



## Advisory report on the Human Papillomavirus (HPV) Vaccination Schedule

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## Table of Contents

|   |    |
|---|----|
| List of Abbreviations.....  | II |
| Background and summary.....   | 1  |
| 1 Use of HPV vaccines.....  | 3  |
| 2 The immunogenicity of Fewer Than Three Doses of Vaccine.....                                  | 3  |
| 3 Efficacy of Fewer Than Three Doses of Vaccine against Incident and Persistent Infections..... | 5  |
| 4 Efficacy of Fewer Than Three Doses of Vaccine against CIN2+ and Cancers.....                  | 6  |
| 5 Efficacy of Fewer Than Three Doses of Vaccine against Anogenital Warts.....                   | 8  |
| 6 Results with Mixed Vaccination Schedules.....   | 9  |
| 7 Safety of Different Vaccines.....   | 10 |
| 8 Data on a Single-Dose HPV Vaccine Schedule.....   | 10 |
| 9 Economic considerations and impacts of vaccination already observed.....                      | 11 |
| 10 Feasibility.....   | 12 |
| 11 Conformity.....  | 12 |
| 12 Acceptability.....   | 12 |
| 13 Equity and Ethics.....   | 13 |
| 14 Conclusions and Recommendations.....   | 13 |
| 15 Evaluation in case of use of a mixed vaccination schedule.....                               | 13 |
| References.....   | 14 |
| List of CIQ members.....  | 18 |
| Annexe 1 Summary of declarations of interest.....   | 19 |

## List of Abbreviations

|       |   |
|-------|---|
| CIQ   | Comité sur l'immunisation du Québec           |
| CIRC  | International Agency for Research on Cancer   |
| ELISA | Enzyme-Linked Immunosorbent Assay             |
| GAVI  | Global Alliance for Vaccines and Immunization |
| GBS   | Guillain-Barré Syndrome                       |
| GMT   | Geometric mean titers                         |
| HPV   | Human papillomavirus                          |
| MSSS  | Ministère de la Santé et des Services sociaux |
| NCI   | National Cancer Institute of USA              |
| PBNA  | Pseudovirion-Based Neutralization Assay       |
| VAERS | Vaccine Adverse Events Reporting System       |
| VSD   | Vaccine Safety Datalink                       |
| WHO   | World Health Organization                     |

## Background and summary

### Background

In 2008, when a program was launched to vaccinate girls in Grade 4 against a number of strains of human papillomavirus (HPV), the *Comité sur l'immunisation du Québec* (CIQ – Quebec immunization committee) recommended the use of Gardasil, a quadrivalent vaccine. Although the Cervarix vaccine provides protection against HPV strains associated with cancer (HPV 16 and 18), the CIQ preferred Gardasil, which in addition to being effective against HPV 16 and 18, also protects against the HPV strains that cause a great majority of anogenital warts (HPV 6 and 11). This position was reiterated in the recommendations of the 2012 report on scientific knowledge updates. In 2013, in light of studies showing that two doses administered to pre-adolescent girls six months apart were sufficient to provide high levels of antibodies, the CIQ recommended against administering a third dose in Grade 9. Quebec has accordingly always used a two-dose schedule in its routine program, administered in Grade 4. Since September 2016, both girls and boys in Grade 4 have been eligible to HPV vaccination. At the same time, the quadrivalent Gardasil vaccine used in Quebec's public program was replaced by the nonavalent Gardasil-9 vaccine, which added protection against five other types of HPV (31, 33, 45, 52 and 58) associated with cancer.

In 2014, the MSSS asked the CIQ to assess whether Cervarix might fit into the public vaccination program. The literature review carried out at the time demonstrated that Cervarix was highly immunogenic and effective in preventing infections and cancer precursors associated with HPV 16 and 18. It also seemed to induce cross-protection against HPV 31, 33 and 45. Note that HPV 16 and 18 are responsible for some 70% of cases of cervical cancer, a large majority of other cancers in women, and almost all cancers attributed to HPV in men. However, Cervarix offers little or no protection against anogenital warts. The same review also showed that there were no data on the use of different HPV vaccines in single individuals.

In light of the foregoing, the CIQ recommended the following:

- Assessing the population efficacy and cost effectiveness of a potential mixed vaccination program based on one dose of bivalent vaccine (Cervarix) and one dose of nonavalent vaccine (Gardasil-9)
- Continuing the immunogenicity study of two doses of Gardasil by giving participants a third dose of either Gardasil or Cervarix
- Conducting an immunogenicity study of two doses of Gardasil-9 versus a single dose of Gardasil-9 and a single dose of Cervarix

In July 2017, given:

- The fact that there was already an HPV vaccination program for both girls and boys,
- The encouraging results of mixed-schedule studies, and
- GSK's offer to provide Cervarix at considerably lower cost,

The *Ministère de la Santé et des Services sociaux* (MSSS— Department of health and social services) asked the CIQ the following question:

What role could Cervarix play within the current vaccination program in the perspective of optimizing the prevention of diseases attributed to the human papillomavirus?

The results of the study on the expected population efficacy and cost-effectiveness of a mixed vaccination schedule based on one dose of Cervarix and one dose of Gardasil-9 were submitted to the CIQ in December 2014. The results of the study on the safety and immunogenicity of a single dose of Cervarix administered after two doses of Gardasil were presented to the CIQ in 2015, and the results of a study on a mixed schedule consisting of one dose of Cervarix and one of Gardasil-9 were presented in June and September 2017. (For more details, see the section on mixed schedules.)

## Summary

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A lot of new data on the immunogenicity, efficacy and effectiveness of fewer than three doses of HPV vaccine have become available since the publication of the CIQ report on the 2012 knowledge update. The two-dose schedule has become a standard that is widely accepted around the world. Such schedules are currently in use in more than half (48/82) of the countries offering HPV vaccination programs. The same schedule has been approved and recommended by the World Health Organization (WHO) and the Global Alliance for Vaccines and Immunization (GAVI).

A number of clinical and ecological studies have even come up with some interesting and promising results in terms of the immunogenicity and efficacy of single-dose HPV vaccination. Immunogenicity studies have shown that sero-conversion rates after a single dose of vaccine are often in excess of 95%, although with considerably lower geometric mean titers (GMTs) than those observed after two or three doses. However, antibody titers observed after a single dose are higher ( $\approx$  4 to 11 times greater) than titers observed in infected women who have managed to eliminate the virus. Antibody avidity after a single dose of vaccine is similar to that observed after two or three doses, and antibody levels remain stable for at least four years. Clinical efficacy studies seem to indicate that a single dose of vaccine protects against incident infections (70–90%) and persistent infections (85–100%) caused by the types of viruses included in the vaccine. This degree of protection is similar to that provided by two or three doses of vaccine. The results of ecological studies show more variance. However, these studies are subject of major biases that could lead to an underestimate of the efficacy of one or two doses of vaccine.

