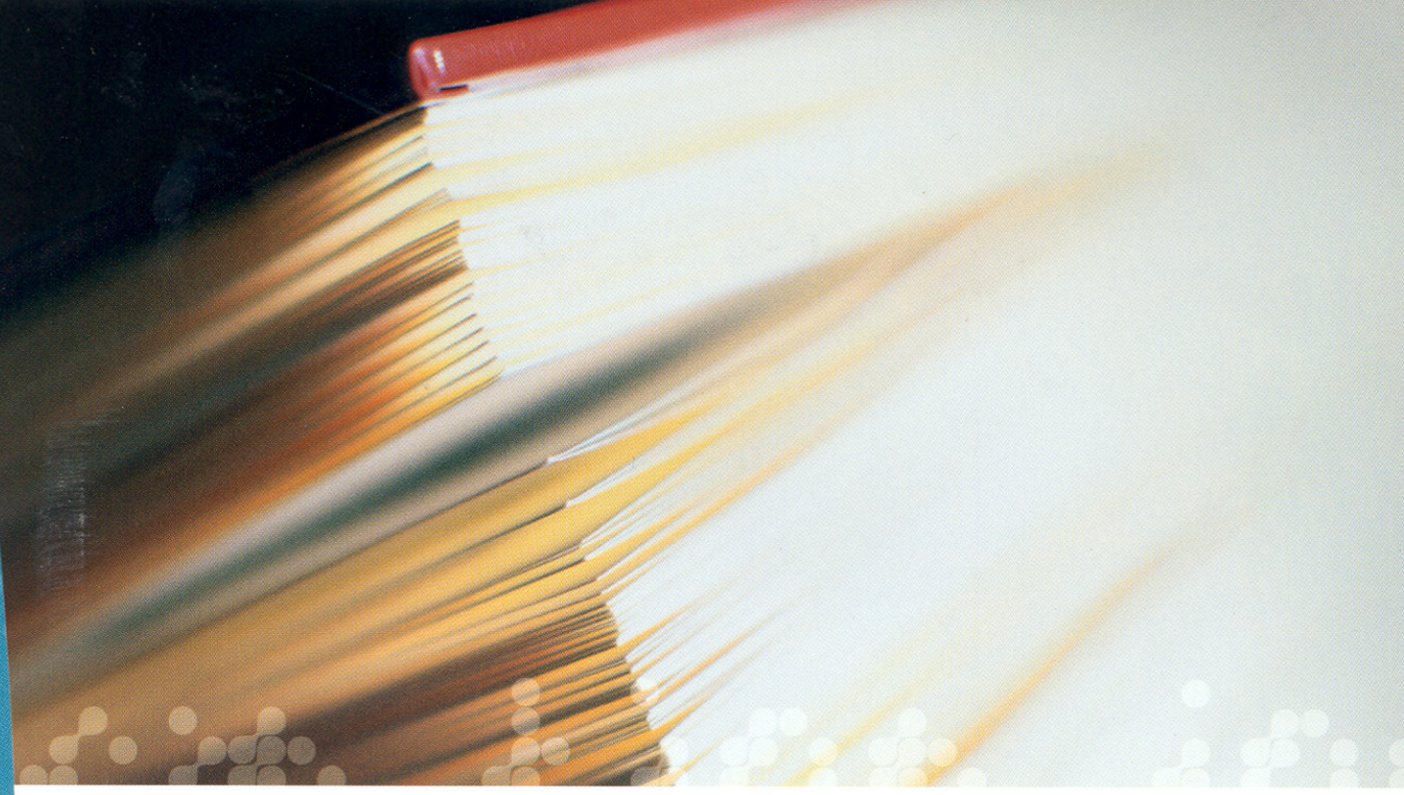

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Caroline Quach, Montreal Children's Hospital
Louis Valiquette, Département de microbiologie et infectiologie, Faculté de médecine, Université de Sherbrooke

IN CONSULTATION WITH THE FOLLOWING MEMBERS OF THE HPV GROUP:

Ève Dubé, DRBEO, INSPQ
Marc Dionne, DRBEO, INSPQ
Evelyne Fleury, DRBEO, INSPQ
Eliane Franco, McGill University, Oncology Department
Patricia Goggin, DRBEO, INSPQ
France Lavoie, Unité de recherche en santé publique du CHUL
Marie-Hélène Mayrand, Hôpital Saint-Luc du CHUM
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BACKGROUND

In September 2007, the Ministère de la Santé et des Services sociaux (MSSS) du Québec announced that a new vaccination program against human papillomavirus (HPV) would be implemented in Fall 2008.

