Population-Level Impact of the Bivalent, Quadrivalent, and Nonavalent Human Papillomavirus Vaccines: A Model–Based Analysis

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Background
Bivalent and quadrivalent human papillomavirus (HPV) vaccines are now licensed in several countries. Furthermore, clinical trials examining the efficacy of a nonavalent vaccine are underway. We aimed to compare the potential population-level effectiveness of the bivalent, quadrivalent, and candidate nonavalent HPV vaccines.

Methods
We developed an individual-based, transmission-dynamic model of HPV infection and disease in a population stratified by age, gender, sexual activity, and screening behavior. The model was calibrated to highly stratified sexual behavior, HPV epidemiology, and cervical screening data from Canada.

Results
Under base case assumptions, vaccinating 12-year-old girls (70% coverage) with the bivalent (quadrivalent) vaccine is predicted to reduce the cumulative incidence of anogenital warts (AGWs) by 0.0% (72.1%), diagnosed cervical intraepithelial neoplasia lesions 2 and 3 (CIN2 and -3) by 51.0% (46.1%), and cervical squamous cell carcinoma (SCC) by 31.9% (30.5%), over 70 years. Changing from a bivalent (quadrivalent) to a nonavalent vaccine is predicted to reduce the cumulative number of AGW episodes by an additional 66.7% (0.0%), CIN2 and -3 episodes by an additional 9.3% (12.5%), and SCC cases by an additional 4.8% (6.6%) over 70 years. Differences in predicted population-level effectiveness between the vaccines were most sensitive to duration of protection and the time horizon of analysis. The vaccines produced similar effectiveness at preventing noncervical HPV-related cancers.

Conclusions
The bivalent vaccine is expected to be slightly more effective at preventing CIN2 and -3 and SCC in the longer term, whereas the quadrivalent vaccine is expected to substantially reduce AGW cases shortly after the start of vaccination programs. Switching to a nonavalent vaccine has the potential to further reduce precancerous lesions and cervical cancer.
prevent HPV6- and HPV11–associated cervical lesions, AGWs, and, potentially, recurrent respiratory papillomatosis. On the other hand, recent results suggest that the bivalent vaccine may confer greater cross-protection against high oncological risk HPV11, -33, -45, -52, and -58 (10,12,14) and, potentially, longer duration of protection (16,17). The timing of health benefits will also be different between the HPV vaccines: substantial reductions of AGW cases have been currently observed shortly after the start of quadrivalent vaccination programs (18), whereas the potential additional gains in prevention of cervical lesions and cancer from higher bivalent cross-protection may not be observed for decades. Given their different characteristics, the decision to switch vaccines within ongoing programs can also lead to changes in the dynamics of HPV-related diseases over time. Decision makers thus require evidence on how the added cross-protection measured for the bivalent vaccine within clinical trials translates into incremental gains in HPV-related cancer prevention over time at the population level and how this compares to the added benefits of the quadrivalent vaccine at preventing AGWs.

If the nonavalent HPV vaccine proves safe and effective, policymakers will also have to decide whether or not to introduce this second-generation vaccine. Given that the current HPV vaccines have demonstrated partial efficacy against the additional HPV types included in the nonavalent vaccine (HPV31, -33, -45, -52, and -58), evidence is required on how this may impact the incremental gains of the candidate vaccine. Finally, there are concerns that adding more types to the current HPV vaccines may produce immune interference (eg, lower antibody titers to the individual types) and thus result in lower type-specific efficacy for the nonavalent vaccine. Thus, evidence is required about the level of vaccine efficacy and duration of protection necessary in order for the nonavalent to be noninferior to the current HPV vaccines in terms of cancer prevention.

Decisions regarding infectious disease control are increasingly made with substantial input from mathematical models (19). These models provide a formal framework to synthesize and project results from various sources (eg, clinical trials and epidemiological studies) to examine questions that cannot be answered in a clinical trial setting. Currently, there is little available evidence about the population-level effect of the bivalent and quadrivalent vaccines in terms of magnitude and timing of incidence reduction of HPV-related diseases. The few modeling studies that have examined this question did not incorporate type-specific cross-protection (20–23) and/or herd immunity (20,22,24,25) and did not examine the impact of switching HPV vaccines within ongoing programs on the dynamics of HPV-related diseases. Furthermore, studies have yet to examine the potential additional benefits of a candidate nonavalent vaccine, or the level of vaccine efficacy and duration of protection required for a nonavalent vaccine to be noninferior to the bivalent and quadrivalent vaccines in terms of population-level effectiveness.

