Evaluation
HR	High oncogenic risk
ICER	Incremental cost-effectiveness ratio
INSPQ	Institut national de santé publique du Québec
LLPCs	Long-lived plasma cells
LSPQ	Laboratoire de santé publique du Québec
MND	Mandatory notifiable disease
MSM	Men who have sex with men
MSSS	Ministère de la Santé et des Services sociaux
QALY	Quality-adjusted life years
VD	Vaccine duration
VLP	Virus-like particle
WHO	World Health Organization

1 BACKGROUND

In 2007, the Comité sur l'immunisation du Québec (CIQ) recommended an extended schedule for vaccinating against the human papillomavirus (HPV) starting in grade 4 (0, 6, 60 months), noting that "the third dose would be dispensed…if this were deemed necessary."

The objective of proposing an extended schedule was to ensure adequate protection of the highest possible number of women through the most effective use of available resources.[1]

Arguments supporting the recommendation of this schedule can be divided into two categories: immunological and operational.

Immunological arguments

HPV vaccines are highly immunogenic and trigger the development of significantly higher antibody titres than those caused by natural infection.[2-4]

The immune response in children aged 9 to 11 is particularly strong, reaching higher post-two-dose titres than those observed in young women aged 16 to 26 vaccinated with three doses in whom the clinical efficacy of the vaccine has been demonstrated.[5-7]

It is a known fact that higher antibody titres are generally achieved by spacing intervals between the administration of vaccine doses.[8-9] This has been clearly shown for the hepatitis B vaccine, another recombinant vaccine administered to pre-adolescents and adolescents.[9-10] Moreover, no conclusive justification exists for the 0, 1, 6 and 0, 2, 6 month schedules proposed by manufacturers.

The 0, 1, 6 and 0, 2, 6 month schedules are generally used to provide protection as early as possible in life. Infants do not respond as well to vaccination as older children and frequently need multiple doses of the vaccine to be protected. They also frequently require booster doses later in life. The situation of adolescents is different; epidemiological risk can often be used to identify the best time for vaccination, and the immune response is generally much higher at this age than that observed following vaccination of infants.

Administration of a booster dose five years after primary vaccination generally results in very high geometric mean titres (GMTs) that are higher than those following primary vaccination. This has been observed for both hepatitis B (Québec cohorts)[11-12] and HPV vaccines.[13] With respect to HPV, maximum protection immediately prior to the start of sexual activity with the administration of a third dose in grade 9 appears justified based on existing knowledge in 2007. The lack of data on the duration of protection conferred by HPV vaccines provides additional justification, as the objective of the extended schedule is to achieve the highest possible antibody titres through the administration of a final vaccine dose in school. The need to maximize antibody levels for clinical protection remains unknown.

Operational arguments

Vaccination in grade 4 allows achieving high vaccination coverage rates at a relatively low administration cost. This is the best time for administering the hepatitis B vaccine on grounds of the quality of the immune response and the efficiency of administration in school. After obtaining conclusive data,[10] Québec introduced a two-dose schedule for hepatitis A and B by using a bivalent vaccine. The two vaccines (HAV/HBV and HPV) are administered simultaneously without an additional third vaccination session.

The administration of two doses rather than three in grade 4 increases acceptability both by students and parents and by health professionals, while also keeping down program costs and enabling vaccination of more girls using the same resources.

This schedule is not a deviation from the approved schedule. The principle of not starting up a new immunization schedule with extended intervals is well accepted in vaccinology.[14]

Since the introduction of the HPV immunization program in Québec in 2008, similar programs have been introduced in Mexico and British Columbia with the subsequent option of considering the need for a third dose.[15-16] In 2012, meanwhile, Switzerland's committee of immunization experts recommended a schedule comprising two doses administered six months apart.[17-18] Studies have been published on the immunogenicity of HPV vaccines administered according to alternative schedules, with other studies presently underway to document efficacy following administration of one, two or three doses at different time intervals.

Following up on its 2007 advisory report, the CIQ has prepared this document to summarize the main scientific data available on the pertinence of administering the third dose of the HPV vaccine 60 months after the first dose, based on the categories in the theoretical framework put forward by Erickson et al.[19] The possibility of expanding the program during the course of its implementation to include the vaccination of boys was also reassessed. For additional data concerning HPV vaccination, particularly the burden of HPV-related diseases and details on HPV vaccines, please refer to the advisory report entitled *La vaccination contre les VPH au Québec : mise à jour des connaissances et propositions du comité d'experts* (HPV Immunization in Québec: Updated Knowledge and Recommendations of the Expert Committee) published in July 2012 and available on the website of the Institut national de santé publique du Québec (INSPQ).[20] Appendix 1 hereto also provides a summary of the declarations of interest made by CIQ members in July 2012.

2 EFFICACY OF HPV IMMUNIZATION

2.1 EFFICACY DATA FOR VACCINATION OF PRE-ADOLESCENTS (AGE < 15)

To our knowledge, there are no good quality data (e.g., from a randomized trial) on the efficacy of the schedules recommended by manufacturers (0, 1, 6 or 0, 2, 6 months) when vaccinating pre-adolescents. Similarly, no efficacy data have emerged to date from studies that have used a two-dose schedule with a six-month interval (0, 6 months) or an extended schedule (0, 6, 60 months).

The long-term study (Merck Protocol 018) of the quadrivalent vaccine in pre-adolescents and adolescents aged 9 to 15 is a cohort study in which all individuals were vaccinated and monitored (i.e., no control group).[21] The results after 96 months of continuous monitoring showed the absence of high-grade (CIN2 or more severe) cervical lesions related to HPV-16 or HPV-18 (absence of breakthrough cases) despite very low or undetectable levels of HPV-18 antibodies in a certain number of participants (according to the competitive Luminex-based immunoassay [CLIA]). The principal author concluded that even very low antibody levels appear to provide highly effective protection post-vaccination. The same conclusion has been drawn in other studies.[22-23]

Analysis of vaccination and pathology records in Denmark[24] has shown a decrease in the number of lesions in girls vaccinated at age 13–15 since 2008 as part of a catch-up program. In that country, the vaccination coverage of the routine (age 12) and catch-up (age 13 to 15) programs exceeds 80%. However, vaccination coverage ranges between 1 and 29% among older women who had to pay for the vaccine. A 50 to 69% decrease in atypical squamous cells of undetermined significant (ASCUS +) has been observed for younger cohorts among women who have received at least one dose of the quadrivalent vaccine. In older women, for whom vaccination coverage of less than 5% has been reported, this decrease has not been observed.

Researchers in Sweden[25] have assessed the efficacy of vaccination against genital warts administered at ages 10–16 and 17–19 based on registries and podophyllotoxin and imiquimod prescriptions. The efficacy of three vaccine doses against genital warts in the two age groups studied was 70 to 79%. The efficacy of vaccination with three doses was 26 to 37% higher in comparison to vaccination with two doses administered two months apart. However, efficacy was comparable between the two following groups: girls aged 10 to 16 receiving two doses and girls aged 17 to 19 receiving three doses.

The impact of using a broad age group (10 to 16 years) on antibody levels resulting from vaccination at age 10 in comparison to age 16 was not assessed during this study. Moreover, the authors did not rule out the possibility that younger girls may have had a better chance of receiving three doses (as part of the routine program) than older women who generally had to pay for the vaccination. Lastly, differences in sexual activity between those who completed the immunization schedule and those who dropped out could also not be ruled out.

2.2 EFFICACY DATA FOR ALTERNATIVE IMMUNIZATION SCHEDULES FOR WOMEN AGED 15 AND OVER

To our knowledge, no good data (e.g., from a randomized trial) have been published on the efficacy of vaccination with fewer doses of the quadrivalent vaccine. However, some results from observational studies have been presented at recent conferences. At the most recent International Papillomavirus Conference, held in San Juan, Puerto Rico, in December 2012, data based primarily on population registries indicated that there was no conclusive evidence of better protection after three vaccine doses than after two doses.[26]

Other registry-based data showed that three vaccine doses have a higher efficacy than two doses typically administered two months apart. These studies mainly involved cohorts of women vaccinated outside of a public program.[27]

Meanwhile, the efficacy of a schedule comprising one, two (0, 1 months) or three (0, 1, 6 months) doses of the bivalent vaccine administered to young women in Costa Rica was assessed approximately four years post-vaccination. A total of 5,967 women aged 18 to 25 were initially randomized for administration of the bivalent HPV vaccine or the control vaccine. Of these women, 802 received two doses and 384 received a single dose of the HPV vaccine. The incidence of persistent infections lasting one or more years was found to be independent of the number of vaccine doses received: the efficacy of one, two or three doses of the bivalent vaccine against persistent HPV-16- or HPV-18-related infections was 100% (95% CI 66.5–100%), 84.1% (95% CI 50.2–96.3%) and 80.9% (95% CI 71.1–87.7%), respectively.[28]

3 IMMUNOGENICITY OF HPV VACCINATION

3.1 GENERAL CONSIDERATIONS

Apart from the criterion established by the World Health Organization (WHO) for HPV-16 type,[29] no standard exists for serologic testing, and HPV vaccine manufacturers have used a variety of tests in clinical research.[14, 30] Moreover, since the licensing of HPV vaccines, independent laboratories have developed new tests that have often replaced the original tests in more recent publications, complicating the interpretation of results from longitudinal studies.[31]

According to WHO, protection against HPV is governed by neutralizing antibodies.[32] This finding is based primarily on results from animal models, in which passive antibody transfer has been shown to provide protection against virus challenges.[33-34]

Using the same test, it is possible to measure and compare the geometric mean titres (GMTs) of antibodies in vaccinated individuals and those occurring due to natural infection. It is also important to note that the antibody titres produced by natural infection do not necessarily confer protection against subsequent HPV infections of the same or a different type.[35-36] The studies also show that approximately half of all individuals develop HPV serum antibodies following infection.[37] Insofar as natural infection is primarily intraepithelial, the virus is present on the mucosal surface and there is very little to no viremia. Viral antigens therefore have very limited access to the lymphocytes and lymph nodes where the immune response is initiated. HPV vaccines, however, are administered via intramuscular injection, providing immediate access to the vascular and lymphatic systems. From there, virus-like particles (VLPs) become attached to the antigen-presenting cells (APCs) or other immunocytes and are transported into the lymph nodes, where priming of the naive B cells occurs and an entire cascade of events results in protective immunity.[38]

It is also to be noted that a linear correlation has been observed between antibody titres in serum and antibody titres in cervicovaginal secretions.[39] The clinical significance of the presence of antibodies in cervicovaginal secretions remains unknown.

It has also been established that following natural infection, HPV-16 antibody titres remain stable for a period of at least four years. However, little data exist on the mechanisms explaining the long-term persistence of antibodies in the absence of periodic antigenic stimulation. A peak in antibody titres is typically observed approximately one month after vaccination. It is followed by a decline in titres over the next several months before these levels then more or less stabilize.[13, 23, 40-41] For example, in the case of smallpox (live attenuated vaccine), specific memory B cells remain detectable for more than 60 years post-vaccination, while stable antibody titres have been observed for 10 to 60 years post-vaccination (in the absence of exposure to the antigen during this period).[41] As for the quadrivalent vaccine, at least one study has shown similar antibody titres observed 24, 30, 36, 54 and 60 months following vaccination of women aged 16 to 23 with three vaccine doses.[13] The exact mechanism supporting the maintenance of antibodies at stable levels with or without periodic antigenic stimulation has yet to be confirmed; however, this plateau effect is consistent with the notion that a certain proportion of cells secreting antibodies

become transformed into long-lived plasma cells (LLPCs) and that these cells continue to maintain the serologic memory.[38] The example of hepatitis B vaccination during pre-adolescence is interesting in that two characteristics shared with HPV have appeared to limit infection: the long incubation period of the disease and a highly effective anamnestic response in vaccinated individuals, even in the absence of detectable antibody levels.[8]

One study has shown that in the first 12 months following vaccination with the quadrivalent vaccine of HIV-positive children on antiviral treatment who are only slightly immunocompromised, antibody titres dropped 2.2- to 6.3-fold from the levels observed one month post-vaccination (between months 7 and 12) but dropped only 1.1-fold between months 12 and 18 of the study.[42] These data clearly support the assumption that the rate of decrease in HPV antibodies slows over time post-vaccination.

Clinical studies consistently show that both HPV vaccines are highly immunogenic. More than 98% of non-immunocompromised individuals taking part in the clinical studies had antibodies for the HPV types included in the vaccines one month after the third dose.[6, 43-36] The immunogenicity of both vaccines is higher when administered to pre-adolescents and adolescents aged 9 to 14.[47-48]

In the direct comparison study of the immunogenicity of the bivalent and quadrivalent vaccines, 100% of women aged 18 to 45 who were seronegative for HPV-16 and HPV-18 (n = 210) prior to vaccination had seroconverted (ELISA test) four to five months following the second vaccine dose administered one to two months after the first dose. Neutralization testing was also used in that study: tests to detect neutralizing antibodies showed that in both study groups, 99 to 100% of women aged 18 to 26 had seroconverted for HPV-16 and 93 to 99% for HPV-18 four to five months following administration of two vaccine doses at close intervals.[6]

There is currently no consensus concerning the seroprotective titre following HPV vaccination. However, it is to be noted that an anamnestic response was reported in the great majority (> 83%) of women aged 16 and over who were vaccinated 60 months earlier with the quadrivalent vaccine and in all of the women vaccinated with the bivalent vaccine 84 months earlier.[13, 49] The authors mention that the antibody GMTs one month after the booster dose were (1.2 to 4.2 times) higher than the GMTs observed one month following primary vaccination, which points to the presence of a robust immune memory.[13] The anamnestic response typically shows the presence of memory B cells with the capacity to provide rapid antibody production (within 3 to 7 days) following a booster dose or a virus challenge.[38]

With regard to HPV, however, the role of the immune memory in protecting against clinical diseases remains the subject of relatively few studies[38, 50] and the response after one booster dose of the vaccine cannot be directly extrapolated to the response arising from exposure to the virus (generally localized infection of the mucosa).