In October 2007, the Comité sur l'immunisation du Québec (CIQ) tabled a report entitled "Prévention par la vaccination des maladies attribuables aux virus du papillome humain au Québec" [Prevention of diseases caused by human papillomaviruses through vaccination][1]. At the time that report was being drafted, only one vaccine – Gardasil – was authorized for sale in Canada. The report did not directly compare the Gardasil and Cervarix vaccines.

Given the likelihood that the Cervarix vaccine would be approved, the Direction générale de la santé publique (MSSS) submitted a request to the Institut national de santé publique du Québec (INSPQ) on December 19, 2007, asking the latter to produce an advice with respect to the following question: "Do the two HPV vaccines have an equivalent ability to achieve the stated goal of the immunization program, which is to reduce the incidence of and mortality associated with cervical cancer?"

Establishing an appropriate comparison between Gardasil and Cervarix poses an unusual problem. Both vaccines are designed to prevent infections caused by HPV-16 and HPV-18, the genotypes most commonly associated with anogenital cancers, including cervical cancer. Globally, genotype 16 is associated with 55% of cervical cancers and genotype 18 is linked to 16% of these cancers[2]. The exact proportions in Quebec and Canada have not yet been established. However, Gardasil also contains HPV-6 and 11, which are primarily associated with non-cancerous diseases, such as anogenital condyloma and recurrent respiratory papillomatosis (RRP). Although they constitute lesser priorities as intervention targets, these diseases increase the morbidity burden associated with HPV.

Consequently, the two vaccines cannot be viewed as equivalent.

Since cancer prevention is a greater public health priority than the prevention of non-cancerous diseases, the amount of useful information found in the scientific literature is far more abundant on the subject of cancer. For the same reason, the vaccination program decision-making process (in which the 13 components of the Erickson-De Wals model[3] are systematically documented) has not yet been carried out for non-cancerous diseases related to HPV. It is not this document's purpose to provide such an analysis. However, a brief discussion of the burden related to HPV-6 and HPV-11-associated diseases and their prevention is presented in section 3 of this document.

This document seeks to compare the performance of the two vaccines. However, in order to protect a larger proportion of the population, the cost of the vaccines is another important factor that must be taken into account. The Quebec experience has shown that having at least two vaccines available for a single program can help reduce costs, while also making it possible to vaccinate and protect more people.

CONTENTS

TABLE LIST

1. CHARACTERISTICS OF THE VACCINES AND KEY RESULTS OF PHASE III CLINICAL TRIALS

The two vaccines against human papillomavirus are subunit vaccines that contain virus-like particles (VLPs) produced through recombinant technologies. The vaccines are obtained through the expression of a gene that encodes for the L1 HPV protein. These vaccines contain no live biological product or DNA that can infect cells or reproduce themselves[4-6], nor do they contain any preservatives or antibiotics. Both are prophylactic vaccines and neither has demonstrated any therapeutic effect[4].

The composition of the two vaccines is different:

- Gardasil™ is a quadrivalent vaccine containing L1 VLPs for two viruses associated with a high risk of cancer (40µg HPV-16 and 20µg HPV-18) and L1 VLPs for two low-risk viruses (20µg HPV-6 and 40µg HPV-11). Amorphous aluminum hydroxyphosphate sulfate is the adjuvant used in the Gardasil™ vaccine.
- Cervarix™ is a bivalent vaccine that contains L1 VLPs for two viruses associated with a high risk of cancer (20µg HPV-16 and 20µg HPV-18). Aluminum hydroxide 50µg combined with 20µg 3-deacylated monophosphoryl lipid A (AS04) is the new adjuvant used in the Cervarix™ vaccine[1].