Worldwide, considerable effort has been put in place to better assess the immunogenicity and efficacy of single-dose vaccine schedule or schedules based on two doses administered several months, or even several years, apart. More reliable results on this topic are expected in coming years.

The safety and immunogenicity of a mixed schedule based on the use of different HPV vaccines given to the same individual have been assessed in at least

three clinical studies. The results of these studies show that the safety profile of two- or three-dose mixed schedules is acceptable and quite similar to that using one vaccine schedules.

The results of clinical studies carried out in Quebec indicate that after a single dose of vaccine, 99% to 100% of children 9-10 years old have antibodies to viruses covered by the vaccines. The few children who had no antibodies to certain types of HPV, as determined by ELISA (Enzyme-Linked Immunosorbent Assay) and re-tested by PBNA (Pseudovirion-Based Neutralization Assay) had all neutralizing antibodies.

The use of one dose of Gardasil-9 followed by another of Cervarix resulted in an acceptable safety profile. To note, that this mixed schedule induces antibodies against the nine types of HPV covered by Gardasil-9 in all children tested (100%). The GMTs of HPV 16 and 18 antibodies were higher in the group that received one dose of Gardasil-9 and one dose of Cervarix (or vice versa) than in the group that received two doses of Gardasil-9. On the other hand, the GMTs against the 7 types of HPV covered by Gardasil-9 but not by Cervarix were higher in the groups that received two doses of Gardasil-9. In these two studies conducted in Quebec, a three- to nine-fold increase in GMTs against HPV 31, 33, 45 and 52 was observed after Cervarix was administered to participants having received one dose of Gardasil-9. The anti-HPV 58 GMTs were already relatively high after the single dose of Gardasil-9 and increased 1.5-fold after administration of Cervarix. In the same subjects, after one dose of Cervarix, anti-HPV 6 and 11 GMTs increased by a factor of 1.6 to 1.8. Note that the clinical importance of different antibody titers remains unknown. However, the increase in antibodies to virus types not covered by Cervarix is consistent with the results of studies having shown some cross-efficacy from this vaccine.

Economic analysis shows that in Quebec, the cost of a mixed-schedule program would come in at about \$3 million less per vaccinated birth cohort than the current two-dose program with Gardasil-9.

It is also estimated that the feasibility of the mixed schedule should be quite similar to the current vaccination schedule, particularly in the case of school-based vaccination.

The schedule making use of Cervarix vaccine alone was not considered because it offers little or no protection against anogenital warts. The current two-dose schedule of Gardasil-9 provides assurance that the province would not sacrifice any acquired immunization against the HPV burden. However, the CIQ believes that a mixed schedule maximizes the type 16 and 18 HPV immune response while providing good immunity against seven other types of HPV covered by the Gardasil-9 vaccine. In other words, assuming the unit price of Cervarix is lower than that of Gardasil-9, the mixed schedule is the most efficacious option.

## Recommendations

In a vote, the active members of the CIQ unanimously expressed a preference for a mixed schedule for healthy youths between 9 and 17 years of age rather than a schedule comprising Gardasil-9 alone, provided the difference in price is appreciable.

Whatever the MSSS decides, the epidemiological monitoring of infections and illnesses associated with HPV will need to be pursued, notably when it comes to anogenital warts. Should any modifications be made to the epidemiology of the disease, the CIQ's recommendation can be reviewed and the program adapted accordingly.

For individuals 18 years of age and older and for certain other groups (e.g., the immunosuppressed) the vaccination schedule remains unchanged. The PIQ can be consulted for details about the different vaccination schedules.

### 1 Use of HPV vaccines

At the time of writing, i.e., November 2017, the Gardasil vaccine was approved for use in 134 countries, the Cervarix vaccine in 135 countries and the Gardasil-9 vaccine in 34 countries (written communication from Merck and GSK, November 2017). HPV vaccination is included in the national vaccination programs of 82 nations worldwide. Eleven of these countries provide vaccination for both girls and boys— 71 of them for girls only (1). The Cervarix vaccine is used in the public programs of 31 countries—Gardasil or Gardasil-9 vaccine in 64 countries. In 13 countries, both vaccines are used in the case of certain jurisdictions or groups.

As of early 2017, 48 countries used a two-dose vaccination schedule (2).

Since HPV vaccines were approved in 2006, more than 270 million doses have been distributed (3). Some 170 million of these doses were Gardasil, 32 million of them were Gardasil-9, and 71 million were Cervarix (written communication from Merck and GSK, November 2017).

### 2 The immunogenicity of Fewer Than Three Doses of Vaccine

The results of two systematic literature reviews (4,5) indicate that the immunogenicity of 2 doses of HPV vaccine in children 9 to 14 years of age is non-inferior to that of 3 doses administered to women 15 to 25 years old, age group in which efficacy was demonstrated (5). A World Health Organization (WHO) briefing note, dated May 2017 (6), specifies that the immunogenicity of a two- or three-dose schedule was compared in four randomized clinical studies, one on quadrivalent vaccine, two on bivalent vaccine and one on nonavalent vaccine (7–10), and two non-randomized studies on quadrivalent and bivalent vaccines (11,12). In the randomized studies, the two-dose schedule for girls induced geometric mean titers (GMTs) that were non-inferior, and in some cases were higher, than the three-dose schedule for young women. As for sero-conversion one month after the last dose, there was no notable difference observed between groups having received one, two or three doses of the vaccine.

In both non-randomized studies, the GMTs were non-inferior for HPV 11 and 18, although they were inconclusive for HPV 6 and 16, as the results varied among the different studies. The sero-conversion data were not available (4,6). Another study compared the immunogenicity of nonavalent vaccine administered as per a two-dose schedule to both girls and boys, or a three-dose schedule administered to young women. One month after the last dose of vaccine, the immune antibody response (sero-conversion and GMT) in girls and boys having received two doses of vaccine six to twelve months apart was non-inferior to the response observed in young women having received three doses (13).