The goal of this paper is to use mathematical modeling to 1) compare the population-level effectiveness of current HPV vaccine strategies at preventing HPV-related diseases over time, including recent evidence on type-specific cross-protective efficacy and herd-immunity, 2) assess the potential impact of switching HPV vaccines within current vaccination programs, and 3) examine the potential incremental gains of using a nonavalent vaccine.

**Methods**

**Model Structure**

We developed Agent-based Dynamic model for Vaccination and Screening Evaluation (HPV-ADVISE), the first calibrated, individual-based, transmission-dynamic model of sequential partnership formation and dissolution and natural history of multitype HPV infection and disease (26). An individual-based modeling approach was chosen to be able to represent the various levels of heterogeneity across the HPV-related disease control spectrum: sexual behavior, health-seeking behavior (vaccination and screening), and type-specific HPV transmission, infection, progression toward disease, and vaccine efficacy. The model contains five fully integrated components: 1) sociodemographic characteristics, 2) sexual behavior and HPV transmission, 3) natural history of HPV-related diseases, 4) vaccination, and 5) screening and treatment. An in-depth description of the model structure, model parameterization, calibration data, and parameter values and figures of model fit are available on the author’s website (http://www.marc-brisson.net/HPVadvise.pdf).

**Sociodemographic Characteristics.** Individuals enter the simulated Canadian population prior to sexual debut. The modeled population is heterosexual, open, and stable (ie, age-specific death rates balance the birth rate). In the model, individuals are attributed three different risk factors for HPV infection and/or disease: gender, four levels of sexual activity, and five screening behavior levels.

**Sexual Behavior and HPV Transmission.** The sexual behavior and transmission component is described in detail in Van de Velde et al (26). HPV transmission is assumed to depend on sexual behavior (level of sexual activity and mixing patterns), per sex-act probability of transmission, and natural history of infection (duration of infectiousness and natural immunity). Partnership formation and dissolution are based on gender-specific, age-specific, and level of sexual activity–specific partner acquisition and separation rates and mixing patterns. Eighteen HPV types are modeled individually: HPV16, -18, -6, -11, -31, -33, -45, -52, -58, -35, -39, -51, -56, -59, -66, -68, -73, and -82. These types are assumed to be independent (no synergy or competition) with respect to transmission, infection, persistence, and disease progression; thus, any combination of multiple infections is possible. Following clearance, individuals may develop same-type natural immunity (ie, same-type reinfection is possible).

**HPV-Related Diseases.** HPV-ADVISE was developed to capture the potential impact of HPV vaccination on AGWs, cervical cancer (squamous cell carcinoma [SCC] and adenocarcinoma), and other HPV-related cancers (vulva, vagina, anus, and head and neck): Anogenital warts. Once infected with HPV6 or -11, individuals have a joint probability of developing and being diagnosed with AGWs or clearing their infection. Individuals can experience multiple episodes of AGWs through recurrence of a persistent infection, reinfection with a previously cleared HPV type, or infection.
with a new HPV type. We assume that HPV6 and -11 are responsible for 85% of all AGW cases (3).

Squamous cell carcinoma. The natural history of SCC is represented by nine mutually exclusive health states: three HPV infection states (susceptible, infected, and immune), three grades of CIN lesions (CIN1, -2, and -3), and three stages of cancer (localized [I], regional [II], and distant stages [III]) (27). Transition rates between these states are type-specific.

Other HPV-related cancers. Similar to Smith et al (28), we estimate the long-term impact of HPV vaccination on HPV-related cancers by applying model predictions of the relative reductions in type-specific HPV prevalence at equilibrium to the HPV-type distribution among cervical adenocarcinomas and cancers of the vulva, vagina, anus, and head and neck in North America (7–9).