Table 1 presents phase III clinical trial results made available before September 2007[7].

Table 1 Key results of phase III clinical trials with HPV vaccines*

Vaccine	Gardasil	Cervarix
Follow-up period	36 months (advanced)	15 months (interim)
HPV types included	6, 11, 16, 18	16, 18
Efficacy of HPV-16 or HPV-18 against CIN2+	Demonstrated	Demonstrated
Efficacy of HPV-16 against CIN2+	Demonstrated	Demonstrated
Efficacy of HPV-18 against CIN2+	Demonstrated	Not yet reported[a]
Efficacy of HPV-16 or 18 against CIN2	Demonstrated	Demonstrated
Efficacy of HPV-16 or 18 against CIN3	Demonstrated	Not yet reported[a]
Therapeutic efficacy	None	None
Efficacy against VIN2/3	Demonstrated	Not yet reported
Efficacy against VAIN2/3	Demonstrated	Not yet reported
Efficacy against anogenital condyloma	Demonstrated	Not targeted
Safety after 6 years of follow up	Safe[b]	Safe[c]
Cross-protection (persistent HPV infections)	6 months	12 months
Cross-protection (lesions)	Reported	Not yet reported
Duration of protection[d]	5-6 years	5-6 years
Immunogenicity in pre-adolescents	Demonstrated	Demonstrated
Immunogenicity in older women	Demonstrated	Demonstrated
Immunological memory 6 years after vaccination	Demonstrated	Not yet reported[e]

[a] demonstrated in the combined analysis of phase II and phase III study results
[b] in post-approval evaluation
[c] in clinical studies
[d] corresponds to the duration of clinical trials in 2007
[e] not relevant, since all subjects had detectable antibodies (note added)
CIN : cervical intraepithelial neoplasia
VIN: vulval intraepithelial neoplasia
VAIN: vaginal intraepithelial neoplasia

* Courtesy of Dr. Xavier Bosch, Epidemiology and Cancer Registry Unit, IDIBELL,– Catalan Institute of Oncology, Barcelona, Spain.

2. PREVENTION OF CERVICAL CANCER

2.1. IMMUNOGENICITY

There are no standards for HPV serology[8] and each manufacturers of the two vaccines have developed their own serological tests. Consequently, direct comparison of study results on different vaccines is not possible. What is more, the correlation between antibody titre and protection against HPV remains unclear. Given that the titres for reference serums are not identical, no direct conclusion can be drawn with regard to the relative immunogenicity of the different genotypes included in the same vaccine. This potential difference between reference serums also limits the ability to directly compare vaccines by establishing geometric mean titre (GMT) ratios of persons vaccinated to persons observed following a natural infection.

Notwithstanding this caveat concerning the interpretation of differences, the two vaccines containing L1 VLPs have been shown to be immunogenic in different population groups. In clinical trials, subjects who received HPV vaccines produced antibody titres that were substantially higher than subjects who had had a natural infection[4, 9-12].

The new adjuvant used in the Cervarix vaccine produces an increase in memory cells that is 2.2 to 5.2 times greater than that observed with the formulation containing aluminum salts[13].

Existing results appear to show that the two vaccines are equivalent with respect to the HPV-16 component. However, the results are different for the HPV-18 component: after one month, the GMT ratio (GMT of persons vaccinated with HPV-18 / GMT of persons having had a natural infection) was 4.3 times higher in subjects who had received the Cervarix vaccine[14,15], than in those given the Gardasil vaccine. Whether such high titre levels are actually needed to ensure clinical efficacy has yet to be determined. Furthermore, the proportion of vaccinated subjects whose titre levels were low has not been published with respect to either vaccine.

Conclusion: The immunogenicity of the two vaccines is equivalent with respect to HPV-16, but HPV-18 appears to be more immunogenic in the Cervarix vaccine. The clinical significance of this difference has not been determined.