More recently, two follow-up studies measured the persistence of immunity in girls vaccinated with two or three doses of bivalent vaccine (14,15). In one of these studies, girls 9 to 14 years of age were initially randomized 1:1 to receive two doses of the vaccine either six or twelve months apart. A third group included women 15 to 25 years of age having received three doses of vaccine (at 0, 1 and 6 months). The 36-month follow-up demonstrated non-inferiority for sero-conversion and GMTs among girls after two doses of vaccine, and among women after three doses. (14) The second study, carried out in the Netherlands, compared the persistence of immunity in girls vaccinated at the age of 12, either with two doses of bivalent vaccine at 0 and 6 months or three doses at 0, 1 and 6 months. In this ecological study, a stratified analysis was conducted for the time elapsed since the first dose (0–2, 2–3, 3–4 or 4–4½ years). The antibody GMTs for HPV 16 and 18 were non-inferior for all of the periods, with the exception of HPV 18 two to three years after the first dose. Moreover, antibody avidity was similar in both study groups. The avidity index for cross-reacting HPV 31/33/45 antibodies was also non-inferior in the group having received two doses of vaccine as compared to the three-dose group.

Furthermore, a systematic literature review and meta-analysis comparing the immunogenicity of two versus three doses of HPV vaccines was published in 2017 (2). Seven clinical studies were included in this meta-analysis.

In the randomized studies (n=3), the HPV 16 and 18 antibody GMTs were either non-inferior or inconclusive (due to the variability of results among the different studies) up to 24 months after vaccination. In non-randomized studies (n=4), the GMTs among adolescent girls after two doses of the vaccine were either non-inferior or superior to the GMTs observed in women after three doses of vaccine (2). The results of this meta-analysis point to the same conclusion as those of two previous literature reviews, which indicate that two doses of HPV vaccine induce a satisfactory immune response when administered to adolescent and pre-adolescent girls (4,5).

The threshold level of HPV antibodies defining protection remains unknown, but it seems to be quite low. It would even be possible for the titer of antibodies necessary for protection after vaccination to be below

the detection thresholds of the serological tests currently in use (16). The foregoing hypothesis is supported by studies demonstrating an absence of lesions associated with the HPV types covered by the vaccine, even though the antibodies in some vaccinees are no longer detectable eight to ten years after vaccination (17). The assumption is also supported by the results reported in animal models showing that very low titers are sufficient to provide protection (18). Also, antibody titers induced by two doses of vaccine were at least 11.7 times higher (as determined by ELISA, the enzyme-linked immunosorbent assay) and 4.8 times higher (by PBNA, the pseudovirion-based neutralization assay) than the antibody titers found in women carrying the virus who had managed to eliminate the infection (19). It is also plausible that in the long term, the immune memory as well as the affinity and avidity of the antibodies remain in excess of antibody titers. Studies have shown that antibody avidity is similar after three or two doses, and even a single dose, of vaccine (20,21). Similar results were also reported in terms of the number of memory B cells and T CD4 cells after two or three doses of the vaccine. These immunobiological evidences support the notion that two doses of vaccine may be enough to induce long-term protection. There is also the theoretical possibility—yet to be demonstrated, however—that in people who are vaccinated, the natural infection triggers an immunological booster response which induces a sufficient number of antibodies to neutralize the virus in mucous membranes (17,19).



### 3 Efficacy of Fewer Than Three Doses of Vaccine against Incident and Persistent Infections

At least five studies have shown strong vaccine efficacy after administration of a single dose of quadrivalent or bivalent vaccine (21–25). These studies include women who have never received the entire series of vaccinations, which complicates the interpretation of results, notably due to the non-randomization of subjects as to the number of doses, the relatively small size of samples given fewer than three doses, and the low number of incident and persistent infections (6). However, the results of all these studies consistently show high efficacy against incident infections (first detection of HPV) and persistent infections (detection of the same strain of HPV in at least two subsequent visits, six or twelve months apart), regardless of the number of doses (23).

The first study, which assessed the efficacy of fewer than three doses against persistent infection (12 months) was carried out in Costa Rica by the U.S.A.'s National Cancer Institute (NCI) (22). In that particular study, after a 4.2-year median follow-up of women vaccinated between the ages of 18 and 26, the efficacy of one, two or three doses of bivalent vaccine in protecting against persistent HPV 16 and 18 infections was respectively estimated to be 100% (95%CI: 66.5–100.0%), 84.1% (95% CI: 50.2–96.3%) and 80.9% (95% CI: 77.1–87.7%).

The efficacy of two doses of bivalent vaccine against persistent infections was also reported in a sub-analysis of the results of a randomized phase-III study (26). In that study, women 15–25 years of age were recruited (n=977) to receive three doses of vaccine (0, 1 and 6 months). However, 5.2% of the women recruited received only two doses of vaccine. After a 48-month follow-up of women having received two doses (usually 1 month apart), the vaccine's efficacy against persistent HPV 16 and 18 infections (lasting  $\geq 6$  months) was estimated to be 100% (95% CI: 33.1 to 100%) and were non-inferior to that observed after three doses (26).

The results of NCI and GSK studies (the PATRICIA study) were analyzed together as an assessment of the efficacy of three doses of bivalent vaccine (27). In that analysis, the 1,185 women having received two doses of vaccine and 543 women having received a single dose of bivalent vaccine were included. After four years of follow-up (sampling every 12 months), the efficacy of one, two or three doses of vaccine against incident infections was estimated to be 87.5% (95% CI: 60.9–97.1%), 81.2% (95% CI: 59.5–92.3%) and 81.4% (95% CI: 78.7–83.8%). The same analysis showed similar efficacy against persistent infections in groups having received one, two or three doses (6 and 12 months). More specifically, the efficacy against persistent (6-month) HPV 16 and 18 infections after one, two and three doses was respectively 100% (95% CI: 67.4–100%), 87.9% (95% CI: 54.0–98.1%) and 93.6% (95% CI: 91.2–95.5%) (27).

Another randomized study was launched in India in 2009. The purpose of that study was to compare the immunogenicity and efficacy of two and three doses of quadrivalent vaccine administered to girls and young women 10 to 18 years of age (21). The vaccination was stopped by the Indian government for reasons unrelated to the study, but the follow-up of participants was maintained. This discontinuation meant that the randomness of the study was lost but led to the creation of cohorts of women (n=17,729) having received either a single dose (n=4,950), two doses (0 and 2 months; n=3,452), two doses (0 and 6 months; n=4,979) or three doses (0, 2 and 6 months; n=4,348). Fewer than three doses of vaccine induced neutralizing antibodies against the four HPV genotypes covered by the vaccine. After 48 months of follow-up, the GMTs were similar in groups having received two doses 180 days or more apart, or three doses of vaccine, but were considerably lower in the groups having received a single dose, or two doses at short interval.