3.2 IMMUNOGENICITY OF ALTERNATIVE SCHEDULES OTHER THAN 0, 6 MONTHS

Two doses of the quadrivalent or bivalent vaccine, or even a single dose of the bivalent vaccine, induce detectable antibody titres in nearly all individuals independently of the serologic tests used.[6, 47, 51-52] For example, in one study with the bivalent vaccine, all 240 women aged 9 to 25 had HPV-16 and HPV-18 antibodies two months following administration of a single vaccine dose. The GMTs in the women who had HPV-16 and HPV-18 antibodies prior to vaccination (subsequent to natural infection) were 42 EL.U/ml and 19 EL.U/ml, respectively.[52] In women who did not have HPV-16 or HPV-18 antibodies prior to vaccination, the GMTs after the first dose were 222 EL.U/ml for HPV-16 antibodies and 164 EL.U/ml for HPV-18 antibodies. Based on these results, it can be concluded that in this study, in addition to the fact that all women seroconverted after one vaccine dose, the GMTs observed approximately two months after a single vaccine dose were five to eight times higher than the GMTs observed in women who seroconverted as a result of natural infection.[52]

A cluster randomized trial conducted in Vietnam by the PATH Initiative measured the immunogenicity of the quadrivalent vaccine administered to more than 500 girls aged 11 to 13 according to the following schedules: 0, 2, 6 months; 0, 3, 9 months; 0, 6, 12 months; and 0, 12, 24 months. One month following the third dose, immunogenicity with the 0, 3, 9 month and 0, 6, 12 month schedules was not inferior to that observed in the group vaccinated according to the 0, 2, 6 month schedule recommended by the manufacturer. The 0, 12, 24 month schedule induced lower antibody titres.[53] However, it is important to note that the girls vaccinated following the 0, 12, 24 month schedule were older, making it impossible to rule out the impact of the participants' age on their immune response. After 29 to 32 months of follow-up, none of the three alternative schedules assessed were inferior to the 0, 2, 6 month schedule. It should also be noted that the 0, 12, 24 month and 0, 6, 12 month schedules were associated with higher antibody levels than those observed with the 0, 2, 6 month and 0, 3, 9 month schedules.[54]

Safaeian[55] and her colleagues assessed the immune response in each of the four groups of Costa Rican women who had taken part in a clinical trial of the bivalent vaccine: those who received one dose (n = 78), two doses (n = 193, of whom 140 received the second dose one month after the first and 53 received it six months after the first) and three doses (n = 120, selected randomly from among all women who had received three doses), and a group of women seropositive for HPV-16 on entry into the study (n = 103, natural infection).

All three groups of vaccinated participants were comparable in age and seropositivity on entry into the study. After four years of follow-up, 100% of the vaccinated women (one, two or three doses) were seropositive for HPV-16 based on the ELISA test. The GMTs for HPV-16 were 20 times higher in the women who had received three vaccine doses than in the women who were seropositive on entry into the study (natural infection). The GMTs were 11 times (9.5 times in the group vaccinated at one-month intervals and 14.5 times in the group vaccinated at six-month intervals) higher in the women who had received two vaccine doses than in the women who were seropositive on entry into the study (natural infection) ($p < 0.001$). The GMTs were four times higher in individuals receiving one vaccine dose administered four years earlier than in those observed following natural infection.

A similar study was conducted in Uganda with comparable findings.[56]

The manufacturer of the bivalent vaccine conducted a study to compare the immunogenicity of the 0, 1, 12 month schedule versus the 0, 1, 6 month schedule. Non-inferiority with regard to seroconversion rates and GMTs was observed.[52]

Long-term efficacy studies being launched in Québec (ICI-HPV) and elsewhere in Canada (QUEST), described in appendices A and B, will be an important source of information in this regard.

The findings of at least six other studies involving alternative schedules in women and men (NCT00923702, NCT01505049, NCT01381575; NCT01184079; NCT00862810 and NCT00572832)[1] will be forthcoming within the next several years.

3.3 IMMUNOGENICITY OF 0, 6 MONTH SCHEDULES

To our knowledge, two studies—one with the bivalent vaccine, the other with the quadrivalent vaccine—have measured the immunogenicity of the two-dose (0, 6 month) schedule and compared it to the three-dose (0, 1–2, 6 month) schedule. Summaries of both studies follow.

3.3.1 Study with bivalent vaccine

In a study with the bivalent vaccine,[52] 65 participants aged 9 to 14 received two doses of the vaccine (at 0 and 6 months) and 114 participants aged 15 to 25 received three doses of the vaccine (at 0, 1 and 6 months). The main finding of this study was as follows:

In girls aged 9 to 14, two doses of the bivalent vaccine induced immunity non-inferior (at a ratio of nearly 1:1) to that observed following three vaccine doses administered to women aged 15 to 25 in whom clinical efficacy was shown. These findings remained consistent through month 18 of the study (Table 1).[57]

[1] ClinicalTrials. gov: http://clinicaltrials.gov/

Table 1 Ratios and titres of HPV-16 and HPV-18 antibodies observed one month following HPV vaccination in girls aged 9 to 14 given two doses of the bivalent vaccine six months apart versus in women aged 15 to 25 given three doses of the bivalent vaccine at 0, 1 and 6 months[57]

Study group and HPV type	n	GMT (EL.U/ml)	Ratios, 3 doses/ 2 doses (95% CI)
Bivalent, 0, 6 months – age 9–14			
HPV-16	65	11,067	
HPV-18	64	5,510	
Bivalent, 0, 1, 6 months – age 15–25			
HPV-16	111	10,322	0.93 (0.68-1.28)
HPV-18	114	4,262	0.77 (0.59-1.01)

3.3.2 Canadian study with quadrivalent vaccine

In a Canadian study (British Columbia, Nova Scotia and Québec) with the quadrivalent vaccine,[7] 830 participants were randomized into three groups: group 1 (girls aged 9 to 13) was given two doses of the vaccine six months apart, while group 2 (girls aged 9 to 13) and group 3 (women aged 16 to 26) were given three doses of the vaccine according to the 0, 2, 6 month schedule. Samples were taken at months 7, 18, 24 and 36 of the study. At month 7 of the study, and for subjects included in the per protocol analysis, the GMTs of HPV antibodies were, depending on the HPV type, 1.8 to 2.3 times higher in group 1 than in group 3 (women aged 16 to 26 receiving three vaccine doses and representing the comparison group for the main objective of the study for which efficacy data are available).

As part of the same study, 675 participants were monitored through study month 36.[7] By that time, the great majority (> 99%) of participants still had HPV-6/11/16 antibodies, while 79%, 86% and 95% had HPV-18 antibodies in the group aged 16 to 26 given three vaccine doses, the group aged 9 to 13 given two vaccine doses and the group aged 9 to 13 given three vaccine doses, respectively. However, it is to be noted that these results were obtained using the cLIA test. In the same study, 100% of the girls aged 9 to 13 given either two or three vaccine doses and 98.6% of the women aged 18 to 26 given three vaccine doses had a positive total IgG test result (personal communication, Simon Dobson, Vaccine Evaluation Centre, BC Children's Hospital). In another study conducted by Merck using the total IgG Luminex immunoassay, ~80% of negative cLIA test results were positive for the four HPV types included in the vaccine.[58]

At month 36, the non-inferiority criteria between the GMTs observed in the two groups of girls aged 9 to 13 given either two or three vaccine doses were upheld for HPV-16 and HPV-11 but not for HPV-6 or HPV-18. Throughout the study period, however, the GMTs observed in girls aged 9 to 13 given two vaccine doses were non-inferior to (and even tended to be higher than) the GMTs observed in women aged 16 to 26 given three vaccine doses.[7]

The results obtained in groups 1, 2 and 3 of the above Canadian study and the results of the studies conducted by Merck and documented in the monograph of the quadrivalent vaccine

are depicted in Figure 1.[7, 59] A similar downward slope is observed regardless of the data source, age at vaccination or number of doses received.

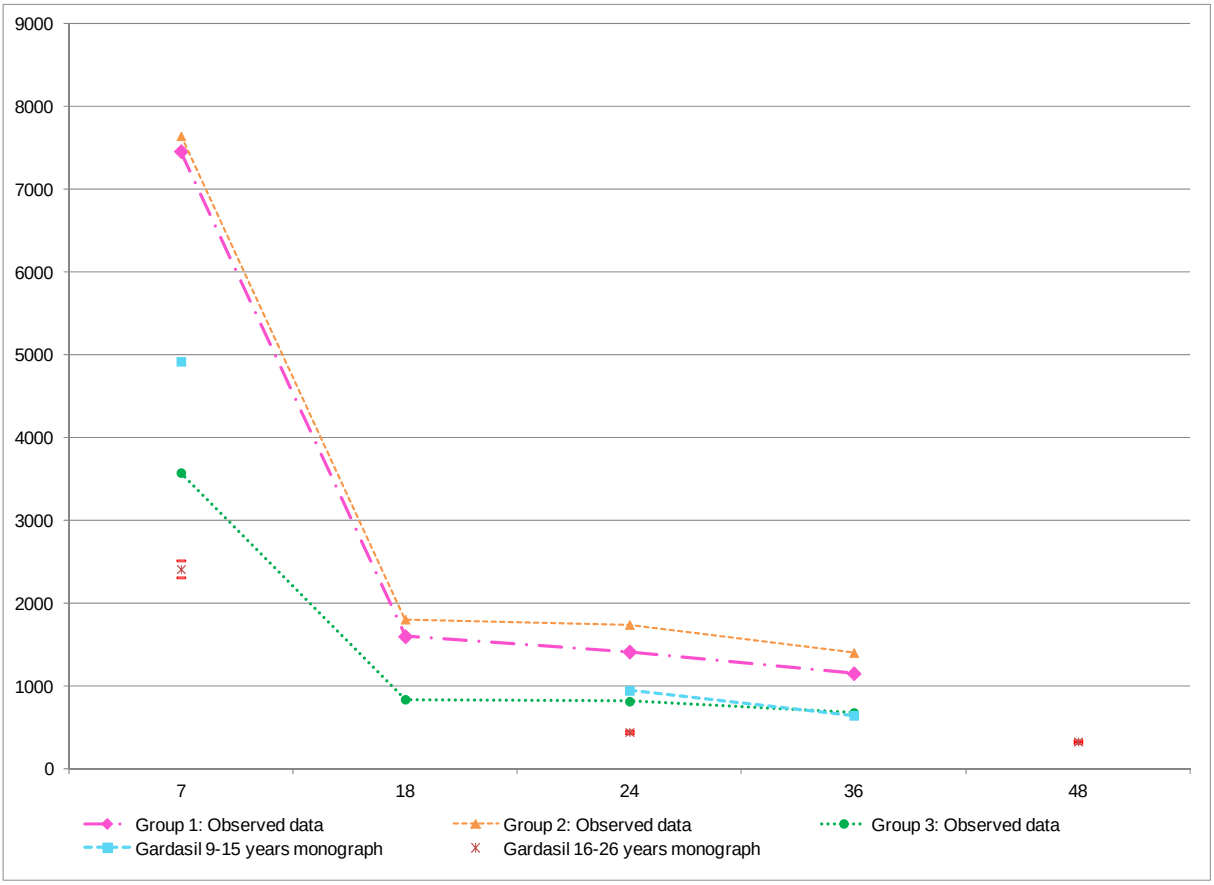


Figure 1 Comparison of GMTs by data source, number of doses and age at vaccination

3.3.2.1 Tests conducted to measure memory B and T cells in the Canadian study

Testing to detect memory B and T cells (ELISPOT) was carried out at month 7 on a sub-cohort of the Canadian study. The authors found that the age at the time of vaccination and the number of doses administered (two or three) have a different impact on the development of memory B and T cells. Younger subject age at the time of vaccination, for example, had positive impact on the generation of HPV-18-specific memory B cells, while administration of a higher number of doses (three) generated more HPV-specific memory T cells for HPV types 6, 16 and 18.[60] The primary role of memory B cells is to produce antibodies within a short time frame following re-exposure to the same HPV types.[61] Memory B cells also appear to play a significant role in long-term antibody persistence. Under these circumstances, a high number of memory B cells may present a predictive biomarker for the long-term persistence of high levels of antibodies.[62] The authors conclude that, at least in terms of generating memory B cells, vaccination at age 9–13 is advantageous and maximizes immune response and the potential efficacy of HPV vaccines. In light of the pivotal role of HPV antibodies shown in relation to the level of protection conferred by the

vaccine and the fact that two vaccine doses induce an optimal memory B response when administered to young girls, the authors suggest that a two-dose schedule be considered.[60]

Although HPV-specific memory T cells play an important role in the regression of infections, the importance and the role of the same cells in the prophylactic protection conferred by the vaccines is less evident.[63-64]

3.3.2.2 Results of 96-month projected data based on Canadian data collected up to 36 months

The HPV-16 antibody titres observed at months 7, 18, 24 and 36 of the Canadian study were modelled in an effort to predict antibody titres 96 months following primary vaccination. A highly conservative approach was used in this modelling process. For instance, the steep downward slope in antibody titres between months 7 and 18 was taken into account in the explanatory model of predicted titres beyond month 36 (Table 2). However, as illustrated in Figure 1, little variation was observed in antibody titres in months 18, 24 and 36. It is also to be noted that with the conservative approach that was used, no statistically significant differences were found between predicted GMTs in month 96 for the two groups of girls aged 9 to 13 (two doses six months apart versus three doses).

Table 2 Observed and predicted values for HPV-16 antibodies

Values observed during study						**Values predicted by model**		
Group	N	Month	GMTs	min. CI	max. CI	Prediction	min. CI	max. CI
Group 1	243	7	7456.55	6387.56	8704.46	6422.7	5436.28	7612.68
Group 1	96	18	1598.11	1332.76	1916.28	2593.76	2263.33	2979.59
Group 1	195	24	1413.65	1234.89	1618.30	1646.58	1425.27	1907.7
Group 1	86	36	1151.07	917.85	1443.54	716.88	597.09	865.23
Group 1		**96**				**37.52**	**27.65**	**52.36**
Group 2	251	7	7639.76	6560.78	8896.17	6621.8	5751.49	7641.31
Group 2	98	18	1804.43	1507.64	2159.66	2940.56	2586.39	3350.25
Group 2	186	24	1739.31	1514.46	1997.55	1950.03	1695.27	2249
Group 2	84	36	1401.71	1114.72	1762.57	912.68	764.05	1095.41
Group 2		**96**				**55.71**	**41.25**	**77.07**
Group 3	246	7	3574.47	3064.92	4168.74	3222.18	2871.2	3622.11
Group 3	92	18	837.14	695.42	1007.73	1455.07	1305.59	1624.32
Group 3	189	24	813.26	708.90	932.97	975.22	863.84	1103.36
Group 3	86	36	677.82	540.49	850.04	467.37	399.4	549.15
Group 3		**96**				**32.9**	**25.42**	**43.46**

3.3.3 Québec study on the co-administration of the Twinrix and Gardasil vaccines

A total of 416 girls took part in phase 1 of this randomized study in 2008–2009 and 366 girls in phase 2 in 2011–2012. The study design is provided in Figure 2.