2.2. EFFICACY

Using cervical cancer as the primary criterion for measuring the efficacy of anti-HPV vaccines in clinical trials would be both unethical and unfeasible, given that screening can prevent a significant proportion of cancers through the identification and treatment of precancerous lesions. What is more, the normal time lag between infection and the onset of cancer is more than 10 years[16-18].

The primary criteria for determining the efficacy of HPV vaccines are their impact on:

- the incidence of persistent infections;
- the incidence of CIN2, CIN3 and adenocarcinoma *in situ*.

In the case of the Gardasil™ vaccine, two other indicators were measured:

- impact on the incidence of condyloma acuminatum (described in section 3); and
- impact on the incidence of vulvar and vaginal cancer precursors.

The efficacy of the two vaccines has been studied in clinical trials in which more than 50,000 women participated. Evaluations of efficacy differed considerably in the way they were carried out, depending on the vaccine. Aspects that differed between the two vaccines included: the criteria used to select subjects for the clinical trials and to define a persistent infection, the tests used and their frequency, the method employed to interpret and present the results, the intervals between vaccinations, and the analyses carried out.

A reduction of more than 90% in the rate of persistent infections and of almost 100% in the number of high-grade cervical lesions associated with the HPV types included in the two vaccines were observed over a period of 5 to 5.5 years after vaccination[10,11,19-21]. The very high degree of efficacy of both vaccines and the low incidence of high-grade dysplasia associated with the virus genotypes included in the vaccines among naïve vaccine recipients (women who were seronegative for genotypes 16 and 18 when vaccination began) prevent us from drawing conclusions regarding the relative efficacy of the two vaccines in preventing the precancerous conditions associated with HPV-16 and HPV-18.

Cross protection against virus types that are genetically similar to HPV-16 and 18 has been reported for both vaccines.

Gardasil shows short-term efficacy in preventing precancerous conditions of the vulva and vagina associated with genotypes 16 and 18 in women who were seronegative for both types prior to vaccination. These indicators have not been measured for the Cervarix vaccine, but there is no reason to believe that the results would be lower.

Conclusion: Both vaccines are effective against persistent infections and cervical cancer precursors associated with HPV-16/18. The short-term data (5-6 years) currently available are not sufficient to confirm or rule out differences in the clinical efficacy of the two vaccines.

2.3. DURATION OF IMMUNITY

The duration of immunity is the crucial element in terms of preventing cervical cancer[22]: the goal is to vaccinate young people first, in order to protect them for decades to come and, hopefully, for life.

Once antibody titres reach their highest point, one month after the last dose of either vaccine is received, a marked decline is observed until months 18-24, after which antibody titres stabilize for a period of at least 60-64 mois[20,23,24]. Generally speaking, the plateau values observed five years after vaccination are higher than the titres observed in women who have had a natural infection, but important differences have been observed in the dynamics of antibodies against the virus genotypes included in the two vaccines (Table 2).

Table 2 Proportion of seropositive women after vaccination with Gardasil and Cervarix

Vaccine	After 18 months		After 33-38 months		After 51-60 months*	
	HPV-16	HPV-18	HPV-16	HPV-18	HPV-16	HPV-18
Gardasil†[19 20]	100%	86%	100%	76%	98.8%	65%
Cervarix‡[23]	100%	99.7 %	99%	99%	100%	100%

*51-53 months for Cervarix; 60 months for Gardasil; †with Luminex test; ‡with ELISA test.

These data show that, in the short term, both vaccines provide good antibody persistence against HPV-16. However, every 2-3 year period after vaccination brings a 10-15% reduction in seropositivity for HPV-18 in women vaccinated with Gardasil.

The absence of measurable antibodies is not synonymous with loss of protection, since most subjects develop immunological memory. In the Olsson study, most of the women showed immunological memory. However, 5 years after vaccination with Gardasil, one seronegative woman in 30 had no response to the booster dose[20], which should be interpreted as a loss of immunological memory. Although these numbers are too low to draw firm conclusions, close attention should be paid to the duration of protection.

A comparison of GMT ratios observed 4.5 and 5 years after vaccination vs. GMTs observed following a natural infection also reveals a difference between the two vaccines (Table 3).