However, the antibody avidity index (as measured at months 7 and 18 of the study) was similar in all 4 study groups. After a median 4.7-year follow-up, no persistent HPV 16 or 18 infection was detected among the 838 women on whom two or more screening tests were carried out, and that was independently of the number of doses received (1, 2 or 3 doses). The authors concluded that two doses of vaccine administered 180 days or more apart were immunologically non-inferior, and that results suggest that one, two or three doses provide equivalent protection against either incident or

persistent HPV 6, 11, 16 and 18 infections over the short to medium term.

The efficacy of fewer than three doses of bivalent vaccine was also reported in an ecological study carried out in Scotland (28). In that study, 5,949 cytological samples were tested for the presence of HPV 16 and 18. There were respectively 1 853, 300 and 177 women having received one, two (0 and 1 month) or three doses of vaccine. More than half (56.4%) of the women were at least 17 years old at the time of the vaccination. The other were 15 or 16 years old. It is therefore possible that many of these women were sexually active and potentially carrying HPV at the time of vaccination. In that study, the age-adjusted vaccine efficacy of one, two and three doses against HPV 16 and 18 were respectively 48.2% (95% CI: 16.8–68.9%), 54.8% (95% CI: 30.7–70.8%) and 72.8% (95% CI: 63.8–80.3%). The HPV 31/33/45 cross-immunity was similar after two and three doses of vaccine (48.3% [95% CI: 7.6–68.9%] and 55.2% [95% CI: 32.6–70.2%]), but absent in women having received only one dose of vaccine (-1.62% [95% CI: -85.1, 45.3%]).

Finally, a study published in 2018 assessed the persistence of antibodies and the cumulative incidence of HPV 16 and 18 infections over an average period of seven years (25). In that study, the comparison was done among women having received one dose (n=134), two doses (0 and 6 months, n=79; 0 and 1 month, n=193) or three doses (n=2,043) of bivalent vaccine. Among the women having received one dose, two doses (0 and 1 months), two doses (0 and 6 months) and three doses, incident or persistent HPV 16 and 18 infections were respectively detected in 1.5% (95% CI: 0.3–4.9%), 3.6% (95% CI: 1.6–7.1%), 3.8% (95% CI: 1.0–10.1%) and 4.3% (95% CI: 3.5–5.3%). The prevalence of other oncogenic and non-oncogenic HPV types, not including HPV 16/18/31/33/45, was similar among all four study groups. The last observation indicates that the low incidence of HPV 16 and 18 infections measured in groups having received one or two doses of vaccine was not due to the absence of exposure to HPV. Note that in this study, seven years after vaccination, all women (100%) remained sero-positive for HPV 16 and 18 antibodies (25).

## 4 Efficacy of Fewer Than Three Doses of Vaccine against CIN2+ and Cancers

Two systematic reviews assessed the efficacy of HPV vaccine in preventing high-grade precancerous lesions across the population, with some highly varying results (from 3% to 84%) (6,29). Most of the studies focused on analyzing administrative databases and were therefore unable to avoid detection biases or to control for sexual behaviours and other possible confusing factors (30–32). Few vaccinated cohorts have reached the age at which screening can identify precancerous lesions of the cervix. Moreover, the process of screening for precancerous lesions is subject of variation in terms of both strategy and frequency. Some of these studies assessed vaccine effectiveness against high-grade lesions for women having been vaccinated with less than three doses (23,30–35). These studies include women who have not received the entire series of vaccinations, and the results must be interpreted cautiously in light of their methodological limitations, notably the non-randomization of subjects as to the number of doses, the relatively small size of samples, the fact that vaccines were administered on a catch-up basis, and the low number of incident and persistent infections (6).

One study conducted in Manitoba assessed the vaccine's effectiveness against high-grade lesions regardless of the HPV type by comparing women vaccinated with one dose or more (with no stratification based on number of doses received) to non-vaccinated women. The study found 53% effectiveness against high-grade lesions in the group of women vaccinated at the age of 15 to 17. This study did not demonstrate efficacy in women vaccinated at a later age (18 or more), or those who had already screened cytologically positive for a lesion before vaccination (32).

The Hariri et al. study carried out in the U.S. assessed vaccine efficacy against high-grade CIN2+ lesions associated with HPV16 and 18. From 2008 to 2012, the proportion of CIN2+ due to these two viruses decreased from 53.6% to 28.4% among women who had received one dose or more of vaccine (P for trend < 0.001).

There was no significant reduction among non-vaccinated women (57.1% vs 52.5%;  $P$  for trend = 0.08) or among women of unknown vaccine status (55.0% vs 50.5%;  $P$  for trend = 0.71) during this same period. The proportion of CIN3/CIS lesions attributed to HPV16 and 18 dropped from 76.0% in 2008 to 60.9% in 2012 ( $P$  for trend = 0.06) among women vaccinated with one or more doses, although no change was observed in the two other categories (non-vaccinated or vaccination status unknown). The efficacy was greater (72% [95% CI: 45–86%]) among women who had initiated their vaccination more than four years before the screening test through which a high-grade lesion was diagnosed. This efficacy was respectively 21% (95% CI: 1–37%) and 49% (95% CI: 28–64%) among women having respectively initiated their vaccination 25 to 36 months and 37 to 48 months before the screening test (30).

The Australian case-controlled study by Crowe et al. (31) was carried out on women qualifying for catch-up vaccination who had already undergone cytological screening. The women who tested normal cytologically were used as healthy controls. The study found 46% vaccine efficacy against high-grade CIN2+ lesions (histologically confirmed after an abnormal screening test) among women having received three doses of vaccine. The study also demonstrated 21% efficacy in women having received two doses (at 0 and 2 months, essentially) and no statistically significant efficacy among those who had received only one dose. The women having received three doses were younger at the time of vaccination (17 years) than those who received two doses and one dose (19 and 21 years, respectively). Moreover, women who got a diagnosis of CIN2+ (the study cases) were found to be socio-economically more disadvantaged. Finally, a number of analyses presented in accompanying documents showed that the protection provided in the group having received one and two doses increased if the analysis started after waiting 180 or 365 days before counting the number of cases, the purpose being to reduce the inclusion of prevalent cases at the time of vaccination in the analysis (i.e., already infected).