Immune response and antibody persistence were measured following administration of one and two doses of Gardasil to girls aged 9 to 10 according to the 0, 6 month schedule (phase 1). To ensure that study participants did not have to provide more than four blood samples, sampling following administration of the first vaccine dose was performed only among group A participants (Figure 2). The impact of administering an additional dose of Gardasil or Cervarix in month 42 of the study was also documented (phase 2).

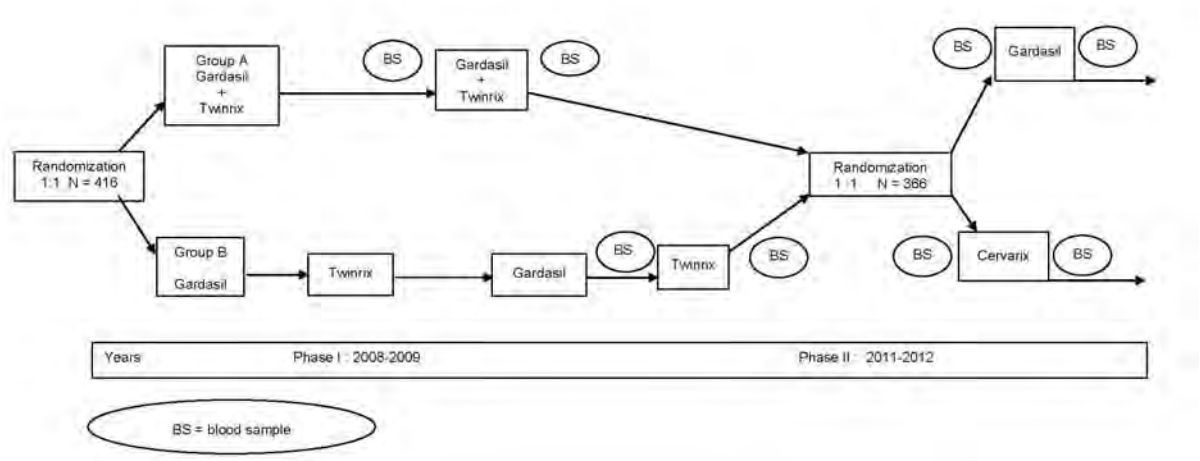


Figure 2 Study design

Serology was performed at the Laboratoire de santé publique du Québec (LSPQ), with the preliminary study findings outlined in tables 3 and 4 and Figure 3. As of April 12, 2013, the serologic results for 324 subjects were available and are included in the present analysis. Antibody titres are presented in Luminex Units (LU).

One of the study objectives was to identify the occurrence of any interference when Gardasil and Twinrix are co-administered. Table 3 sets out the results showing that HPV antibody titres remain comparable regardless of whether the Gardasil vaccine was administered concurrently with or one month before the Twinrix vaccine. The results for participants in groups A and B were consequently combined for presentation of the following findings.

Table 3 Geometric mean titres of HPV antibodies by timing of vaccine administration, either concurrently or one month apart

TIgG Luminex Immunoassay	1 month after 2nd dose		36 months after 2nd dose	
	Gardasil-Twinrix co-administered n = 167	Gardasil-Twinrix 1 month apart n = 154	Gardasil-Twinrix co-administered n = 167	Gardasil-Twinrix 1 month apart n = 155
	(GMTs (LU)) 95% CI	(GMTs (LU)) 95% CI	(GMTs (LU)) 95% CI	(GMTs (LU)) 95% CI
HPV-16 antibodies	3637	3759	294	341
	3261 - 4057	3377 - 4183	248 - 348	289 - 402
HPV-18 antibodies	953	1041	46	63
	841 - 1080	916 - 1183	38 - 57	52 - 76
HPV-6 antibodies	1160	1251	77	85
	1030 - 1306	1107 - 1413	65 - 91	71 - 102
HPV-11 antibodies	4002	4072	307	332
	3642 - 4397	3667 - 4521	265 - 356	284 - 389

Table 4 Geometric mean titres of HPV antibodies by time period following vaccination

TIgG Luminex Immunoassay	6 months after 1st dose N = 167		1 month after 2nd dose N = 321		36 months after 2nd dose N = 322		1 month after 3rd dose of Gardasil N = 163		1 month after 3rd dose of Cervarix N = 160	
	% detectable titres	GMTs 95% CI	% detectable titres	GMTs 95% CI	% detectable titres	GMTs 95% CI	% detectable titres	GMTs 95% CI	% detectable titres	GMTs 95% CI
HPV-16 antibodies	99	47 39 - 56	100	3695 3423 - 3988	100	316 280 - 356	100	4761 4365 - 5193	100	5746 5240 - 6301
HPV-18 antibodies	98	14 11 - 17	100	994 909 - 1087	99	54 47 - 62	100	1789 1589 - 2014	100	2747 2420 - 3119
HPV-6 antibodies	93	12 9 - 14	100	1203 1105 - 1310	100	81 71 - 91	100	1653 1488 - 1837	100	128 111 - 148
HPV-11 antibodies	100	72 61 - 84	100	4035 3762 - 4328	100	319 287 - 355	100	4421 4049 - 4826	100	470 413 - 535

Six months after the first dose, 93 to 100% of participants had detectable antibody titres with GMTs ranging from 11 to 72 LU, depending on the HPV type (Table 4). Antibody titres were probably higher one month following vaccination in keeping with the usual kinetics of antibodies measured post-vaccination,[14] but this data were not collected for this study. One month after the second vaccine dose, 100% of participants had detectable antibody titres with GMTs ranging from 994 to 4035 LU, depending on the HPV type. Three years after the second dose, 100% still had detectable levels of HPV-16, 6 and 11 antibodies and 99% still had HPV-18 antibodies. One month following administration of an additional (challenge) dose of Gardasil or Cervarix 36 months after the second dose, 100% of participants had detectable antibody levels. In both the Gardasil and Cervarix groups, the GMTs of HPV-16 and HPV-18 antibodies were slightly higher than those observed one month after the second vaccine dose ($p < 0.05$). The dynamics of the GMTs for HPV-16 are shown in Figure 3.

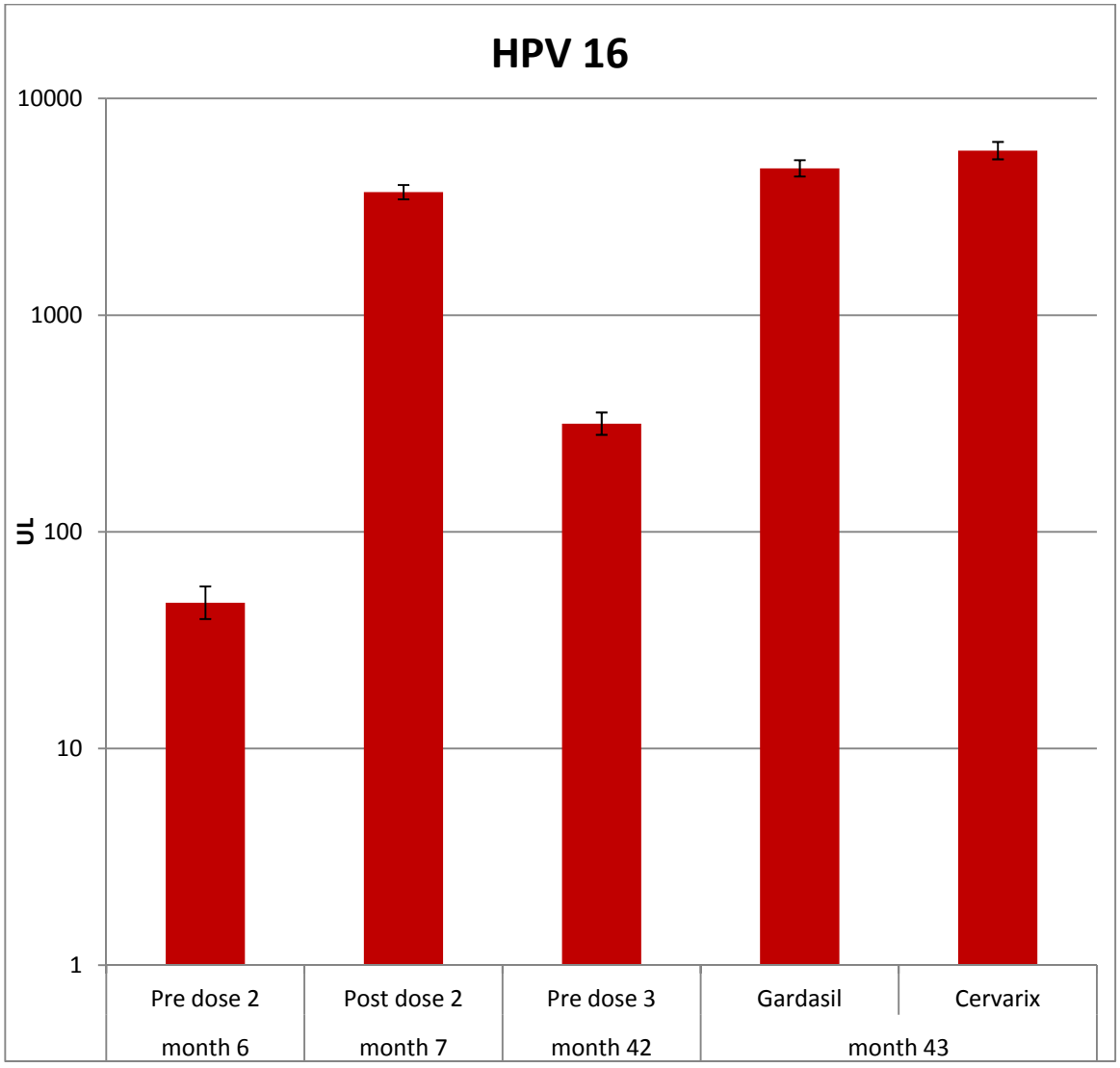


Figure 3 **Geometric mean titres (95% CI) for HPV-16 in study months 6, 7, 42 and 43**

One month after the second vaccine dose, the GMTs increased 56- to 109-fold compared to the GMTs observed prior to administration of that dose. This increase points to a strong anamnestic response after the second vaccine dose.

Administration of the third dose of Gardasil induced GMTs 14 to 33 times higher than those observed immediately before administration of that vaccine dose. These data point toward the persistence of an excellent immune memory 36 months following administration of the second vaccine dose. A comparison of the GMTs observed one month after the third dose and one month after the second dose of Gardasil reveals a 1.1- to 1.8-fold increase, depending on the HPV type.

4 IMMUNIZATION SAFETY

HPV vaccines administered to girls aged 9 to 11 are well tolerated. Since the introduction of the program in 2008, more than 805,000 doses of the HPV vaccine have been distributed throughout Québec (> 100 million doses of the quadrivalent HPV vaccine distributed worldwide). Approximately 250 cases of adverse events following immunization (AEFI) for HPV had been entered into Québec's ESPRI register (register of adverse effects potentially attributable to vaccination) as at July 18, 2011. The overall AEFI rate stands at 32 per 100,000 doses distributed, while the rate of serious AEFI is 2 per 100,000 doses. The reporting rate for AEFI for the 2010–2011 campaign (32 per 100,000) was similar to the rate observed during the first vaccination campaign in 2008–2009 (36 per 100,000). The AEFI reported most frequently are allergic-type reactions (37%) and local reactions (35%). More than 90% of AEFIs reported are expected events benign in nature. Approximately 6% of events reported are classified as serious AEFI. It is to be noted that reporting an AEFI does not necessarily mean that the vaccine was the cause but simply that the event occurred following immunization. Establishing a causal link between the vaccine and an AEFI is a complex process exceeding the scope of the ESPRI monitoring program. The average reporting rate for AEFI in Québec is lower than or comparable to rates reported under passive monitoring programs in other countries.[65]

A two-dose schedule could minimize AEFI compared to a three-dose schedule.

More AEFI are typically reported following vaccination of girls aged 14 to 15 than vaccination of girls aged 9 to 11.[66]

5 POPULATION IMPACT MODEL (HPV-ADVISE) AND ECONOMIC ANALYSES

This section is based on the following report: Brisson, M., J.-F. Laprise and M. Drolet. *Efficacité populationnelle et coût-efficacité de programmes de vaccination contre les VPH à deux ou trois doses* [Population-level efficacy and cost-effectiveness of two- and three-dose HPV vaccination programs]. Report submitted to the INSPQ in March 2013. The English version of this report (the present section) has not been revised by the authors.

This section presents the results of an analysis of the population-level efficacy and cost-effectiveness of administering two or three doses of the HPV vaccine in Québec. The main objective of the analysis was to identify the most effective and cost-effective immunization strategy of the following: 1) two doses for girls (i.e. no third dose is administered); 2) three doses for girls; and 3) two doses for girls and boys. Analyses were also conducted to verify the efficacy and cost-effectiveness ratio of a three-dose vaccination program for girls and boys.

5.1 METHOD

5.1.1 HPV-ADVISE Québec

In short, we used *HPV-ADVISE Québec* (Agent-based Dynamic model for VaccInation and Screening Evaluation)[67–68], a dynamic, individual-based HPV transmission model, which includes sequential sexual partnership formation and dissolution and natural history of multi-type HPV infection (18 types of HPV virus modeled individually) and HPV-related diseases (genital warts, cervical cancers and other HPV-related cancers), as well as cervical cancer screening.[68] The model is described in detail in a previous report[20] and in a number of publications[67–68].

5.1.1.1 Immunization

HPV-ADVISE Québec assumes that HPV vaccination can prevent infection but does not alter the natural history of infection and disease in individuals already infected at the time of vaccination. Table 5 shows the vaccine efficacy values used in the model for the quadrivalent vaccine. In the simulations, the vaccine is assumed to be equally effective for girls and boys and at ages 9 and 14.

Table 5 Vaccine efficacy parameters[69]

HPV Types	Base case
16/18	95.0
6/11	95.0
31	46.2
33	28.7
45	7.8
52	18.4
58	5.5
Other HR HPVs	0.0

HR: High oncogenic risk.
Other HR HPV types: 35, 39, 51, 56, 59, 66, 68, 73 and 82.

5.1.1.2 Men who have sex with men (MSM)

The burden and risks of HPV-related diseases differ for MSM and heterosexual men. In addition, MSM will benefit little from the indirect protection conferred by the vaccination of girls. To take these differences into consideration, the costs and benefits to MSM and heterosexual men were estimated separately and subsequently incorporated into the efficacy and cost-effectiveness predictions for the various immunization scenarios analyzed. For the base case, MSM are considered to account for 3% of the male population in Québec,[70] to be 17 times more likely to develop anal cancer than heterosexual men[71] and to be 3 times more likely to develop genital warts or other HPV-related cancers than heterosexual men[72]. Sensitivity analyses were conducted by increasing the proportion of MSM in Québec to 7% and their risk of developing HPV-related cancers and genital warts to 17.