Table 3 GMT ratios: GMTs 51-60 months after administration of Gardasil or Cervarix/GMTs following a natural infection

Vaccine	HPV-16	HPV-18
Gardasil 60 months after vaccination† [20]	≈16	≈1.3
Cervarix 51-53 months after vaccination‡ [23]	≈17	≈14

†with the Luminex test; ‡with the ELISA test

The post-vaccination / post-natural infection GMT ratios remain fairly high for HPV-16 after the administration of both vaccines. In the case of HPV-18, however, this ratio is 14 after vaccination with Cervarix but less than 2 after vaccination with Gardasil.

In a number of vaccines, the inclusion of additional components has been shown to reduce response to certain antigens[25-28]. A reduction in immune response to one or more antigens may be due to a different bond between the adjuvant and each of the antigens included in the vaccine[27].

Since it is difficult to measure duration of protection in terms of clinical efficacy, due to the characteristics of the disease (relative rareness, long induction period, etc.), immunogenicity is likely to remain the only means of comparing the two vaccines, at least in the medium term. Special attention should be paid to this issue during program's evaluation.

Conclusion: Five years after vaccination, persistence of the HPV-16 antibody response is equivalent for the two vaccines. However, a significant difference was observed in the proportion of women with detectable antibody titres against HPV-18, namely 99-100% after vaccination with Cervarix and 65-86% after vaccination with Gardasil. The long-term clinical significance of this difference is not known.

3. PREVENTION OF DISEASES ASSOCIATED WITH HPV-6 AND HPV-11

The primary diseases associated with HPV-6 and HPV-11 are condylomas and recurrent respiratory papillomatosis.

Anogenital condylomas are relatively common and usually benign[29]. They can, however, cause anxiety and discomfort and many medical visits may be needed to eradicate them[30]. The burden associated with this disease primarily takes the form of psychosocial morbidity and the consumption of medical services to investigate abnormal Pap smears and treat lesions. The annual incidence of this condition is on the order of 0.1-0.2%, according to estimates out of Manitoba. Incidence is highest among persons in their early twenties and the condition is more common in men than in women[31]. Incidence data for Quebec are very limited.

Recurrent respiratory papillomatosis (RRP) can affect young children or adults. While it is uncommon and rarely fatal, RRP can require repeated interventions and can be associated with significant morbidity[32]. In one pediatric hospital in Toronto which specializes in the treatment of RRP, the 67 children treated for the disease during the past 10 years required a total of 926 interventions[33].

3.1. IMMUNOGENICITY

The HPV-6 and HPV-11 components of the Gardasil vaccine have been shown to be highly immunogenic. One month after vaccination, 100% of vaccinated subjects had seroconverted for both genotypes. The GMTs of vaccinated subjects were approximately 10 times higher than those observed in subjects who had had a natural infection[19,34].

Conclusion: Administration of the Gardasil vaccine induces very good HPV-6 and HPV-11 antibody production.

3.2. EFFICACY

The Gardasil vaccine has been shown to be effective against condyloma for at least 5 years after vaccination[35]. The vaccine's level of efficacy in clinical trials exceeded 90%[19,35].

The vaccine's efficacy against RRP has not been evaluated, but it is quite likely that the reduction in condylomas will ultimately translate into a reduction in the juvenile form of RRP, since the infection is primarily transmitted from mother to child during childbirth.

Conclusion: The Gardasil vaccine is very effective against HPV-6- and HPV-11-associated condyloma for at least five years.

3.3. DURATION OF IMMUNITY

The duration of immunity is not known. As with other vaccines, GMTs diminish over time. Five years after vaccination, the GMTs are fairly close to those found in persons who have had a natural infection. The proportion of vaccinees with detectable titres at different points in time is presented in Table 4.

Table 4 Proportion of subjects vaccinated with Gardasil who had detectable HPV-6 and HPV-11 antibody titres

Vaccine	After 18 months		After 36 months		After 51-60 months	
	HPV-6	HPV-11	HPV-6	HPV-11	HPV-6	HPV-11
Gardasil[19 20]	98%	98%	94%	96%	90%	91%

Five years after vaccination, approximately 10% of vaccinees did not have detectable titres against genotypes 6 and 11. Among seronegative subjects who received a booster dose, 75% (6/8) and 86% (6/7) seroconverted for HPV-6 and HPV-11, respectively[20].