Another Australian study, which used two different population registries (cytology and vaccination), assessed a cohort of women who were under 17 and qualified for school vaccination in 2007, and were then screened between 2007 and 2011. That study demonstrated efficacy against high-grade lesions of

close to 40% in women who had received three doses of vaccine, but no statistically significant efficacy for those who had received only one or two doses (at 0 and 2 months interval) (33).

Brotherton et al. (34) analyzed another cohort from the same Australian state using the same registries used in the previous study (33). The women included in this analysis were 26 years of age or younger in 2007 and qualified for free school or catch-up vaccination. They all had to undergo screening during the same period as that used in the previous study, i.e., between 2007 and 2011. The researchers observed protection against low- and high-grade cytological anomalies regardless of the number of doses received, provided the vaccination took place before the screening activities. The protection against high-grade cytological anomalies was 56% for a single dose (RR 0.44; 95% CI: 0.32–0.59), 37% for two doses (RR 0.63; 95% CI: 0.50–0.80) and 47% for three doses (RR 0.53; 95% CI: 0.47–0.60). The research was consistent with the previous study and did not reveal significant protection among women having received one or two doses when the study was limited to women whose cytological status was histologically confirmed for CIN2+. However, further analysis of participants less than 16 years of age at the time of vaccination demonstrated protection against histologically confirmed lesions for both the 1-dose group and the 2-dose group, although the findings were statistically insignificant because the sample size was too small.

As opposed to the previously cited studies, which assessed the quadrivalent vaccine's population efficacy, a sub-analysis of the Pollock et al. study conducted in England assessed the protection provided by the bivalent vaccine against precancerous cervical lesions (35). The protective effect of vaccination was detected in the larger group of women having received three doses, but it was not statistically significant in the groups having received one or two doses.

A first study showing statistically significant vaccine efficacy against invasive cervical cancer was presented at the Eurogin conference held in Amsterdam in October 2017 (abstract: MSS 7-2) further to the longitudinal follow-up of cohorts of non-vaccinated women and women included in the first clinical trials carried out in Finland. Analysis of the 10-year follow-up

showed that 10 of the non-vaccinated women had developed an invasive cancer but that none of the vaccinated women had, for an efficacy rating of 100%. The information on the number of doses was not disclosed, but we can assume that, in light of their ages (16–24 years at recruitment) and the fact that they were vaccinated in the course of a clinical trial conducted by vaccine manufacturer, most of the subjects had received three doses.

## 5 Efficacy of Fewer Than Three Doses of Vaccine against Anogenital Warts

Anogenital warts have a relatively short incubation period, most commonly between 1 and 6 months (min. 2 weeks, max. 8 months), and a far shorter natural history than that of HPV-related cancers (23,36). In this context, reducing the incidence of warts in the population is a rapid measure that demonstrates the effectiveness of HPV vaccines. This evidence was obtained in ecological studies conducted in countries that have introduced the Gardasil vaccination into their national immunization programs and have population databases that track the frequency of anogenital warts and vaccination (36–40). In a literature review conducted in 2015, 16 publications from six countries were included and presented the impact of vaccination on the incidence of anogenital warts. These studies consistently showed a significant decrease in anogenital warts in cohorts eligible for vaccination and the virtual absence of warts among young women vaccinated at the age of 10–16 years. In some of these studies, the efficacy of fewer than three doses of the vaccine has been reported and is detailed below (37,41).

A recent Swedish study has estimated the incidence of warts based on the time interval between the 1st and 2nd doses of the quadrivalent vaccine and the age at the time of vaccination (37). In this study, researchers used population registers. A total of 264,498 girls and women aged 10 to 27 years were included in the study (all vaccinated before the age of 20); 79,042 received two doses and 185,456 received three doses of the vaccine. A diagnosis of anogenital warts was reported in 619 women (0.2%). Generally, the incidence of warts was higher among women who started vaccination at age 17–19 than among women vaccinated at age 16 and under. When analyzed by interval between first

two doses (0–3 months, 4–7 months and 8 months and more), there were many variations in incidence rates, often with non-statistically significant differences between subgroups. The results observed in women who received two doses of vaccine with an interval of 4 to 7 months between the first two doses were similar to the results observed after three doses. Among women vaccinated before age 17 who received two vaccine doses at 4–7 months, the age-adjusted incidence rate was 79/100,000 p.a. (95% CI): 24–133/100 000 p.a.) and among the women who received doses with the first 2 doses also spaced 4-7 months, the rate was 91/100 000 p.a. (95% CI: 28–154/100 000 p.a.). The results were inconclusive for eight months or more, since the number of women was limited and the confidence intervals broader. The authors concluded that two doses of vaccine spaced 4–7 months apart can be as effective against warts as three doses.

Another study reported on the incidence rate ratios (IRR) of warts in a cohort of 1,045,165 girls and young women aged 10 to 24 years (41). A significant reduction in warts was observed among vaccinated women, regardless of the number of doses received. More specifically, the IRR was 0.31 (95% CI: 0.20–0.49), 0.29 (95% IC: 0.21–0.40) and 0.18 (95% IC: 0.15–0.22) respectively among women who received one, two or three doses of quadrivalent vaccine. In this study, group immunity was absent. The authors suggested that the lack of group immunity is due to low vaccination coverage (25%) in the study population.

In another study in Denmark, the efficacy of two and three doses of quadrivalent vaccine against anogenital warts was evaluated. The data included 550,690 women born between 1985 and 1999, 361,734 of whom were vaccinated. Out of the women vaccinated, 25.9% received two doses of vaccine and 58.8% received three doses. In this study, the reduction in incidence rates of anogenital warts among women who received two doses at 5-month intervals or more, or three doses was the same (ratio of rates equal to 1) (42).

To protect against warts, some authors and studies, including the modelling analysis done by Marc Brisson's team in 2014, suggest that, even if protection against types 6 and 11 was of a shorter duration, considering the natural history of different types, it still allow to generate a marked reduction in warts, which is not the

case for high-risk HPV. In Quebec, the median age of individuals with a diagnosis of warts before the implementation of the HPV vaccination was estimated at 27 years (43).

## 6 Results with Mixed Vaccination Schedules

Two studies conducted in Quebec evaluated the immunogenicity and safety profile (I) of two doses of Gardasil and a dose of Cervarix (44) and (II) of two doses of Gardasil-9 versus one dose of Gardasil-9 and one dose of Cervarix.