5.1.2 Immunization scenarios evaluated

Figure 4 illustrates the four immunization strategies that were evaluated using the model. During the first five years of the program, 9-year-old girls were vaccinated with two doses and 14-year-old girls were vaccinated with three doses as part of the catch-up program. The following immunization strategies are currently being considered: 1) vaccinate **girls with two doses** (age 9); 2) vaccinate **girls with three doses** (two doses at age 9 and one dose at age 14); 3) vaccinate **girls and boys with two doses** (age 9); and 4) vaccinate **girls and boys with three doses** (two doses at age 9 and one dose at age 14).

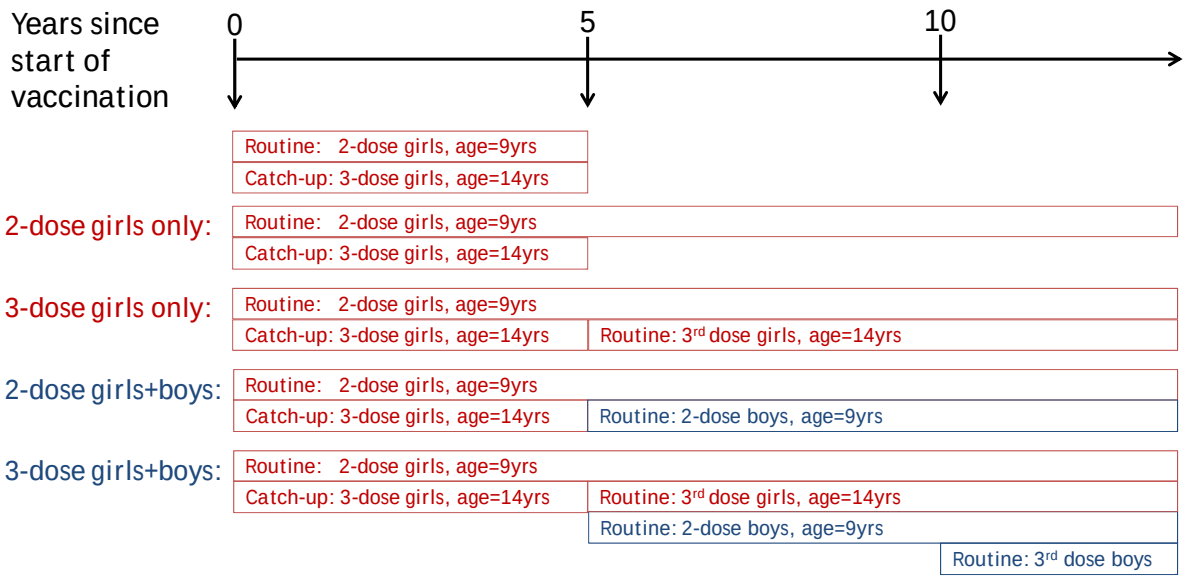


Figure 4 Vaccine strategies evaluated

5.1.3 Vaccination coverage and number of doses

Table 6 shows the vaccination coverage rates by number of doses used in the model. For the two-dose strategies, we assumed that vaccination coverage at age 9 was 80%. For the three-dose strategies, we assumed that the coverage at age 9 was also 80% for the first two doses and that the coverage at age 14 (for those vaccinated at age 9) was 90% for the third dose. In addition, we assumed that 20% of girls not vaccinated at age 9 (through a two- or three-dose strategy) could be reached at age 14 when their immunization record is updated and that they could therefore receive three doses of the vaccine at that time. This would increase the overall coverage by 4% (20% coverage among 20% of girls not vaccinated at age 9 = 4%). Lastly, we assumed that vaccination coverage was 80% for the three doses of the catch-up program during the first five years of the program. For the mixed immunization strategies, we assumed that the coverage was identical for girls and boys. However, no catch-up vaccinations for boys were considered, as we assumed that the catch-up program would be completed by the time boys began receiving the vaccine.

Table 6 Vaccination coverage and number of doses

	Vaccination Coverage	
Program	Age 9	Age 14
2 doses	80% (2 doses)	20% (3 doses) for those not vaccinated at age 9 (overall 4%)
3 doses	80% (2 doses)	90% (1 dose) for those vaccinated at age 9 20% (3 doses) for those not vaccinated at age 9 (overall 4%)
Catch-up	----	80% (3 doses)

5.1.4 Economic analyses

The economic analysis outlook is that of the MSSS. A 3% annual discount is applied to costs and benefits. The timeline is 70 years (i.e. the approximate life span of the first cohort), and the cost per vaccine dose is $85, including administration costs.

5.1.5 Sensitivity analyses

Table 7 shows the assumptions for the base case and sensitivity analyses with respect to the duration of protection and efficacy of the two- and three-dose vaccination programs. In the base case, we conducted analyses involving 20- and 30-year durations of protection from the two-dose vaccination, and for each of these durations, we assumed that 1) the third dose provided the same duration of protection as the two previous doses or 2) the third dose provided longer duration of protection than the two previous doses (30 years or lifelong protection for the 20-year scenarios involving two doses and lifelong protection for the 30-year scenarios involving two doses). It is important to note that, when the third dose is assumed to provide the same duration of protection as the two previous doses, gains in duration of protection could still be made since the third dose is administered five years after the first two doses. In the base case, the duration of protection was therefore calculated as starting after administration of the third dose. We also conducted a sensitivity analysis in which the duration of protection was calculated as starting after the second dose. Lastly, we conducted sensitivity analyses by assuming that the duration of protection for a two-dose program would be 10 years or lifelong and that the vaccine would be less effective against the vaccine types (90%) for a two-dose program.

Univariate sensitivity analyses were also conducted by varying the economic parameters (costs and QALYs lost), vaccine price, proportion of MSM in the population and relative risk of disease for MSM compared to heterosexual men.

Table 7 Assumptions regarding duration of protection and vaccine efficacy

Scenarios	2 vs. 3 doses					
	Base case			Sensitivity analysis		
Duration (years)	20	vs.	20	10	vs.	20
		vs.	30	lifetime	vs.	lifetime
		vs.	lifetime			
	30	vs.	30			
		vs.	lifetime			
Efficacy	95%	vs.	95%	90%	vs.	95%
Booster				The third dose does not extend the duration		

5.2 RESULTS AND DISCUSSION

5.2.1 Population-level effectiveness

5.2.1.1 Cancer cases prevented

Figure 5 illustrates the number of cancer cases prevented by the various immunization strategies.

Two-dose vaccination, 20-year duration of protection

Under baseline assumptions (vaccination coverage = 80%, vaccine efficacy for vaccine types = 95%) and assuming a 20-year duration of protection, *HPV-ADIVSE Québec* predicts that, on average, vaccinating girls with two doses would prevent 130 cancer cases per year (over a 70-year period). Approximately half of these prevented cases would be cervical cancers. Adding a third dose for girls only would prevent 17 to 34 additional cancers per year (over a 70-year period), depending on the duration of protection conferred by the third dose (20 years, 30 years or lifetime). The model also predicts that extending two-dose vaccination to boys (two-dose program for boys and girls) could prevent 18 more cancer cases per year (over a 70-year period) than two-dose vaccination of girls only.

Two-dose vaccination, 30-year duration of protection

Also under baseline assumptions (vaccination coverage = 80%, vaccine efficacy for vaccine types = 95%) and assuming a 30-year duration of protection, *HPV-ADIVSE Québec* predicts that, on average, the two-dose vaccination of girls only could prevent 140 cancer cases per year (over a 70-year period). Adding a third dose for girls only would prevent 7 to 15 additional cancers per year (over a 70-year period) for the 30-year or lifelong duration of protection of a three-dose program, respectively. Extending two-dose vaccination to boys (two-dose program for boys and girls) could prevent 16 additional cancer cases per year (over a 70-year period).

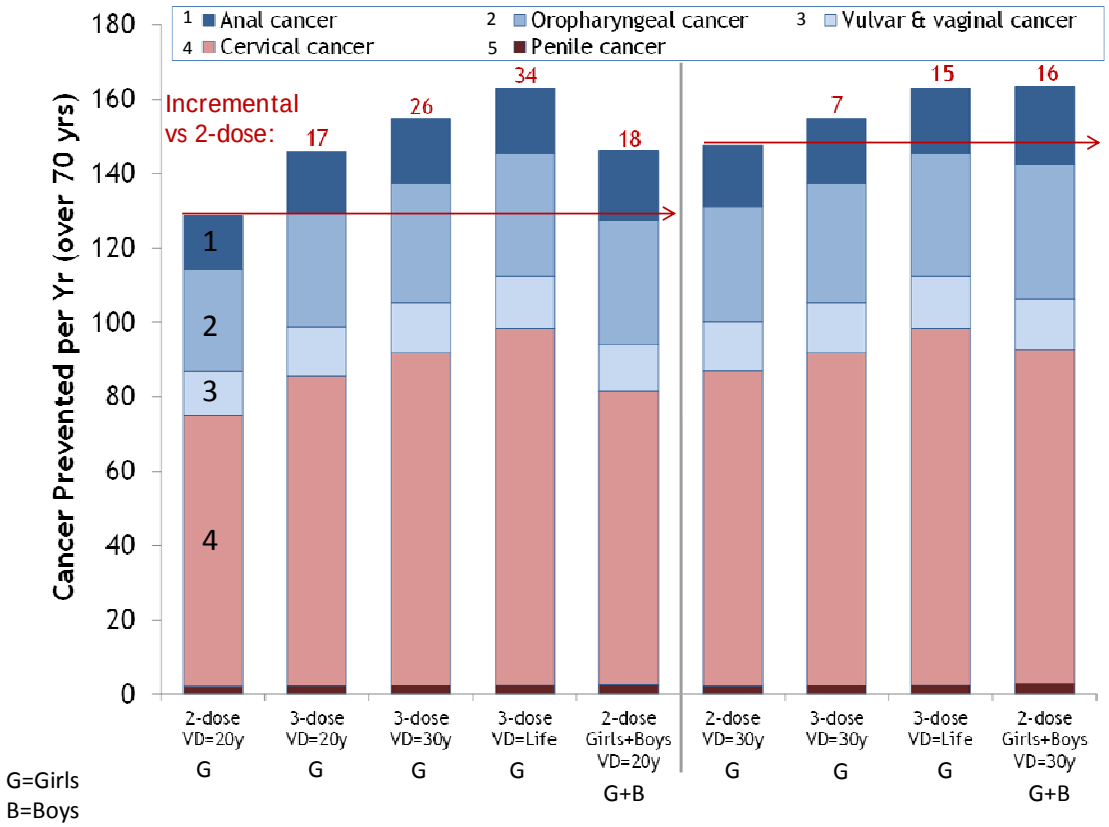


Figure 5 **Cancer cases prevented by the various immunization strategies (undiscounted, population = 7 million, vaccination coverage = 80%, vaccine efficacy for vaccine types = 95%)**

VD: Vaccine duration.

It is important to note that, even assuming that the third dose provides a duration of protection similar to that of the two previous doses, this dose could act as a booster dose and delay the loss of protection. To take this potential effect into account, we assumed that the loss of protection would be calculated as starting after the third dose, that is, five years later than expected with a two-dose program. Therefore, for a 20-year duration of protection, girls vaccinated with two doses at age 9 will, on average, be protected until age 29, while those who receive a third dose at age 14 will, on average, be protected until age 34. As

illustrated in Figure 6, this delays the gradual loss of protection and therefore the increase in the incidence of infection. This booster dose has an even greater impact when the duration of vaccine protection is shorter.

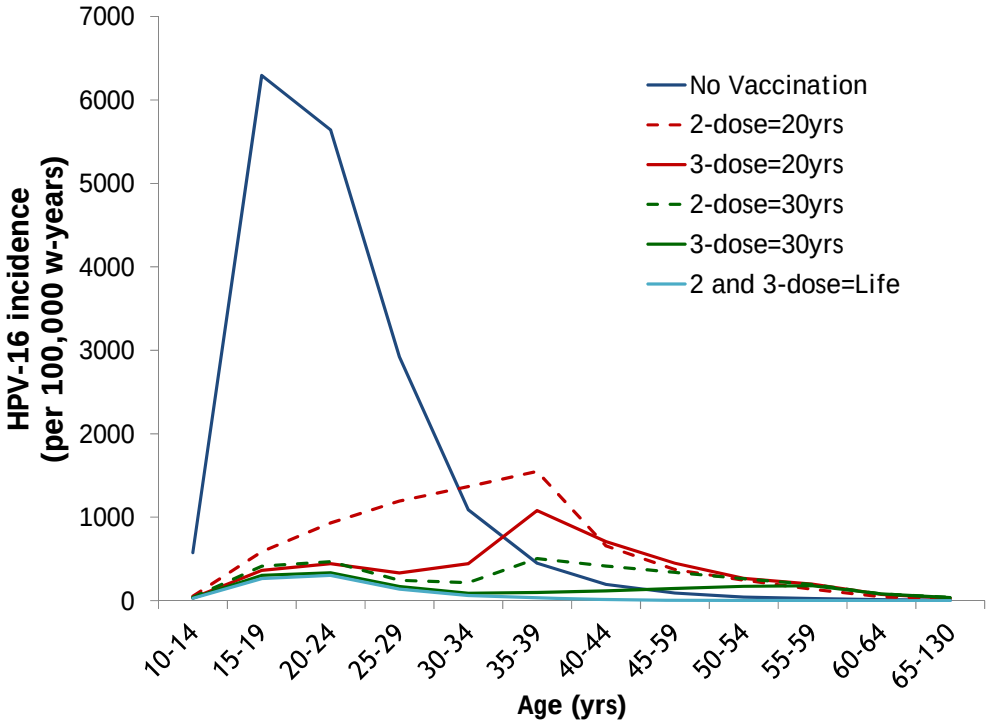


Figure 6 Impact of booster dose on the incidence of HPV-16 and age at infection

5.2.2 Cost-effectiveness gains

5.2.2.1 In QALYs and health care cost savings

Figures 7 and 8 show the QALY gains and health care cost savings over a 70-year period, respectively, as predicted by *HPV-ADVISE Québec* for the various two- and three-dose immunization strategies. It is important to note that the health care cost savings do not include the cost of the vaccination program.