Conclusion: The vast majority of subjects vaccinated with Gardasil have detectable antibodies 5 years after vaccination against HPV-6 and HPV-11. Reductions in antibody titres below the threshold of detectability and non-response to booster doses in even a modest proportion of subjects five years after vaccination argue in favour of long-term immunological and clinical monitoring if the Gardasil vaccine is selected. One or more booster doses should be given if vaccinated women lose their protection over time.

4. SAFETY

In phase II and phase III clinical trials, the two vaccines were found to be safe and generally well-tolerated[10,15,20,36,37]. The proportion of subjects who had local reactions after receiving either the Gardasil or the Cervarix vaccine was 6-25 % higher than in the placebo group. The most common post-vaccination side effect was a short-term local reaction at the injection site (71-93%). The frequency of systemic side effects was similar in the vaccinee and placebo groups. The most commonly reported systemic side effect was a transitory headache (33-62%). The proportion of vaccinees who reported a local or general reaction after the second or third dose was slightly lower than after the first dose. Girls aged 10-15 reported fewer local reactions than women aged 16-23. However, younger subjects were more likely to report a fever of ≥37.8ºC[37]. Both HPV vaccines are contraindicated for pregnant women and for persons who are hypersensitive to components of the vaccines[38-40].

It should be noted, however, that the Cervarix vaccine contains a relatively new adjuvant and theoretically poses a higher risk of rare or long-term side effects than Gardasil, which contains a conventional adjuvant that has been used for a long time in a variety of vaccines.

The number of girls aged 9-10 who are vaccinated against HPV remains relatively low and the safety of the vaccines, particularly in this age group, should be monitored.

Conclusion: Both vaccines have an acceptable safety profile. Closer monitoring for rare or unexpected side effects should be put in place if the Cervarix vaccine is selected.

5. COADMINISTRATION WITH OTHER VACCINES

Although recombinant vaccines generally show little or no interaction with other vaccines[41-43], there is little data on the simultaneous administration of HPV vaccines with other vaccines. Still, even though no increase in side effects is anticipated with an extended calendar (0, 6, 60 months)[20] or with the coadministration of HPV vaccines with Twinrix or Boostrix, long-term monitoring will be needed[1].

The NACI statement on the Gardasil vaccine states that "concomitant administration of Gardasil vaccine and hepatitis B vaccine at all three doses does not diminish the response or GMTs to either vaccine"[6]. However, a 2008 study on the safety and immunogenicity of Gardasil coadministered with the Recombivax vaccine, showed a 33% reduction in anti-HBs GMTs in the group to whom the two vaccines were coadministered (534.9 vs. 792.5 MUI/ml)[34], although the rate of seroconversion was very high for all components.

The clinical significance of this reduction in anti-HBs titres is not known and a post-marketing evaluation should be initiated if coadministration of the HPV vaccine with another vaccine becomes the preferred option.

To our knowledge, no data have been published on the co-administration of Cervarix vaccine with hepatitis B vaccines, but at least four studies on the coadministration of Cervarix with Engerix-B, Boostrix-IPV, Boostrix/Menactra and Twinrix are currently under way (www.clinicaltrials.gov; NCT00534638; NCT00426361; NCT00369824; NCT00578227). Other studies of Gardasil with DTaP-IPV or DTaP-Meningo are also under way (NCT00337428; NCT00325130).

Conclusion: While no significant interaction is expected when the HPV vaccines are coadministered with other vaccines, the results of current and future studies into the coadministration of HPV vaccines with other vaccines will have to be monitored.