In the first study, 416 9–10-year-old girls were enrolled and randomized (1:1) to receive Gardasil and Twinrix co-administration (0–6 months) or one month apart. Six months after the first dose of Gardasil, antibodies against HPV 6, 11, 16 and 18 were present in 94%, 100%, 99% and 96% of the girls, respectively. One month after the second dose of Gardasil, all participants (100%) were positive for the four HPV types included in the vaccine. Thirty-six (36) months after the second dose of Gardasil, 99% of participants remained sero-positive for anti-HPV 18 and 100% for anti-HPV 6, 11 and 16 (44). To evaluate the third dose, the remaining 366 participants at Month 36 of the study were randomized (1:1) to receive either one booster dose of Gardasil or Cervarix.

One month post-booster dose of Gardasil, at least a four-fold increase of antibody titers against HPV 6, 11, 16 and 18 was observed in 94%, 89%, 88% and 98% of participants, respectively. In the group receiving a booster dose of Cervarix, a four-fold increase in antibody titers against HPV 16 and HPV 18 was observed in 93% and 99% of participants, respectively. In addition, GMTs for HPV 16 and HPV 18 were statistically higher after a booster dose of Cervarix than after a booster dose of Gardasil ( $p = 0.002$  and  $p < 0.001$ , respectively). After administration of the Cervarix vaccine, a 1.6-fold increase in GMTs ( $p < 0.0001$ ) and 1.4-fold increase ( $p = 0.0002$ ) was observed for HPV 6 and HPV 11, respectively. However, for HPV 6 and 11 the GMTs were significantly lower than after the third dose of Gardasil (both  $p < 0.0001$ ) (44).

In the second study, 371 9–10 year olds (186 males and 185 females) were recruited and randomized (1:1) to receive either two doses of Gardasil-9 or one dose of Gardasil-9, and one dose of Cervarix 6 months apart. The group receiving one dose of Gardasil-9 and one dose of Cervarix was randomized a second time (1:1) to receive the two vaccines in two different sequences (Gardasil-9 + Cervarix or Cervarix + Gardasil-9). The presence of antibodies against the nine (9) virus types included in the Gardasil-9 vaccine was tested for at months 1, 6 (before the second dose administration) and 7 of the study (one month post-second dose).

At one and six months after one dose of Gardasil-9 ( $n = 88$  and  $n = 177$ ), all participants (100%) had antibodies against the 9 types of HPV included in the vaccine. Six months after a dose of Cervarix ( $n = 86$ ), 100% of participants had antibodies against HPV 16 and 18. Between 51% and 78% had antibodies against the other seven types of HPV included in the Gardasil-9 vaccine. One month after two doses of Gardasil-9 or one dose of Gardasil-9 and one dose of Cervarix (regardless of the vaccine sequence), 100% of the participants had antibodies against the nine types of HPV included in Gardasil-9.

Anti-HPV 16 and HPV 18 GMTs were higher in the groups receiving one dose of Gardasil-9 and one dose of Cervarix, and the GMTs for anti-HPV 6, 11, 31, 33, 45, 52 and 58 were higher in the group receiving the two doses of Gardasil-9. It is important to note that, after administration of the Cervarix vaccine to participants who received one dose of Gardasil-9, a 3- to 9-fold increase in GMT for HPV 31, 33, 45, and 52 was observed. Anti-HPV 58 GMTs were already quite high after the dose of Gardasil-9 (AU 68/ELISA) and increased 1.5-fold after Cervarix administration. In the same subjects, after administration of one dose of Cervarix, the GMTs for anti-HPV 6 and 11 increased 1.6-1.8 fold, but remained relatively low compared with the GMTs observed after two doses of Gardasil-9.

This latter finding is consistent with the results of the study where a booster dose of Cervarix was given 36 months after the primary vaccination with two doses of Gardasil (44). As already mentioned above, the clinical importance of antibody titers remains not well understood, and in clinical studies subjects vaccinated with at least one dose of the vaccine have shown a high level of protection against persistent

infections, anogenital warts and cancer precursors despite the low antibody titers observed for some types of HPV (6). However, if a mixed schedule is used, enhanced monitoring of the prevalence of warts should be put in place to ensure that the lower immune response for HPV 6 and 11 provides adequate protection in the medium and long term.

## 7 Safety of Different Vaccines

Clinical studies conducted by HPV vaccine manufacturers have shown that these vaccines have a very good safety profile. In addition, WHO considers these vaccines extremely safe (3,45). Post-vaccination adverse reactions at the injection site (e.g., pain) or systemic site (e.g., headache) may occur, but they are mostly short-term and require no medical intervention (46,47).

Since the approval of the HPV vaccine in 2006, the WHO has reviewed international safety data six times, the latest and most recent being in June 2017 (3,48).

Following the implementation of vaccination programs, cases of anaphylaxis and post-vaccination syncope were examined. The risk of anaphylaxis was characterized as approximately 1.7 cases per million doses, and syncope was recognized as a common reaction to injection, associated with vagal shock or anxiety rather than the composition of the vaccine.

Numerous studies—some carried out on millions of people—have found no association between the HPV vaccination and Guillain-Barré Syndrome (GBS) (49–57). In contrast to all the others, two ecological analyses carried out in France using the same database showed some increase in the risk of GBS among the girls having received the vaccine (58,59).

GBS has also been selected as an evaluation criterion in studies conducted in the United States using the *Vaccine Adverse Events Reporting System (VAERS)* and *Vaccine Safety Datalink (VSD)*. Data reported by VAERS following 60 million doses and by VSD after more than 2.7 million doses of vaccine showed no association between the HPV vaccine and GBS. This study and the one conducted in the United Kingdom after more than 10 million doses were administered concluded that a risk greater than 1 case per million doses could be ruled out. These data are consistent

with the results of the recent Quebec study that found no association between the HPV vaccination and GBS (57).

In July 2017, the WHO concluded: “We have now accumulated safety studies covering several million people and comparing the risks for a wide range of evaluation criteria in vaccinated and unvaccinated individuals. For all evaluation criteria, evidence from randomized controlled trials was confirmed by good-quality cohort studies, with no observed difference in rates of serious adverse events selected in individuals who had been exposed and in individuals who had not been exposed to the anti-HPV vaccine” (3).

## 8 Data on a Single-Dose HPV Vaccine Schedule

The results of Phase-3 studies (*Costa Rica HPV Vaccine Trial* conducted by the NCI, *PATRICIA Trial* conducted by GSK and *India HPV Vaccine Trial* conducted by the International Agency on Research on Cancer (IARC) (21,27) and several Phase-4 studies suggest that even a single dose of the HPV vaccine may be sufficient to provide protection against HPV-related diseases.