Two-dose vaccination, 20-year duration of protection

A two-dose immunization strategy for girls only (20-year duration of protection) would generate gains of 14,500 QALYs over a 70-year period. Most of these gains would be due to the prevention of cases of cervical cancer. A two-dose immunization strategy for girls only would cost an estimated $260 million, but it would save $180 million in health care costs over 70 years (total cost of $152 million = program costs – health care cost savings). The prevention of precancerous cervical lesions accounts for most of these cost savings. The addition of the third dose for girls would generate additional gains of 2,000 to 3,500 QALYs over 70 years and additional health care cost savings of $16 million to $42 million, depending on the duration of protection provided by the third dose. However, a three-dose immunization

strategy for girls only would cost $337 million over 70 years (i.e. $76 million more than the two-dose immunization strategy for girls). Lastly, a two-dose immunization strategy for girls and boys would generate fewer additional QALY gains (approximately 1,400 QALYs over 70 years) and health care cost savings of only $10 million over 70 years. In addition, this strategy would cost an estimated $440 million over 70 years (i.e. $180 million more than a two-dose immunization strategy for girls only).

Two-dose vaccination, 30-year duration of protection

A two-dose immunization strategy for girls only (30-year duration of protection) would generate gains of 16,400 QALYs over a 70-year period. The cost of this strategy is also $260 million over 70 years, but it would save $131 million in health care costs (total cost of $129 million). When the administration of two doses of vaccine is assumed to provide a longer duration of protection (30 years compared to the 20 years in the previous scenario), the additional benefits of adding the third dose are lower. Therefore, adding the third dose for girls only would generate additional gains of 400 to 1,500 QALYs over 70 years and health care cost savings of $5 million to $20 million, depending on the duration of protection provided by the third dose. However, this strategy would entail additional immunization costs of $76 million (compared to the two-dose vaccination of girls). Lastly, the two-dose immunization strategy for girls and boys would generate very limited additional gains (< 1,000 QALYs and savings of $7 million over 70 years) at an additional cost of $180 million, compared to the two-dose vaccination of girls only.

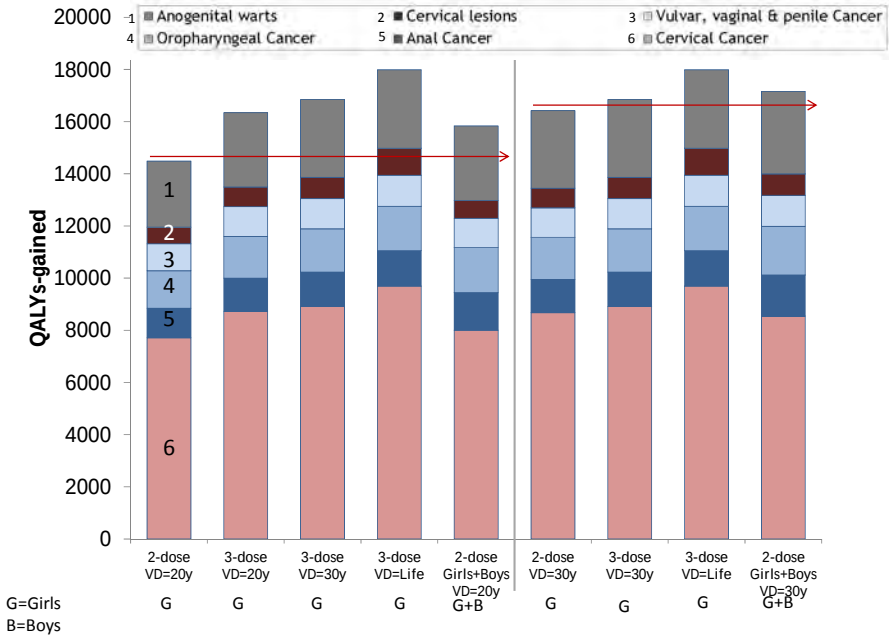


Figure 7 **QALY gains for the various immunization strategies (discounted at 3% per year, population = 7 million, timeline = 70 years)**

VD: Vaccine duration.

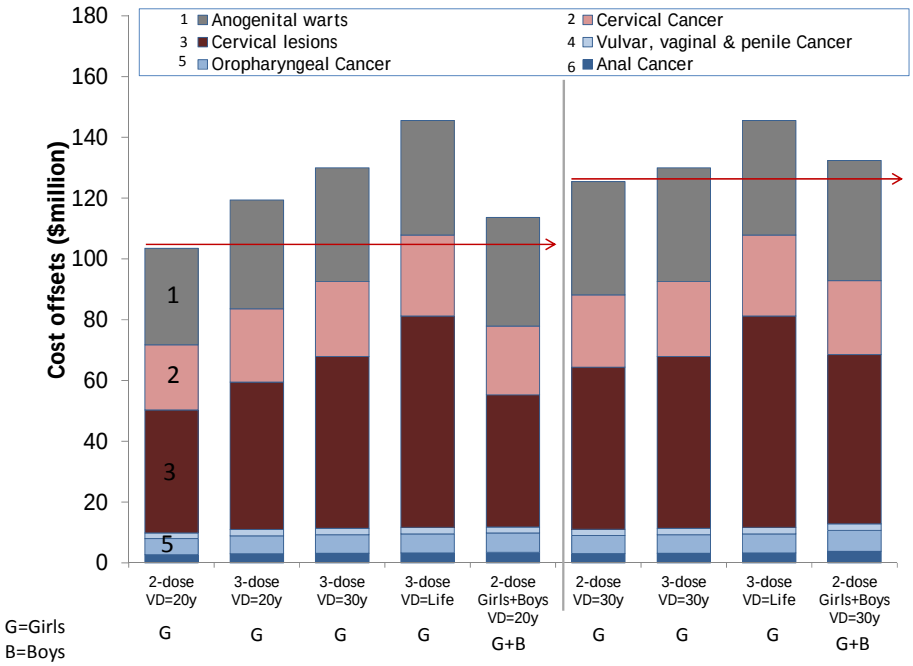


Figure 8 **Health care cost savings for the various immunization strategies (discounted at 3% per year, population = 7 million, timeline = 70 years)**

VD: Vaccine duration.

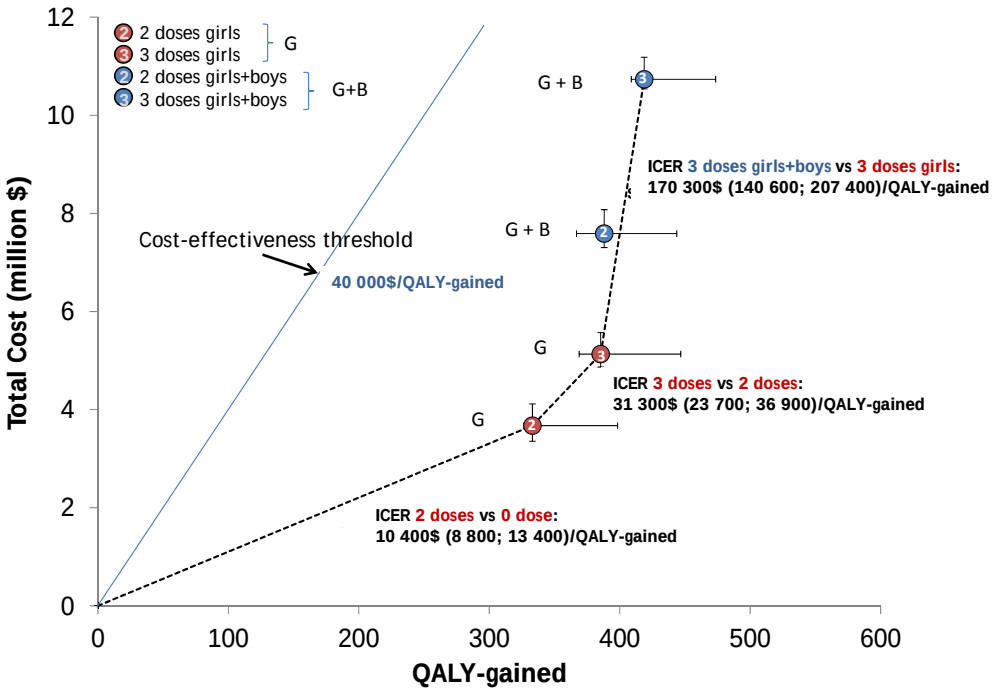
5.2.2.2 Cost-effectiveness of the various immunization strategies

Figures 9 a–f illustrate the incremental cost-effectiveness ratios (ICERs) of the different immunization strategies, which were predicted by *HPV-ADVISE Québec* based on various durations of protection assumed for two or three doses of the vaccine. The different strategies are identified with red circles (strategies involving girls only) or blue circles (strategies involving girls and boys) and are positioned on the graph according to their total cost (program costs – health care cost savings) and their QALY gains. The figures in the circles represent the number of doses. The value of the slope linking two strategies is the ICER of shifting from one strategy to the other. The slope of the blue line represents the cost-effectiveness threshold of $40,000/QALY gained. Therefore, slopes linking two strategies below the slope of the blue line represent cost-effective strategies at the $40,000/QALY gained threshold.

Figures 9 a–f indicate that, based on all the assumptions regarding durations of vaccine protection, the two-dose vaccination of girls only is a far more cost-effective strategy than the absence of vaccination (ICER ranging from $6,400/QALY gained to $10,400/QALY gained, depending on the duration of protection provided by two doses). Likewise, the addition of the third dose is a more cost-effective strategy than a two-dose immunization strategy for girls only, except when the two doses of the vaccine are assumed to provide protection of 30 or more years (figures 9 d–f). In this case, the ICER between the addition of the third dose and the two-dose immunization strategy for girls is greater than $39,500/QALY gained (durations of protection: 2 doses = 30 years and lifetime, 3 doses = lifetime).

Figures 9 a–f also show that, in most scenarios, the two- or three-dose vaccination of girls and boys is a less cost-effective strategy than the three-dose vaccination of girls (at the current cost of the vaccine). In fact, the two-dose vaccination of girls and boys is a dominated strategy, that is, it provides benefits that are lower than or equal to those of the three-dose vaccination of girls but at a much higher cost. The only scenario in which this strategy is not dominated would be when the duration of protection from two doses of the vaccine is assumed to be lifelong (Figure 9f). Under this assumption, the two-dose vaccination of girls generates substantial QALY gains, and the addition of the third dose for girls does not offer any additional benefits. At this time, adding the two-dose vaccination of boys could generate additional QALY gains but at a very high cost. Therefore, while this strategy is not dominated, its ICER ($121,500/QALY gained) remains well above the $40,000/QALY gained threshold. As for the three-dose vaccination of girls and boys, this also offers more QALY benefits than the three-dose vaccination of girls only in all scenarios (figures 9 a–f), but its very high cost results in ICERs that are well above the cost-effectiveness threshold ($130,800/QALY gained - $170,300/QALY gained). In order for the immunization strategies for girls and boys to become cost-effective, the vaccine for boys would have to cost half the price of the vaccine for girls. It is also important to note that, even if vaccine prices for boys and girls decrease by equal amounts, the strategies that involve vaccinating boys will, in most scenarios, remain less cost-effective than the immunization strategies for girls only.

A) Duration of protection: 2 doses = 20 years, 3 doses = 20 years



B) Duration of protection: 2 doses = 20 years, 3 doses = 30 years

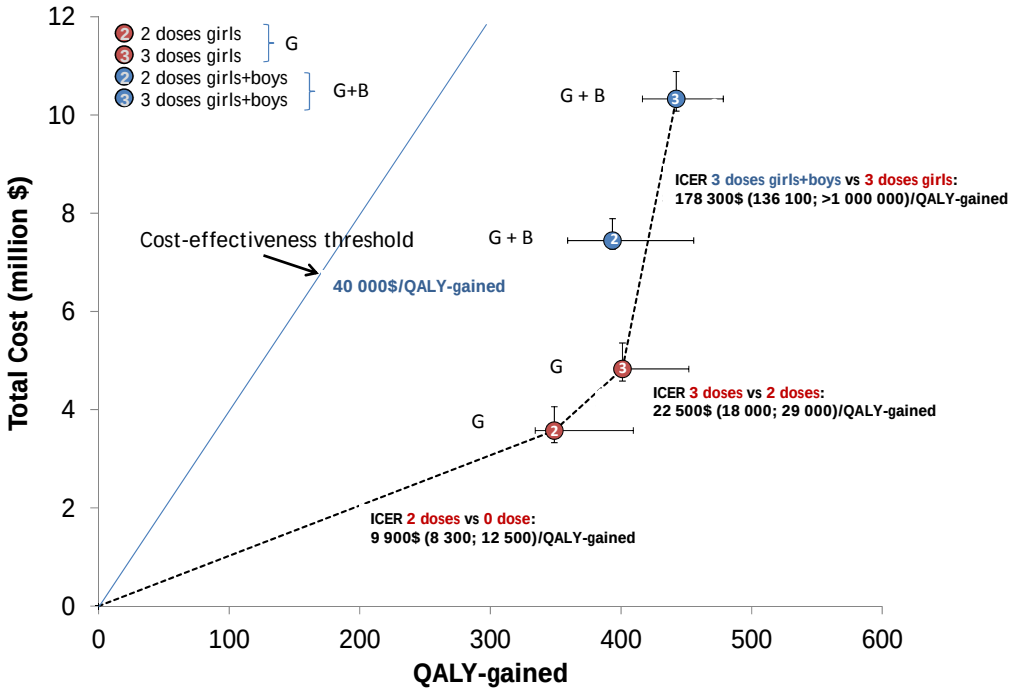
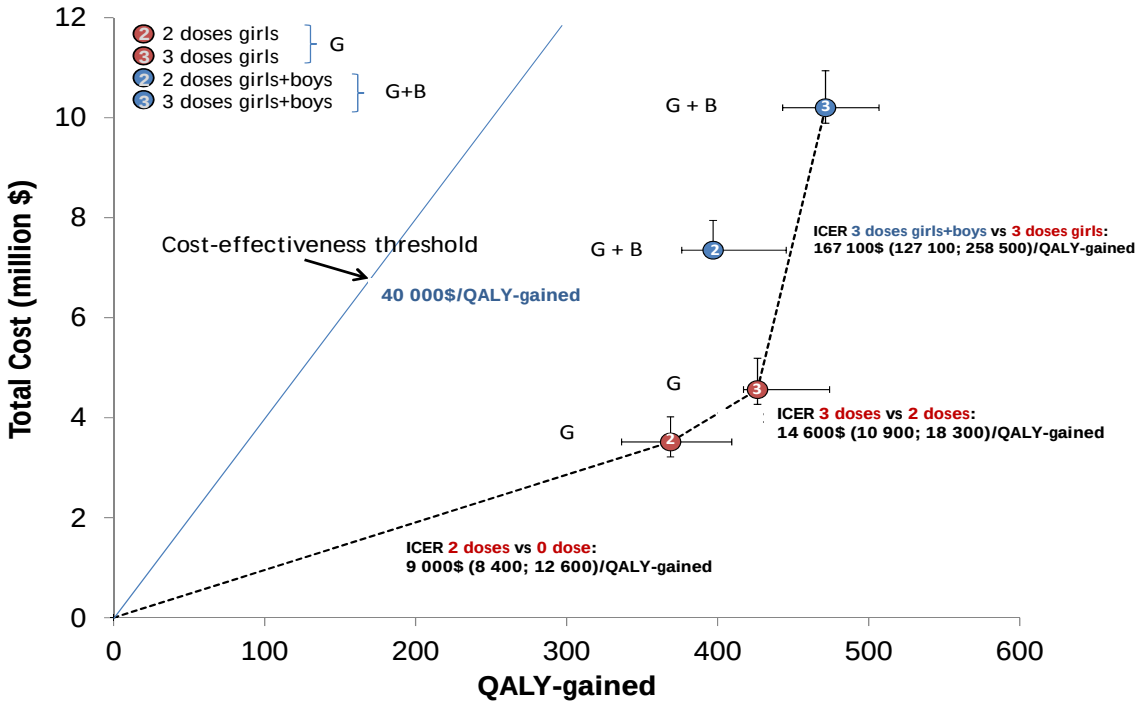