Vaccination. HPV-ADVISE assumes that HPV vaccines prevent infection but do not alter the natural history of disease in individuals already infected by a vaccine type. Different vaccine efficacy can be applied to any of the 18 HPV types included in the model to examine the potential impact of cross-protection or the nonvalent vaccine. Type-specific cross-protective vaccine efficacy values were based on a comprehensive review of published clinical trials results (10,12–14,29), including recently published results from Wheeler et al (30). In our base case, vaccine efficacy against HPV vaccine types is 100% (10,11,31), vaccine efficacies against non-vaccine HPV types are the published type-specific efficacy against persistent infection among HPV-naive females (Table 1), and vaccine protection (including cross-protection) is lifelong. Sensitivity analysis was performed to explore the impact of vaccine efficacy and duration on model predictions. In scenarios with limited vaccine duration, each vaccinated individual is given a specific duration of protection against the vaccine types sampled from a normal distribution (µ = 20 years; σ = 6). Hence, under this scenario, 3%, 20%, and 50% of individuals will have lost their protection 9, 15, and 20 years after vaccination, respectively. These assumptions reflect available clinical data showing no evidence of waning after 9.5 years of follow-up (32) and evidence of immune memory 8.5 years following vaccination (33).

Screening and Treatment. HPV-ADVISE mimics various screening algorithms at the individual level by tracking and simulating each woman's screening history. In this study, the model represents cervical cancer screening in Canada, which is cytology-based. Screening rates are a function of a woman's screening behavior level, previous screening test results, and age. The model incorporates five screening behavior levels, which represents the average time between two routine Papanicolaou tests in the absence of an abnormal result (from screening every 1.25 years [level 0] to never [level 4]). Screening behavior parameters were estimated using Canadian-specific, population-based data (34,35). Algorithms for the management and treatment of women with an abnormal cytology (eg, repeat cytology, colposcopy or biopsy, treatment) are dependent on the test result (ASC-US/LSIL, HSIL/ASC-H/SCC (Atypical Cells of Undetermined Significance [ASC-US], Low-grade Squamous Intraepithelial Lesion [LSIL], High-grade Squamous Intraepithelial Lesion [HSIL], Atypical Squamous Cells, cannot rule out a High grade lesion [ASC-H], and SCC) and were based on Canadian guidelines (36–38) and validated using empirical data (35). The sensitivity and specificity of cytology and colposcopy are lesion-specific and were estimated from two systematic reviews on the performance of cervical cancer screening cytology (39,40) and a review of papers assessing the success of colposcopy at diagnosing cervical lesions (41–44). Finally, women with SCC have a stage-specific probability of developing symptoms and being diagnosed outside of routine screening.

Model Calibration

Individual-based models require a considerable amount of calibration data in order to provide robust and valid predictions (parameters for which values were derived through calibration are presented in Supplementary Table 1, available online). The calibration procedure developed in prior publications (26,45) was used to identify multiple

Table 1. Vaccine efficacy (VE) against nonvaccine human papillomavirus (HPV) types in HPV-naive females

<table>
<thead>
<tr>
<th>HPV type</th>
<th>VE persistent cervical infection, %</th>
<th>VE CIN2+* (including lesions co-infected with HPV16 and/or -18), %</th>
<th>VE CIN2+ (excluding lesions co-infected with HPV16 and/or -18), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bivalent</td>
<td>Quadrivalent</td>
<td>Bivalent</td>
</tr>
<tr>
<td>31</td>
<td>77.1 (14)</td>
<td>46.2 (12)</td>
<td>89.4 (14)</td>
</tr>
<tr>
<td>33</td>
<td>43.1 (14)</td>
<td>28.7 (12)</td>
<td>82.3 (14)</td>
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<tr>
<td>45</td>
<td>79.0 (14)</td>
<td>78.1 (12)</td>
<td>100.0 (14)</td>
</tr>
<tr>
<td>52</td>
<td>8.3 (73)†</td>
<td>18.4 (12)</td>
<td>27.6 (73)†</td>
</tr>
<tr>
<td>58</td>
<td>0.0 (73)†</td>
<td>5.5 (12)</td>
<td>28.5 (73)†</td>
</tr>
<tr>
<td>Other high oncogenic risk types¶</td>
<td>0.0#</td>
<td>0.0#</td>
<td>0.0#</td>
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</tbody>
</table>

* CIN = cervical intraepithelial neoplasia.
† Data from end of study according-to-protocol cohort for efficacy cohort, not naive cohort.
‡ We used 0 in the model for negative VE estimates.
§ There were zero cases in the control group.
¶ Assumed to be 0%. VE against CIN2+ excluding co-infected lesions with HPV16 and/or -18 were not published in the literature at the time of simulation.
¶ Other high oncogenic risk types: HPV35, -39, -51, -56, -59, -66, -68, -73, -82.
# Assumed to be 0%.
parameter sets that fit highly stratified Canadian sexual behavior, natural history, and screening data from the literature, population-based datasets, and original studies (see Table 2, available online) and to account for conjoint parameter uncertainty. The procedure is as follows:

1. Plausible prior distributions are defined for each of the 87 calibrated model parameters (minimum and maximum values for each parameter are derived from the literature).
2. Different combinations of parameter values are drawn from the prior distributions using Latin hypercube sampling [an efficient sampling method of parameter space (56–58)].
3. Parameter sets are qualified as producing a “good fit” and included in the posterior parameter sets if the associated model predictions fall simultaneously within all prespecified targets (ranges) of the observed data.

Such a procedure is computer and data intensive. Of 285000 different combinations of parameters sampled (1850000 runs and $2 \times 10^{13}$ person-years simulated) from the prior parameter distributions, 10 parameter sets produced model results within the 639 prespecified data targets.

**Model Outcomes**

Population-level vaccine effectiveness predictions are presented for three primary outcomes: AGWs in males and females, diagnosed CIN2 and -3, and SCC. Outcomes were modeled over 70 years post-vaccination because 1) it is the time horizon required to reach a stable post-vaccination equilibrium, 2) it allows the illustration of the pre-equilibrium incidence dynamics, and 3) it shows the maximum differences in effectiveness between the different vaccines.

**Statistical Analyses**

Variability of model predictions is presented as the median, 10th, and 90th percentiles of results from the posterior parameter sets, referred to as the 80% range (80% R). Univariate sensitivity analysis was performed by varying vaccination coverage, vaccine-type efficacy, cross-protective efficacy, and duration of vaccine protection.

**Results**

**Population-Level Effectiveness of the Bivalent and Quadrivalent Vaccines**

Figure 1 compares the population-level impact of vaccinating 12-year-old girls with the bivalent and quadrivalent vaccines, taking into account cross-protection and assuming 70% coverage. The model predicts that quadrivalent vaccine programs will lead to a rapid decrease in the incidence of AGWs (eg, median = 10 years [80% R = 9–11] to reach a 50% reduction in incidence) and that at equilibrium (after 70 years) AGW cases will be reduced by 84.4% (80% R = 77.7–85.0) (Figure 1, A). Overall the quadrivalent vaccine is estimated to reduce the cumulative incidence of AGWs by 72.1% over 70 years. In countries where the bivalent vaccine is used, the

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**Figure 1.** Estimated population-level impact of vaccinating 12-year-old girls with the bivalent and quadrivalent vaccines. Estimated percentage change following vaccination in the incidence of anogenital warts (AGWs) in males and females (A), diagnosed cervical intraepithelial neoplasia 2 and 3 (CIN2 and -3) (B), and squamous cell carcinoma (SCC) (C). Reduction in incidence of CIN2 and -3 and SCC in females over the first 70 years of a girls-only vaccination program (D). Base case: vaccine coverage = 70%, vaccine duration = lifetime, vaccine-type efficacy = 100%, cross-protective vaccine efficacy presented in Table 1. Average pre-vaccination incidence rate of AGWs in women = 124 per 100000 women-years, AGWs in men = 157 per 100000 men-years, diagnosed CIN2 and -3 = 91 per 100000 women-years, and SCC = 6 per 100000 women-years. Population of 25x170000 individuals. Incidence of SCC is presented using a 3-year moving average.
incidence of AGWs will remain unaltered by vaccination (ie, 0.0% reduction in AGW cases).