More specifically, in the NCI study, the efficacy of a bivalent vaccine dose against persistent infections with HPV 16 and HPV 18 was estimated at 100% (95% CI: 79–100%). In this study, no persistent infection was observed after a 4-year follow-up of 196 women who received a single dose of vaccine (22). In the PATRICIA study, after a 4-year follow-up, the efficacy of a single dose of bivalent vaccine (n = 102 women) against incident infections with HPV 16 and HPV 18 was estimated at 72% (95% CI: 14 to 92%), these results were not inferior to those observed after two and three doses, respectively of 73% (95% CI: 40–89%) and 77% (95% IC: 74–79%) (27). In the IARC study conducted in India after a 7-year follow-up in 1,558 women who received a single dose of quadrivalent vaccine, no persistent infection with HPV 16 and HPV 18 was observed. The proportion of women who had an incident infection with these two viruses was 1.4%, 0.8%, 1.5% and 0.9%, respectively after 1 dose, 2 doses spaced 6 months, 2 doses spaced 2 months and 3 doses (all 95% CI overlap). These three studies are ongoing and 10-year follow-up results are expected in the next

3-4 years. The IARC study in India provides plan for a follow-up of 15 years and the final results are expected by 2025.

Phase-4 evaluation studies to date show more heterogeneous results after a single dose of vaccine. These studies often have important methodological limitations. Noteworthy among these limitations (I) is selection bias, since women who received fewer doses of vaccine are older and initiated sexual activities at a younger age and (II) person-times are calculated differently (counted the day after the first dose or after the third dose given 6 months later), which increases the chance of detecting prevalent infections among women who received fewer doses of vaccine. Infections already present at the time of vaccination artificially decrease vaccine efficacy among individuals who received fewer doses. This latter bias is less important in the case of vaccination at an earlier age. Phase-4 studies are continuing in several countries.

At least three randomized trials with 1, 2 or 3 doses of vaccine begin in 2017–2018. An immunogenicity and efficacy study conducted by the NCI started in December 2017 in Costa Rica. This study provides for the recruitment of 20,000 girls and young women who will be vaccinated with one or two doses of Cervarix or Gardasil-9. Preliminary results of this study are expected for 2022 and the final results for 2024–2025. An immunogenicity study (DoRIS) of 1, 2 and 3 doses of Cervarix or Gardasil started in Tanzania (personal communication of Dr. Debby Watson-Jones). This study involves the recruitment of 900 girls who will be followed for three years. The results of this study are expected in 2018 (month 7 of the study), in 2020 (month 24) and in 2021 (month 36). Another immunogenicity study of 1 and 2 doses of Gardasil-9 is expected to begin in 2018 in The Gambia. This study involves the recruitment of 300 girls aged 9–15 and 150 women aged 16–26 (personal communication by Dr. Ed Clarke).

A non-randomized study with 2 doses of Gardasil-9 spaced at two years apart is underway in the United States. A total of 143 girls and 57 boys aged 9–10 were recruited. The presence of antibodies will be measured before the first dose, 6, 12, 18 and 24 months after the first dose and 6 months after the second dose (personal communication of Dr. Aimée Kreimer).

## 9 Economic considerations and impacts of vaccination already observed

In the school setting, an average of 130,000 doses of HPV vaccines are given annually in Quebec (80,000 x 80% coverage x 2 doses). This currently represents an annual expense of \$ 11,000,000. In the event of an open call for tenders to both manufacturers of HPV vaccines, it is highly likely that a mixed vaccination schedule for girls and boys will be more cost-effective than the current schedule (details were presented by the Marc Brisson's team at CIQ in December 2014).

If a mixed schedule with a dose of Gardasil-9 and a dose of Cervarix is used in Quebec, the annual cost of the program could be \$ 3,000,000 less per vaccinated birth cohort than in the current program, which involves two doses of Gardasil-9.

Note that in the HPV prevalence study conducted in Quebec in 2013–2014, the HPV types included in the quadrivalent vaccine had a very low prevalence among women aged 17–19 who had been eligible for school vaccination (0.3%) and virtually absent in women who had received at least one dose of vaccine before sexual activity began (60). In this study, as in many others previously conducted, low prevalence of HPV 31, 33 and 45 was observed in cohorts eligible for vaccination (61–64).

Although below the target, vaccine coverage of more than 70% obtained in Quebec since the program was introduced has already significantly reduced the circulation of HPV included in vaccines in age cohorts eligible for free vaccination (60,65).

Adding boys to the provincial HPV vaccination program since 2016 is expected to further decrease the circulation of virus types included in vaccines and minimize the risk of diseases related to these viruses.

## 10 Feasibility

Different vaccines are already administered at different ages in Quebec (e.g., DTaP-polio-Hib vaccine and DTaP-HBV- polio-Hib, RRO and RROV, PCV-10 and PCV-13). Using two vaccines as part of a mixed schedule may, however, cause small logistical difficulties in the field, including inventory management or vaccine and delivery errors. However, as part of the school program, given that a dose of vaccine is administered in the fall and another in the spring, the probability of a person receiving two doses of Cervarix is considered minimal. It is estimated that the feasibility of using a mixed schedule should be quite similar to that of the current immunization schedule, especially for school-based immunization. In addition, since the order of administration of Gardasil-9 and Cervarix does not appear to have any important impact on sero-conversion measured 1 month after both doses, the administration of either vaccine first should not be considered a mistake requiring additional interventions. However, as it is expected that approximately 4-5% of youth who received the first dose will not receive on schedule the second dose, it would be better to start vaccination with Gardasil-9. This approach should maximize the number of vaccinees protected against warts and cancers associated with the five types of HPV included in Gardasil-9, but not in Cervarix.

## 11 Conformity

A vaccination program with a dose of Gardasil-9 and a dose of Cervarix will not be in accordance with vaccine manufacturers' recommendations. However, studies indicate sero-conversion against each of the genotypes contained in the vaccines in virtually all subjects who have been vaccinated with one dose of each of these vaccines, regardless of the order in which they are administered. In addition, cumulative experience over the last decade indicates that two and even one dose of the HPV vaccine is effective against persistent infections, anogenital warts, and precancerous lesions. The very significant reduction in the prevalence of HPV included in vaccines in age cohorts eligible for vaccination is reassuring and indicates the presence of group immunity in addition to the direct protection of vaccinated individuals

Cross-immunity reported in several studies (6,15,27,28) and increased antibody titers against 9 HPV types in subjects receiving a dose of Cervarix following a dose of Gardasil-9 are also good reasons to believe a mixed schedule should provide protection against HPV diseases included in the Gardasil-9 vaccine.