Figure 9 **Cost-effectiveness of immunization strategies by varying durations of vaccine protection (vaccination coverage = 80%, vaccine efficacy for vaccine types = 95%, discounted at 3% per year)**

C) Duration of protection: 2 doses = 20 years, 3 doses = lifetime



D) Duration of protection: 2 doses = 30 years, 3 doses = 30 years

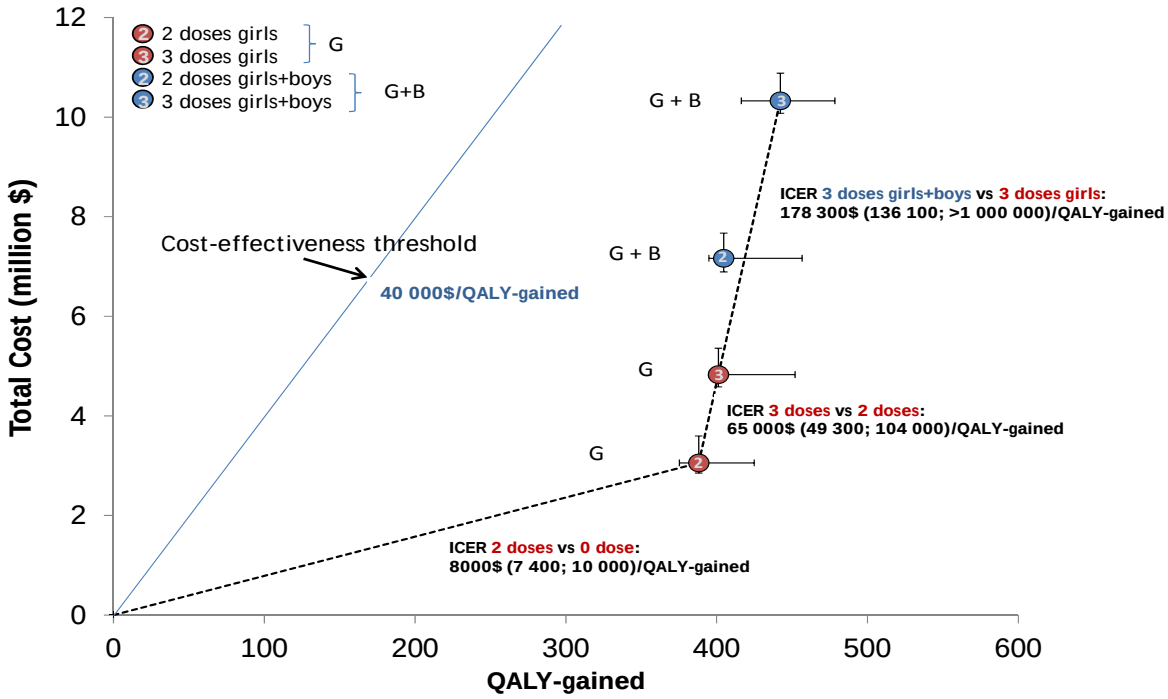
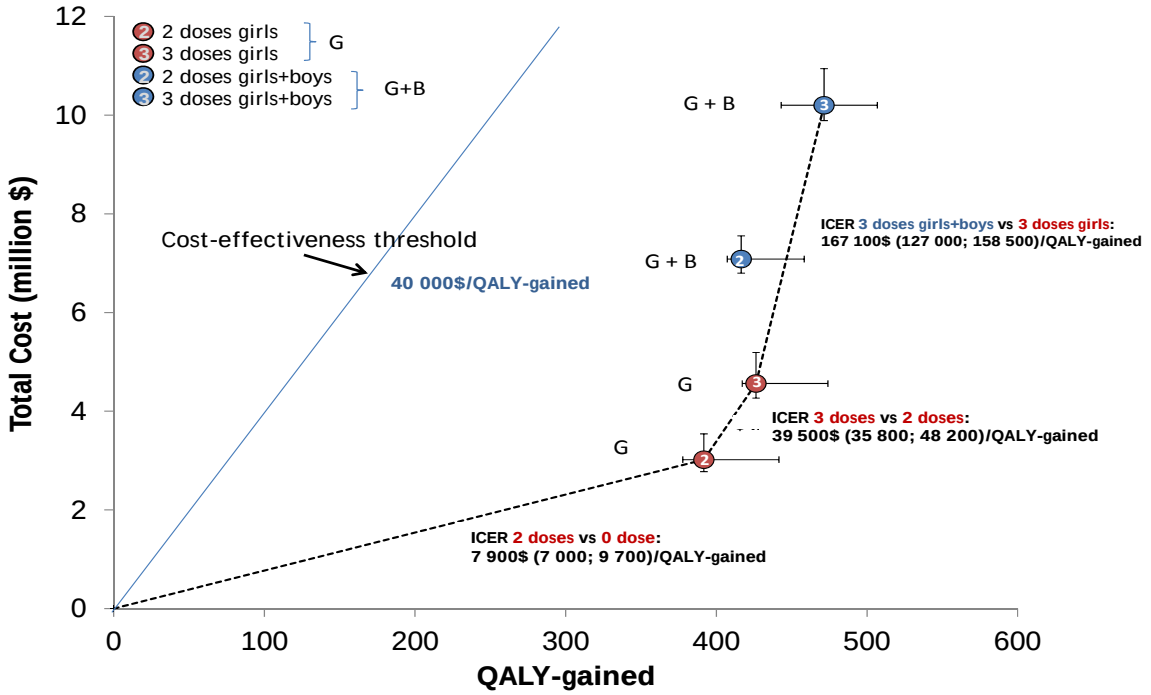


Figure 9 **Cost-effectiveness of immunization strategies by varying durations of vaccine protection (vaccination coverage = 80%, vaccine efficacy for vaccine types = 95%, discounted at 3% per year) (cont'd)**

E) Duration of protection: 2 doses = 30 years, 3 doses = lifetime



F) Duration of protection: 2 doses = lifetime, 3 doses = lifetime

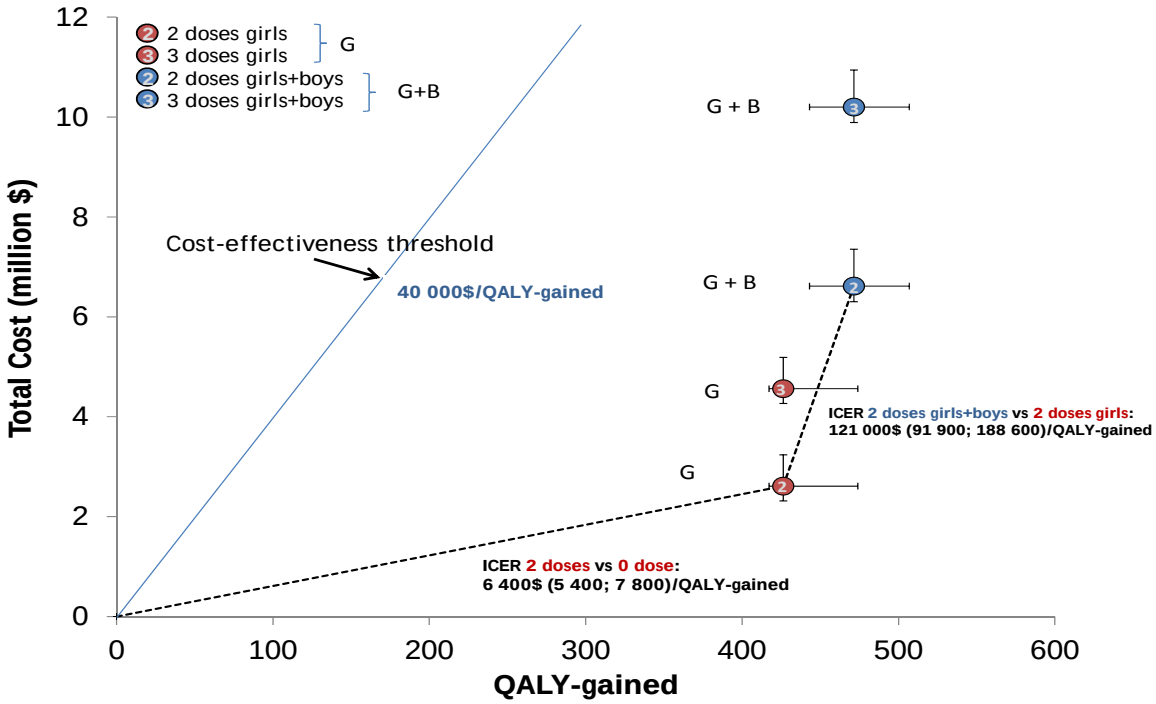


Figure 9 **Cost-effectiveness of immunization strategies by varying durations of vaccine protection (vaccination coverage = 80%, vaccine efficacy for vaccine types = 95%, discounted at 3% per year) (cont'd)**

Table 8 summarizes the cost-effectiveness results for each strategy evaluated based on various assumptions regarding the duration of protection from two or three doses of the vaccine. The key findings suggest the following:

1- Of all the strategies examined, the two-dose vaccination of girls is the most cost-effective.
2- Adding the third dose for girls is a cost-effective strategy when the duration of protection from two doses is assumed to be less than 30 years.
3- The two-dose vaccination of girls and boys is generally dominated by the three-dose vaccination of girls, meaning that it offers very few or no additional benefits despite being more costly.

Table 8 Summary of cost-effective strategies at the $40,000/QALY gained threshold by varying durations of vaccine protection

			2 doses			
			Vaccine duration			
			10 years	20 years	30 years	lifetime
3 doses	Vaccine duration	20 years	**2 doses** **3 doses**	**2 doses** **3 doses***		
		30 years	**2 doses** **3 doses**	**2 doses** **3 doses**	2 doses	
		lifetime	**2 doses** **3 doses**	**2 doses** **3 doses**	**2 doses** **3 doses***	2 doses

* Strategies with an ICER that is very close to the cost-effectiveness threshold.

5.2.2.3 Sensitivity analyses

In addition to varying the duration of vaccine protection, we also conducted sensitivity analyses by varying the vaccine efficacy of two doses, the starting point from which the duration of protection is calculated, the burden of HPV-related diseases, the proportion of MSM and the burden on MSM for strategies with an ICER that was close to the cost-effectiveness ratio. Table 9 shows that the findings presented in Table 8 are similar when the vaccine efficacy of two doses is decreased to 90% (with the assumption that the vaccine efficacy of three doses would be 95%). The findings in Table 8 are also similar when the duration of protection is calculated as starting immediately after the second dose (and not five years after the third dose), except when the duration of protection of two and three doses is assumed to be 20 years. In this case, adding the third dose does not provide any additional benefits because the duration of protection is the same for two and three doses, and the third dose does not delay the start of the protection loss.

Table 9 Summary of cost-effective strategies at the $40,000/QALY gained threshold by varying vaccine efficacies

			2 doses	
			Vaccine efficacy	
			90%*	95%
3 doses	Vaccine duration	20 years	**2 doses** **3 doses**	**2 doses** **3 doses**
		30 years	2 doses	2 doses
		lifetime	2 doses	2 doses

* Vaccine efficacy of 3 doses = 95%.

Lastly, the sensitivity analyses in Table 10 indicate that adding the third dose for girls would no longer be cost-effective when a minimum burden of HPV-related diseases is assumed (all burden parameters are simultaneously set at the minimum value identified in the literature). In addition, a two-dose immunization strategy for girls and boys would be cost-effective if the proportion of MSM is assumed to be 7% and if the risk of all HPV-related diseases and cancers is 17 times greater for MSM than for heterosexual men. A two-dose immunization strategy for girls and boys could also be cost-effective when it is assumed that there will be a lifelong duration of protection from two and three doses of vaccine and a lower vaccine cost for boys ($40, including administration costs).

Table 10 Summary of cost-effective strategies at the $40,000/QALY gained threshold by various assumptions regarding the burden of disease, proportion of MSM and vaccine cost

	Duration of 2-Dose / 3-Dose Vaccine		
	20 / 20 years	30 years / lifetime	Lifetime / lifetime
Baseline assumptions	2 doses 3 doses*	2 doses 3 doses*	2 doses
Minimum burden of disease	2 doses 3 doses*	2 doses	2 doses
Maximum burden of disease	2 doses 3 doses	2 doses 3 doses	2 doses
% MSM = 7%	2 doses 3 doses*	2 doses	2 doses
RR_{MSM} = 17	2 doses 3 doses*	2 doses	2 doses 2 doses, girls + boys*
% MSM = 7% RR_{MSM} = 17	2 doses 2 doses, girls + boys*	2 doses 2 doses, girls + boys*	2 doses 2 doses, girls + boys*
Cost = $40/dose	2 doses 3 doses	2 doses (savings#) 3 doses*	2 doses (savings#) 2 doses, girls + boys*

Maximum (minimum) burden: all parameters are set at their maximum (minimum) value.

Baseline assumption: 3% MSM, RR_{MSM} for genital warts and other HPV-related cancers = 3, RR_{MSM} for anal cancer = 17.[71].

***** Cost-effectiveness ratio near the $40,000/QALY gained threshold.

\# Scenarios that involve money savings (cost savings from administering the vaccine would be higher than the immunization costs).