6. COST EFFECTIVENESS

The cost effectiveness of anti-HPV vaccination was estimated using at least three different mathematical models: cohort, dynamic and hybrid. Very different hypotheses were included in the calculations. Cost per QALY (Quality Adjusted Life Year) ranged from $4,000 US to $4,863,000 US[44]. However, in the hybrid and dynamic models, where there is less risk of under-estimating the positive impact of vaccination, variations in cost-effectiveness ratios were less pronounced. In most of these models, cost per QALY remained below $50,000 when the model limited vaccination to girls only[1, 45].

In modelling on Canadian data[46] concerning vaccination of 12-year-old girls (efficacy = 95%, lifetime protection, cost of vaccination = $400 CA), the cost per QALY gained was $31,000 (80% CrI* $15,000-$55,000) and $21,000 (80% CrI** $11,000-$33,000) with the Cervarix™ and Gardasil™ vaccines, respectively. Cost was observed to be highly sensitive to age at time of vaccination, as well as to the duration of protection, the cost of the vaccine, and QALYs lost due to anogenital condyloma. The authors concluded that vaccinating adolescent girls against HPV appears to be cost effective and that the main benefit of vaccination will be a reduction in cervical cancer mortality. However, if the screening of vaccinated women is not modified, treatment-related savings will be insignificant when compared to the cost of vaccination[46].

In another Canadian model, estimates took into account the potential duration of protection. In this model, the lifetime risk of developing cervical cancer decreases by 61% if the vaccine confers lifetime protection and by a mere 6% if protection lasts 30 years[47]. The number of vaccinees needed to prevent one episode of condyloma was estimated to be 8 and the number needed to prevent one case of cervical cancer was 324, assuming that the vaccine confers lifetime protection. However, if 3% of vaccinated women become susceptible every year, 9,080 women would need to be vaccinated to prevent one case of cancer. In the latter scenario, the number of vaccinees needed to prevent one case of cancer drops to 480 if a booster dose is administered. These results support the idea that duration of immunity is the most important factor to take into account when choosing a vaccine[22].

* Credibility interval: this approach is used primarily when available data are limited. This interval does not necessarily coincide with the confidence interval. Calculation of the confidence interval is based on data only, while the credibility interval also includes contextual elements emanating from the initial distribution.

CONCLUSION

In the short term (5-6 years), the two vaccines show no significant difference in terms of their efficacy against HPV-16 and HPV-18-associated cervical cancer precursors. Within the same time frame, the Gardasil vaccine also confers good protection against HPV-6 and HPV-11-associated condyloma. While the primary objective of the HPV vaccination program is to prevent the precursors of cancer, certain secondary objectives, such as reducing the clinical and/or economic burden associated with HPV-6 and HPV-11, can also be taken into account.

There are no data on the long-term protection conferred by either vaccine. It may be that booster doses will be necessary for one or both vaccines. However, the reduction in the proportion of women who are anti-HPV-18 seropositive 3 to 5 years after vaccination with Gardasil, as well as the loss of immunological memory for HPV-6, HPV-11 and HPV-18, even in a small proportion of women vaccinated with Gardasil, is a matter of concern. Given these factors, we can not exclude that a booster dose may be required earlier after vaccination with Gardasil than with Cervarix.

Both vaccines have a very good safety profile. Since Cervarix contains an adjuvant that is relatively new, a closer monitoring for rare or unanticipated side effects should be put in place if this vaccine is selected.

Unfortunately, because of several uncertainty factors, it is difficult at present to quantify the added value of the HPV-6 and HPV-11 components and thereby estimate an acceptable price differential between the two vaccines. Duration of immunity emerges as the most important factor in the analysis of cost effectiveness.

The existing scientific data show that both the Gardasil and Cervarix vaccines could be used in Quebec's regular vaccination and catch-up program in order to "reduce the incidence of and mortality associated with cervical cancer." Use of the Gardasil vaccine would also provide protection against diseases associated with HPV-6 and 11.

It should be noted that the CIQ advised for a safety net in its recommendations, in the form of an extended calendar for girls aged 9-10. This calendar (0, 6 and 60 months) will permit adjustments to be made based on future data concerning the duration of immunity conferred by the two vaccines. In Quebec, an evaluation plan and a scientific vigilance will be implemented in order to address questions that remain unanswered.

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