However, at this time, no country uses a mixed schedule. In the event of the use of such a schedule, enhanced monitoring of the prevalence of HPV, anogenital warts and precancerous lesions should be implemented.

Also note that the Cervarix vaccine is not licensed for boys. However, existing data indicate that this vaccine has the same safety and immunogenicity profile in girls and boys (66). The results of the Quebec study conducted using a dose of Gardasil-9 and a dose of Cervarix are congruent with those of previous studies and show the same safety and immunogenicity profile in boys and girls aged 9-10 years.

## 12 Acceptability

Some clinicians and experts are likely to prefer the use of a higher number of doses (e.g., 3 doses instead of 2) and vaccines containing more antigens. They may be reluctant to adopt a different schedule than those who are licensed. A fairly aggressive promotion is being made by some pharmaceutical company representatives to vaccinators in their practice setting and at scientific conferences to the effect that more antigens and more doses always provide better protection. This could be cause for concern for vaccinators and affect the acceptability of a mixed vaccination schedule.

However, a mixed schedule including a dose of Gardasil-9 and a dose of Cervarix could be seen as reassuring for those recognizing that the main burden of HPV is related to HPV 16 and HPV 18, that significant cross-immunity against HPV 31, 33 and 45 is observed after Cervarix use and even a single dose of vaccine provides important protection against HPV-related diseases.

A mixed schedule allows for a stronger immune response against HPV types 16 and 18 while providing protection against the other 7 types of HPV included in the Gardasil-9 vaccine. Since HPV 6 and HPV 11 antibody titers measured 1 month after the last dose are lower



after a mixed schedule than after 2 doses of Gardasil-9, one can question the efficacy of a single dose of Gardasil-9 for the prevention of anogenital warts. The follow-up of the ongoing immunogenicity study in Quebec on the mixed schedule will make it possible to measure antibody levels in the medium term and to address this question. However, data available to date indicate that a vaccine dose containing HPV 6 and HPV 11 (Gardasil) antigens provides good protection against anogenital warts. The fact that we observe a growth in antibody titres for all types when a dose of Cervarix is administered after a dose of Gardasil or Gardasil-9 is also very reassuring.

### 13 Equity and Ethics

As a routine HPV vaccination is already in place in Grade 4 since 2008 for girls, and since 2016 for boys and girls, from an equity point of view, it would be appropriate to continue providing vaccination to subsequent cohorts. To reduce inequities the same vaccination schedule should be used for both boys and girls.

### 14 Conclusions and Recommendations

- Data from clinical and observational studies and surveillance data consistently show that HPV vaccines are safe, highly immunogenic, and provide protection against HPV-related diseases included in vaccines, as well as some cross-protection against other types of HPV.
- The two-dose HPV vaccine schedules for pre-adolescents and adolescents have become a standard practice in many countries around the world.
- Existing data suggests that even a single dose of vaccine provides good protection against HPV-related diseases. However, for the time being, the CIQ deems that the available data are not robust enough to recommend a single-dose schedule.
- Vaccination of pre-adolescents and adolescents 9 to 17 years of age against HPV should be continued using a two-dose schedule.
- The schedule making use of the Cervarix vaccine alone was not considered since it offers little or no

protection against warts. The current two-dose schedule of Gardasil-9 provides assurance that the province would not sacrifice any acquired protection against the HPV. However, the CIQ believes that a mixed schedule maximizes the type 16 and 18 HPV immune response while providing good immunity against seven other types of HPV covered by the Gardasil-9 vaccine.

- The mixed schedule is the most efficient option assuming a lower unit price for Cervarix than for that of Gardasil-9.
- In a vote, the active members of the CIQ unanimously expressed a preference for a mixed schedule for healthy youths between 9 and 17 rather than a schedule comprising Gardasil-9 alone, on the condition that the difference in price is significant.
- Whatever the MSSS decides, the epidemiological monitoring of infections and illnesses associated with HPV will need to be pursued, notably when it comes to warts. Should any modifications be made to the epidemiology of the illness, the CIQ's opinion can be reviewed and the program adapted accordingly.
- For individuals aged 18 years or older and for certain other groups (e.g., immunosuppressed), the vaccination schedule remains unchanged. The PIQ can be consulted for details about the different vaccination schedules.

### 15 Evaluation in case of use of a mixed vaccination schedule

- Continue the medium-long term follow-up of the Quebec immunogenicity study of the mixed schedule (1 dose of Gardasil-9 and 1 dose of Cervarix);
- Periodically measure the prevalence of warts in Quebec;
- Consider repeating a prevalence study of HPV types in Quebec (PIXEL 2).

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## Annexe 1 Summary of declarations of interest

### Summary of declarations of interest by the members of Comité sur l'immunisation du Québec (CIQ)

JANUARY 2018

The Institut national de santé publique du Québec (INSPQ) asked the members of the Comité sur l'immunisation du Québec (CIQ) to produce a supplementary declaration of any potential conflict of interest situations in the past three years in relation to the Advisory report on the Human Papillomavirus (HPV) Vaccination Schedule.

#### 1 No conflicting interests declared:

François Boucher, Marjolaine Brideau, Dominique Biron, Nicholas Brousseau, Ngoc Yen Giang Bui, Hélène Gagné, Rodica Gilca, Vladimir Gilca, Maryse Guay, Catherine Guimond, Patricia Hudson, Monique Landry, Richard Marchand, Céline Rousseau, Caroline Quach, Chantal Sauvageau, Bruno Turmel.

#### 2 Research grants obtained as principal investigator or co-investigator connected with private corporations whose products or activities are related to HPV vaccination:

Alex Carignan: GSK;

Gaston De Serres: GSK;

Philippe De Wals: GSK;

Marc Dionne: GSK, Merck;

Bruce Tapiéro: GSK, Merck.

#### 3 Consulting/speaking fees or travel costs (TC) received from private corporations whose products or activities are related to HPV vaccination:

Julie Bestman-Smith: Consulting/speaking fees paid to her organization: Merck, TC for conferences: Merck;

Gaston De Serres: Honorary for expert testimony: GSK;

Philippe De Wals: TC for consulting services: GSK;

Marc Lebel: Fees and TC for speaking engagement: Merck, consulting fees: GSK, TC for consulting services: GSK.







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