5.3 CONCLUSION OF MATHEMATICAL MODELING

To our knowledge, this is the first study to examine the population-level effectiveness and cost-effectiveness ratio of two-dose HPV vaccination. It is therefore impossible to compare results at this time. In addition, unlike other studies that have previously assessed the cost-effectiveness ratios among various HPV immunization strategies, this analysis includes all HPV-related cancers as well as the burden on MSM. However, the model's predictions are still subject to the limitations imposed by the lack of epidemiological data (e.g., on the long-term vaccine efficacy of two or three doses of vaccine, cross-protection for boys, future public participation in screening activities, immunogenicity in boys who receive two doses of the vaccine and vaccination coverage for boys) and the uncertainty of existing data. For this reason, we conducted a wide range of sensitivity analyses, which showed that the conclusions were robust under various assumptions. In addition, certain assumptions about the vaccination of boys (e.g., same vaccination coverage as for girls while data suggest that it could be lower for boys[73-74]) tend to overestimate the actual impact the vaccination of boys might have. Therefore, at the current cost of the vaccine and even in a scenario potentially overestimating the impact of vaccinating boys, extending the vaccination to boys is a less economically desirable strategy than the vaccination of girls only.

6 ACCEPTABILITY AND FEASIBILITY

The vaccination coverage for the extended schedule (0, 6, 60 months) remains unknown, as the first girls to receive the two vaccine doses in grade 4 will be entering grade 9 in fall 2013. The vaccination coverage of the catch-up program involving three doses of HPV vaccine in grade 9 is similar to that obtained in grade 4, which may indicate that one dose in grade 9 should have as much acceptability as that currently observed with three doses.[75–76]

The vaccination coverage for all Québec girls in grade 4 (two doses) was estimated at 81% in 2008–2009, 76% in 2009–2010 and 78% in 2010–2011. Regional vaccination coverages ranged from 66 to 93% in elementary schools in 2010–2011.[65]

A schedule with similar effectiveness and fewer doses is generally more likely to be accepted by the public and vaccinators.[77–78]

Acceptability by health care professionals has not been assessed by any specific study on this topic and could potentially be negative, as the extended schedule, with its advantages over the approved schedule (0, 2, 6 months), is the schedule that has been promoted since 2007. Having no representatives from the Association of Obstetricians and Gynecologists of Québec (AOGQ), the CIQ met with the executive of the AOGQ in February 2013. After examining the available data, members of the executive acknowledged that there were advantages and disadvantages to both scenarios and that they found both proposed schedules to be acceptable. They also reiterated their support for vaccinating pre-adolescent boys and appreciated the fact that the two-dose schedule could further pave the way for introducing this measure.

In terms of feasibility, the vaccination coverages obtained in grade 4 (two doses six months apart) and grade 9 (three doses rather than a single dose) since 2008 show that both strategies are possible. In addition, some girls who were not vaccinated in grade 4 could receive a full course of vaccination in grade 9.

If the third dose of the HPV vaccine were administered, there would be three recommended vaccines (DTaP, meningococcal C and HPV) in grade 9 as of 2013–2014. This could pose a challenge, as data indicate lower acceptability when three injections must be administered during a single visit.[79]

7 ABILITY TO EVALUATE

In Canada, two studies on the effectiveness of vaccination in pre-adolescence have been started to evaluate the two schedules discussed in this document (appendices A and B).

The evaluation plan implemented for HPV vaccination will follow, regardless of which schedule is selected.[80] Plans for completing this evaluation are proposed in the last section of this advisory report.

8 ETHICAL ISSUES

Administering a third vaccine dose that would not prove useful could raise important ethical considerations. A basic principle is to administer only vaccine doses that are necessary to achieve the efficacy deemed acceptable for the population (e.g., one dose of conjugate meningococcal vaccine for infants).

However, if the two-dose schedule were less effective in the long term, other important ethical considerations could be raised. If this were the case, the evaluation projects and studies underway would be helpful in assessing the need for an additional vaccine dose before women become at high risk of developing cancerous diseases that could be prevented with HPV vaccines. Cervical cancer screening activities remain in place and complement vaccination. However, such screening activities are not available for other HPV-related diseases.

If a third dose proves necessary, women who received two doses of the quadrivalent vaccine could benefit from a dose of second-generation (e.g., nonavalent) vaccines covering a larger proportion of HPV types and possibly more HPV-related diseases. However, vaccination may be less effective at a later age, and it may be more difficult to offer this vaccination to the entire target population outside the school setting.

If the efficacy of the nonavalent vaccine currently under study is as high as that observed with the quadrivalent vaccine and more types are covered, it may be advantageous to delay the administration of a third dose (if required) so that this vaccine can be used at a later point. We do not know when this product will be approved.

In recent experience with new vaccines (e.g., pneumococcal, meningococcal, hepatitis A, hepatitis B), adjustments to the schedules initially recommended by manufacturers have been necessary. More specifically, a few years after the introduction of certain programs, the number of doses initially recommended by the manufacturers was reduced by one or two doses.

Note also that a high level of herd immunity was reported in regions with vaccination coverages similar to that in Québec.[81–84] These data support the idea that the risk of HPV infections within the population should be considerably reduced, even in certain unvaccinated sub-populations.

9 LEGAL AND POLITICAL CONSIDERATIONS AND CONFORMITY OF PROGRAMS

The extended schedule (0, 6, 60 months) does not really constitute a deviation from the monograph, which also proposes a three-dose schedule with doses administered within a six-month interval (0, 2, 6 months). The principle of not starting up a new immunization schedule with extended intervals is well accepted in vaccinology.[14]

At this time, the schedule comprising two doses six months apart clearly differs from the approved schedule. However, a number of other vaccines that had been approved in recent years for use at three to four doses are currently used at one to two doses: one dose of hepatitis A vaccine (recommended by WHO; 2012)[85] versus the three doses initially approved; pneumococcal vaccine at two + one doses versus three + one doses; meningococcal vaccine at one dose versus three to four doses; and hepatitis B vaccine at two doses versus three to four doses.

The extended schedule has been previously discussed and approved by a number of provincial, federal and international professional associations. At this time, there seem to be few potential political considerations concerning this strategy.

From a societal standpoint, a two-dose schedule is the most affordable and least invasive strategy for schools and the individuals vaccinated. The two-dose schedule would reduce program cost considerably. This money could be used to expand the population groups to be vaccinated against HPV or to fund new vaccination programs. There may be considerable political lobbying by vaccine manufacturers if fewer doses are purchased. However, decisions should be guided primarily by data on the immunogenicity, efficacy and safety of this schedule for girls aged 9 to 11 rather than by political influences. If the extended schedule is selected, an explanation will need to be provided as to why large sums of public funds are being spent on administering a vaccine dose that has not been demonstrated as necessary for clinical protection.

As for conformity of programs, at least two other regions in the world (British Columbia and Mexico)[15–16] are using a schedule comprising two doses administered six months apart, with the option of considering the need for a third dose.

The two-dose schedule has been recommended by Switzerland's committee of immunization experts.[17–18]

Chile's expert committee recently recommended using a two-dose schedule if the bivalent vaccine is used and a three-dose schedule if the quadrivalent vaccine is used (with the option of administering a third dose at a later time).[86]

10 CONCLUSION

In 2007, the CIQ prepared an initial advisory report on HPV immunization and made a number of recommendations. For example, the CIQ recommended using an extended schedule (0, 6, 60 months) for girls beginning their vaccination through the routine school program in grade 4, noting that "the third dose would be dispensed…if this were deemed necessary."

Following this CIQ recommendation, an HPV vaccination program was implemented in Québec in 2008. The first cohort of girls vaccinated in grade 4 will be entering the 60th month of the extended vaccine schedule (in grade 9) in September 2013, and the CIQ was tasked with considering the need for this third dose in the immunization schedule.

The exact mechanisms by which post-vaccination immunity protects against subsequent infection and pathologies are not yet fully understood. All the extensions of indications for using HPV vaccines outside the groups studied in phase III (efficacy) clinical trials were based on a comparison of serum antibody levels (bridging studies). With nearly a decade of hindsight, vaccine efficacy studies, available primarily in regards to women vaccinated at age 16–24, show continued protection in spite of the fact that, in a number of women, the serum antibodies decreased to very low levels or even to ones insufficient for detection by the available tests.

We now have data showing that two doses of HPV vaccine administered six months apart in pre-adolescence elicit an immune response similar and usually superior to that observed with three doses administered following the approved schedules at an older age (16 to 24 years). After the first dose, girls vaccinated at age 9–10 develop antibodies, and a strong anamnestic response is observed after the second dose, administered six months after the first. These results indicate that the first dose elicits a primary response.

In addition, three years after primary immunization at age 9–13, the antibody levels obtained after two doses (0, 6 months) are similar to those measured after three doses (0, 2, 6 months) for HPV types 16 and 11 and slightly lower than those for types 6 and 18, but remain higher than the titres observed in individuals aged 16 to 23 vaccinated with three doses. In all cases, the antibody titres level off after the rapid decrease observed in the months following primary immunization, and the immune memory persists. Girls vaccinated at age 9–13 with two doses administered six months apart therefore retain stable antibody titres that are higher than those measured in older women vaccinated with three doses who have a demonstrated absence of cervical lesions relating to the HPV types included in the vaccine (the accepted measure for establishing the protective effect).

In this context, doubt was cast as to the usefulness of the initially planned third dose of HPV vaccine in an extended schedule. A basic principle underlying Québec's immunization schedules is to offer a high level of protection by avoiding the administration of vaccine doses deemed to be of limited usefulness. We can now assume that vaccination with two doses administered six months apart will provide long-term protection that will stretch over the most active period of sexual activity, the time when the risk of acquiring HPV is particularly high. Moreover, Australian studies have shown that, only a few years after the introduction of the HPV vaccination program for girls and women (vaccine provided free of charge until age 26 during the first two years of the program and until age 18 thereafter), herd immunity had developed, gradually conferring protection to the vast majority of vaccinated and unvaccinated boys and girls. In Québec, where routine and catch-up HPV vaccination has been provided free of charge until age 18 since 2008, the high levels of vaccination coverage achieved are helping create herd immunity. If a minority of vaccinated individuals were to lose their immunity over time, they would remain protected indirectly owing to the low probability of exposure to the virus. Cervical cancer screening activities also provide an additional safety net, at least in terms of preventing this health problem.

In terms of the long-term impacts of the various HPV immunization schedules, simulation models predict that a third dose would actually be beneficial only in scenarios involving short durations of protection (i.e. less than 20 years) or if there is a significant gap between the duration of protection from two doses and that from three doses (i.e. 20 years versus lifelong protection). In all the scenarios involving a long duration of protection from two doses at age 9 (20 years or more), adding a third dose at age 14 would be of only limited theoretical benefit.

Another consideration is cost. At the current cost of the vaccine obtained through the public program, the annual cost of offering a booster dose to Québec grade 9 girls would be approximately $3 million. The economic simulations show that a two-dose program provides more favourable cost-effectiveness ratios than a three-dose program, even when the presumed durations of protection vary. If the duration of protection provided by two vaccine doses administered at age 9–10 is approximately 30 years or more, the shift to a three-dose schedule is not cost-ineffective and drifts from the $40,000/QALY threshold used in the economic model.

With a close to 80% HPV vaccination rate among girls and the indirect impact this has on HPV prevention in boys, the CIQ finds that the current vaccination program for girls appears to be highly efficient (< $15,000 per QALY). At the current cost of the vaccine, extending vaccination to all pre-adolescent boys could produce health benefits but, according to economic analyses conducted in Québec and elsewhere, these benefits would not be commensurate with the additional costs incurred at the population level, even with a two-dose schedule. At the current cost of the vaccine, introducing a free vaccination program for all boys could be justified by political or equity-based considerations, primarily for men who have sex with men (MSM). The feasibility, effectiveness and efficiency of a “targeted” approach aimed at vaccinating young men who have or will have sex with men at a point in time when the vaccine is most effective (before they become sexually active) have yet to be demonstrated. Offering vaccination to all pre-adolescent boys appears to be the most feasible approach to protecting MSM.

Three-dose HPV vaccine schedules have been introduced in most countries and in other Canadian provinces. Switzerland has chosen a two-dose schedule; Québec, if it were to arrive at a similar decision, would not be the first jurisdiction to adopt this scientifically defensible strategy.

In the present immunization context (continuing a DTaP booster dose and introducing a booster dose of a conjugate meningococcal vaccine in grade 9), negative impacts on acceptability and vaccination coverage rates would likely occur if a third injection (HPV) were to be administered to girls during the same session.

11 RECOMMENDATIONS

After evaluating the scientific data available and consulting experts, the members of the CIQ recommended by consensus not to administer a booster dose to grade 9 girls vaccinated with two doses in grade 4.

This recommendation is conditional upon the implementation and continuation of effective mechanisms for monitoring HPV epidemiology and timely detecting any signs that might make questionable the reasons for this decision. The key measures to be implemented are as follows:

1 Maintain scientific monitoring of the results of alternative HPV immunization schedules, particularly those comprising two doses. At present, we cannot rule out the possibility that a booster dose may be required later in life with either two-dose or three-dose initial schedules.

2 Monitor antibody levels in the first cohorts of girls vaccinated with two doses at age 9 by comparing the antibody levels in girls who received a booster dose with those in girls who did not. In specific terms, it would be desirable to continue the Twinrix-Gardasil study (section 3.3.3) undertaken in 2008 (measuring antibodies 5, 7 and 10 years after immunization began) and implement the randomized trial called ICI-HPV (Appendix A), with the addition of two supplementary times for measuring antibodies (7 and 13 years after immunization began). The preliminary results, obtained 60 months after initial vaccination, could be used to make a quick bridging study comparison between the results noted for girls vaccinated with two doses (0, 6 months) of the vaccine at age 9–10 who will be participating in the ICI-HPV study and the results noted for girls of the same age who received three doses (0, 6, 42 months) as part of the Twinrix-Gardasil study. If deemed necessary, adjustments could be made to the immunization schedule.

3 Measure the comparative efficacy of the two schedules (0, 6 months and 0, 6, 60 months) by implementing and continuing for several years the ICI-HPV study that will measure persistent HPV infections in girls vaccinated according to one or the other of the two schedules (Appendix A).

4 Monitoring the prevalence of HPV infection in successive cohorts (through cross-sectional studies) of young women who have not been vaccinated, have received three doses during the catch-up phase, have received three doses in grade 9 or have received two doses in grade 4 seems equally important. A study in its early stages will help take a preliminary measurement and its repetition over time will be crucial (Appendix C).[87]

5 Monitoring over time of HPV types detected in precursors and cervical cancers appears to be another component that should be evaluated. This could be achieved using the demonstration zones put in place in the Estrie and Capitale-Nationale regions in 2008. The HPV types identified in cancers that occurred in these regions from 2006 to 2009 constitute a pre-immunization baseline. Repeating these measures over time will be useful for monitoring the development of HPV types found in cancers as the cohorts of vaccinated girls advance in age.

6 The future inclusion of cervical cancer precursors in the cancer registry will also help monitor the frequency of these lesions over time.

7 Another component to be evaluated is the measurement and monitoring over time of the occurrence of lesions detected during screening and in diagnostic and follow-up exams. However, the implementation of demonstration zones in Québec revealed how complex and difficult (manual collection, imprecise denominators, impossibility of knowing how many women from demonstration zones seek services outside the region, difficulty of monitoring the care trajectory because different centres use different identifiers, etc.) it can be to gather, in the absence of a provincial registry, reliable information on screening, diagnostic and test follow-up activities to measure the occurrence of cancer precursors.[88]

Immunization data gathered in schools are entered into the local systems (I-CLSC) of health and social service centres (CSSS) or into regional databases (VAXIN and LOGIVAC) that identify vaccinated individuals and the number of doses they received. Legislation governing the implementation of a provincial immunization registry calls for the recovery of all historical immunization data contained in the various local and regional systems. The data pertaining to girls vaccinated since the program was implemented in 2008 will therefore be entered into this registry, which will facilitate monitoring.

It is also important to continue efforts to reach and maintain levels of vaccination coverage that meet provincial targets (90% in grade 4). Particular attention should be paid to verifying immunization status in grade 9 and to offering the HPV vaccine, ideally in a school setting, to all girls who have no proof of immunization.

In the short term, a communication plan will need to be developed to better explain to the different groups involved and interested in Québec's HPV vaccination program the reasons behind the recommendation not to administer the third dose of the extended schedule as initially planned. It will also be important to emphasize that this recommendation applies only to the immunization of pre-adolescents and that the three-dose schedule (0, 2, 6 months) should be offered to all other age groups.

CIQ members also want to reiterate that the HPV vaccines do not protect against all types of HPV and recommend that cervical cancer screening continue for all vaccinated and unvaccinated women. Furthermore, since HPV vaccines do not confer protection against all sexually transmitted infections, safe sex practices are recommended for everyone, regardless of their HPV immunization status.

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APPENDIX A

SUMMARY OF QUÉBEC'S LONG-TERM STUDY (ICI-HPV: IMPACT OF IMMUNIZATION SCHEDULES IN QUÉBEC)

SUMMARY OF QUÉBEC'S LONG-TERM STUDY (ICI-HPV: IMPACT DE CALENDRIERS D'IMMUNISATION CONTRE LES VPH)[89]

Main objective

To determine whether an immunization schedule comprising two doses of Gardasil administered six months apart is non-inferior to a schedule comprising three doses administered at 0, 6 and 60 months for the prevention **of HPV-16 and HPV-18 infections that persist for at least six months**, up to ten years after the initial vaccination.

Secondary objectives

- To compare the **geometric mean titres of antibodies and seropositivity** (for HPV types 6, 11, 16 and 18) in girls who received two doses of Gardasil (0, 6 months) with the geometric mean titres of antibodies and seropositivity in girls who received three doses (0, 6, 60 months), 60 and 120 months after the initial vaccination.
- To determine whether an immunization schedule comprising two doses of Gardasil administered six months apart is non-inferior to a schedule comprising three doses administered at 0, 6 and 60 months for the prevention of **genital warts**, up to ten years after the initial vaccination.
- To determine whether an immunization schedule comprising two doses of Gardasil administered six months apart is non-inferior to a schedule comprising three doses administered at 0, 6 and 60 months for the prevention of **precancerous and cancerous abnormalities detected by screening tests for cervical cancer**, up to ten years after the initial vaccination.

Specifications

- Randomized **non-inferiority** trial.
- Girls who received two doses of Gardasil five years earlier will be randomly assigned to the "two dose" group, meaning they will not receive supplementary doses, or to the "three dose" group, meaning they will receive a third dose of Gardasil. The data from the "two dose" group will be shared anonymously with the QUEST team. These data will therefore provide information for both studies.
- 4,334 girls to be recruited (via CAI and RAMQ).
- Self-collected vaginal swab at six months and annual questionnaire for all participants.
- The vaginal samples will be tested for the presence of HPV.
- 500 participants (250 per group) will have blood samples drawn to test for immunogenicity.

APPENDIX B

SUMMARY OF THE CANADIAN QUEST STUDY

SUMMARY OF THE CANADIAN QUEST STUDY[90]

Main objective

- To evaluate if a 2 dose regimen of Q-HPV is non-inferior to a 3 dose schedule in the prevention of type specific persistent HPV16, 18, 6 or 11 infection in young women at 19/20 years of age.

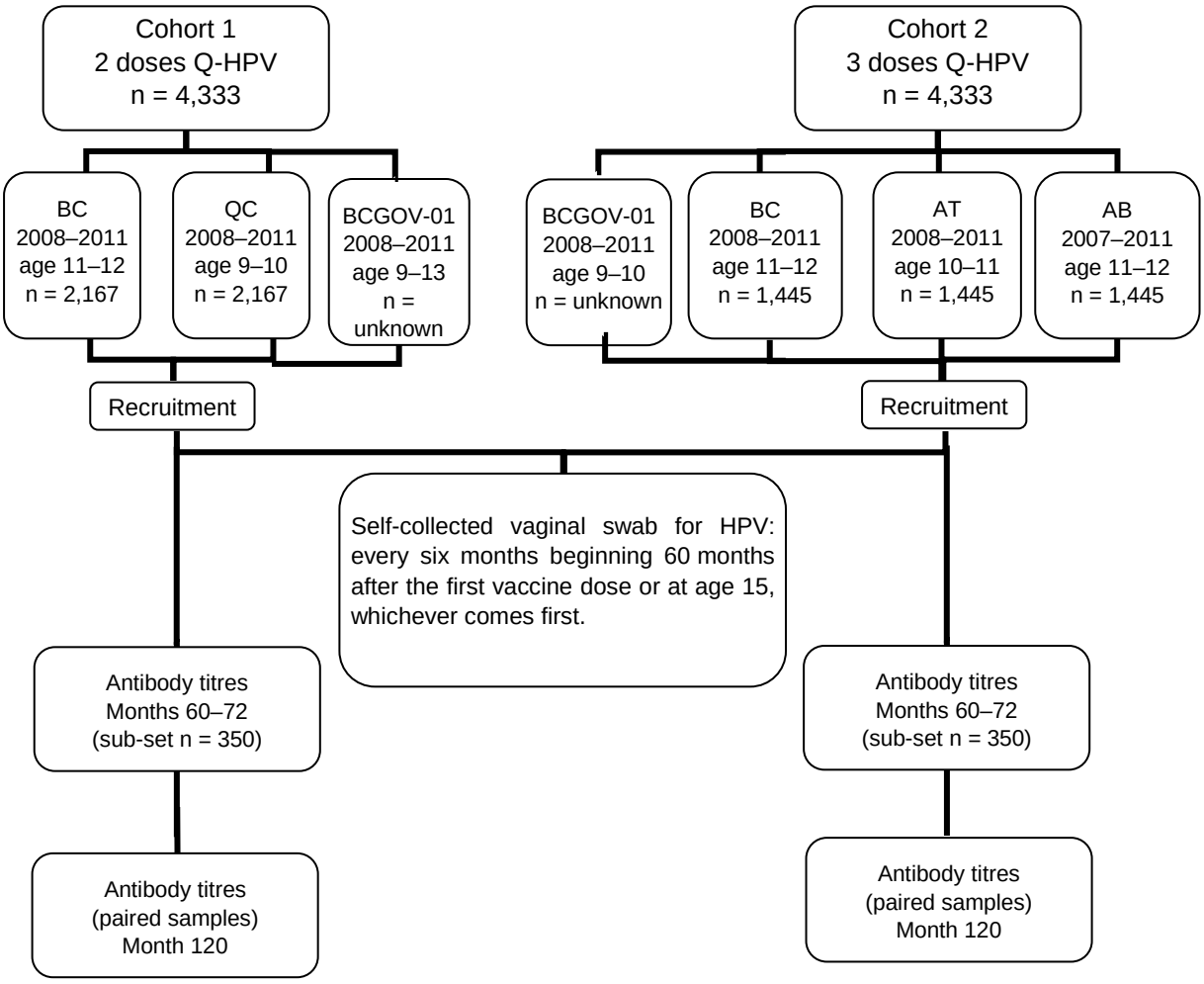
Secondary objectives

- To evaluate if a 2 dose regimen of Q-HPV is non-inferior to a 3 dose schedule in the prevention of type specific persistent HPV16, 18, 6 or 11 infection at month 120 post dose 1 in girls vaccinated at the age of 9 – 12 years.
- To evaluate cumulative type specific persistence of HPV 16, 18, 6 or 11 at months 60, 84, 96 108 and 120 post dose 1 in girls vaccinated at the age of 9 – 12 years.
- To evaluate if a 2 dose regimen of Q-HPV is non-inferior to a 3 dose schedule in the prevention of self-reported anogenital warts in young women.
- To evaluate if a 2 dose regimen of Q-HPV is non-inferior to a 3 dose schedule in the prevention of type specific persistent HPV16, 18, 6 or 11 infection in young women at 15 years of age.
- To evaluate if a 2 dose regimen of Q-HPV is non-inferior to a 3 dose schedule in the prevention of type specific persistent HPV 31, 33, 35, 45, 52 and 59 infection in young women at 19 years of age.
- To compare the mean antibody levels and seropositivity (for HPV types 16, 18, 6, or 11) in girls who have received 2 doses of Q-HPV to levels in girls who have received 3 doses at Months 60 and 120 post vaccination.
- To describe the trend over time of anti-HPV-16, -18, -6 -11 antibodies of those girls who took part in the BCGOV01 study up to month 36 after first immunization and who are now enrolled in this study, through to month 120.

Specifications

- Longitudinal **observational** study of two cohorts of adolescent girls:
  - Cohort 1 will have previously received two doses of HPV vaccine (0, 6);
  - Cohort 2 will have previously received three doses (0, 2, 6).
- Participants will be monitored until they turn 19 or when 120 months have elapsed after the first dose, whichever comes first.
- 8,666 girls must be recruited (Québec, British Columbia, Alberta and the Atlantic provinces).
- Participants will self-collect a vaginal swab every six months.
- The vaginal samples will be tested for the presence of HPV.
- Blood samples taken at age 15 or at 60 months after the first vaccine dose, whichever comes first, and at age 19 in a subsample of 700 participants.

- An on-line health questionnaire asking demographic questions, age-appropriate sexual health questions and questions about sexual practices will be completed every year.



APPENDIX C

SUMMARY OF THE POPULATION-BASED HPV INFECTION PREVALENCE STUDY

SUMMARY OF THE POPULATION-BASED HPV INFECTION PREVALENCE STUDY[87]

Problem

Human papillomavirus (HPV) vaccination programs are costly and require significant resources. The target age group and immunization strategy differ depending on the settings. Important questions remain, such as the duration of protection and the added advantage of vaccinating boys. To guide decision-making, it is therefore critical to assess not only the implementation of programs, but also their impact on health. Expected impacts include the inability to see a reduced occurrence of HPV-related cancers until several years have elapsed because of the long period between infection and disease. Shorter-term indicators must therefore be sought.

Monitoring of HPV infections in the community, specifically by virus genotype, is one of the indicators recognized by several authorities, including WHO, for assessing the early impact of HPV vaccination. Considering that HPV infections are generally asymptomatic and go unreported in Québec's mandatory notifiable disease (MND) file, regular investigations are the best option for this kind of monitoring. Moreover, since infection is ubiquitous and the immunization strategy universal, a "population-based" approach to investigation is still preferable to the targeted monitoring of certain groups.

Study goal and objectives for phase 1: unvaccinated cohort or cohort in which the percentage of vaccinated individuals is still fairly low

The goal of the study is to measure the prevalence of HPV infections in the community before the massive influx of vaccinated cohorts in order to establish a baseline prevalence for the future evaluation of the impact of immunization on the prevalence of infections targeted by immunization (HPV 16, 18, 6 and 11), those not specifically targeted but for which cross-protection was noted in clinical trials, and the other genotypes that could eventually substitute the types that currently occur more frequently.

In the interests of feasibility, the 17–24 age group has been targeted as priority because HPV infections are very frequent in the first years following the start of sexual activity. The impact of immunization should therefore be observable quite quickly. Moreover, a vast population-based investigation on the sexual health of young people aged 17 to 24 has been planned for Québec, allowing for recruitment efforts to be pooled and investigative tools to be shared.

More specifically, the **study's objectives** (HPV component) are as follows:

- To determine the overall prevalence and the prevalence according to genotype of genital HPV infections (cervicovaginal) in young women aged 17 to 24;
- To determine the overall prevalence and the prevalence of the principal genotypes of the oral virus in young men and women aged 17 to 24;
- To compare the rates of infection on the basis of immunization status, sex and age group.

For budgetary and feasibility reasons, research on genital HPV will not be carried out on men. This is because for men, research on two other sexually transmitted infections included in the investigation (chlamydia and gonorrhoea) will be done using a urine sample (which is adequate for these infections but suboptimal for HPV detection), while for women, a vaginal swab is preferable for all three infections. However, since research on oral HPV is not very invasive, it may be used to directly compare the infection's prevalence according to sex, for the same age group and the same period. The method for obtaining a self-collected cervicovaginal swab was already pre-tested in a pilot study in 2009–2010 and proved to be satisfactory among the women who had agreed to participate in the study.

Recruitment plan and collection procedures

The study on the prevalence of HPV infections was integrated into the Étude sur la santé sexuelle des jeunes au Québec [Study of the sexual health of young people in Québec], led by Dr. Gilles Lambert of INSPQ and Johanne Otis, PhD, of UQAM's Chaire de recherche en éducation, and supported by several collaborators (including Dr. Patricia Goggin and Dr. François Coutlée).

Sampling targets approximately 8,000 young people aged 17 to 24 who come from various communities. Recruitment will take into account:

- Québec's administrative regions, grouped into four large entities on the basis of demography and level of urbanization;
- principal occupation, in order to ensure a proportional representation of students and young workers;
- age and sex.

Data collection will involve:

- An anonymous, self-administered questionnaire using a computer-assisted method, on-site in the collection setting. Questions dealing specifically with HPV vaccination (including the number of doses received and the time) for both sexes;
- A urine sample from men or a self-collected vaginal swab from women, as well as an oral rinse for both men and women, also on-site.

Data collection will begin in spring 2013 and will continue until the end of 2013.

Laboratory analyses for the HPV component will be conducted in the virology laboratory at the Centre hospitalier de l'Université de Montréal (CHUM) under the direction of Dr. François Coutlée.

Study follow-ups

This study will help establish the baseline prevalence of HPV infections among Québecers at a time when the percentage of vaccinated individuals is still fairly low. It should be repeated regularly in order to assess the impact of vaccination over time. An interval of three to five years between collections would probably suffice.

Publication n^{o}: 1837

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