The bivalent and quadrivalent vaccines are predicted to produce very similar short-term declines in cervical lesions and cancer incidence (Figure 1, B and C). However, the bivalent vaccine is estimated to produce larger reductions in the long-term. Under base case assumptions (70% coverage, girls-only vaccination), the model predicts that it would take the bivalent and quadrivalent vaccine programs 19 (80% R = 17–23) and 20 (80% R = 19–27) years, respectively, to decrease the incidence of diagnosed CIN2 and -3 by 50% (Figure 1, B), and 40 (80% R = 37–46) and 42 (80% R = 36–49) years, respectively, to decrease the incidence of SCC cases by 50% (Figure 1, C). Furthermore, the bivalent and quadrivalent vaccine programs are estimated to reduce the incidence of diagnosed CIN2 and -3 by 62.1% (80% R = 57.0–71.5) and 58.6% (80% R = 52.3–67.5), respectively, at equilibrium (Figure 1, R), and to reduce the incidence of SCC cases by 70.5% (80% R = 59.9–75.0) and 64.8% (80% R = 51.6–73.2), respectively (Figure 1, C). Overall, the bivalent and quadrivalent vaccines are estimated to reduce the cumulative number of diagnosed CIN2 and -3 by 51.0% (80% R = 44.3–54.8) and 46.1% (80% R = 40.2–51.2), respectively, over 70 years after vaccination and to reduce the cumulative number of SCC cases by 31.9% (80% R = 26.0–38.3) and 30.5% (80% R = 24.5–38.2), respectively (Figure 1, D). These differences in population-level vaccine effectiveness are due to the predicted greater cross-protective efficacy of the bivalent vaccine. For example, cross-protection produces a cumulative reduction of 7.8% and 4.8% in CIN2 and -3 and 4.8% and 3.0% in SCC incidence over 70 years for the bivalent and quadrivalent vaccines, respectively (Figure 1, D).

Switching Vaccine Within Ongoing Vaccination Programs

Figure 2 shows the population-level impact of switching HPV vaccines 5 years into a girls-only vaccination program. Under base case vaccine assumptions (age at vaccination = 12 years; coverage = 70%), switching from a quadrivalent to a bivalent vaccine is estimated to prevent an additional 3.2% diagnosed CIN2 and -3 cases and 1.8% SCC cases over 70 years compared with continuing with the quadrivalent vaccine, but switching increases the cumulative number of AGW cases by 62.7% (Table 2). The increase (rebound) in AGW cases would occur about 5 years after changing to a bivalent vaccine, whereas the gains in CIN2 and -3 and SCC prevention would start accumulating after 15 and 45 years, respectively (Figure 2). Conversely, under the above vaccination assumptions, changing from a bivalent to a quadrivalent vaccine is predicted to increase the number of diagnosed CIN2 and -3 and SCC cases by an additional 3.0% and 1.3% over 70 years, respectively, but to reduce AGW cases by 66.7% (Table 2). Finally, our model predicts that if the nonavalent vaccine proves to be highly effective, switching from a bivalent or quadrivalent vaccine program could yield substantial incremental benefits (Figure 2 and Table 2). Indeed, under base assumptions, changing from a bivalent (quadrivalent) to a nonavalent vaccine is predicted to reduce the cumulative number of AGW cases, diagnosed CIN2 and -3 cases, and SCC cases over 70 years by an additional 66.7% (0.0%), 9.3% (12.5%), and 4.8% (6.6%), respectively (Table 2).

Sensitivity Analysis

Differences in the population-level effectiveness of the bivalent, quadrivalent, and nonavalent vaccines are dependent on vaccination coverage, vaccine efficacy, duration of protection, and the HPV outcome examined (Figure 3).
<table>
<thead>
<tr>
<th></th>
<th>0–30 y Cumulative incidence (80% range)</th>
<th>0–50 y Cumulative incidence (80% range)</th>
<th>0–70 y Cumulative incidence (80% range)</th>
<th>Diagnosed CIN2 or -3*</th>
<th>0–30 y Cumulative incidence (80% range)</th>
<th>0–50 y Cumulative incidence (80% range)</th>
<th>0–70 y Cumulative incidence (80% range)</th>
<th>Squamous cell carcinoma</th>
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<td>Diagnosed CIN2 or -3*</td>
<td>Squamous cell carcinoma</td>
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<td>Bivalent</td>
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<tr>
<td>to quadrivalent†</td>
<td>−44.3</td>
<td>−59.9</td>
<td>−66.7</td>
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<td>0.0</td>
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<td>(−1.4 to 2.0)</td>
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<tr>
<td>to nonavalent‡</td>
<td>−44.0</td>
<td>−59.9</td>
<td>−66.7</td>
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<td>(−44.7 to −40.7)</td>
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<td>(−67.6 to −62.2)</td>
<td>(−6.5 to −3.7)</td>
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<td>(−5.5 to −2.1)</td>
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<tr>
<td>Quadrivalent</td>
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<tr>
<td>to bivalent§</td>
<td>41.5</td>
<td>55.4</td>
<td>62.7</td>
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<td>−1.1</td>
<td>−1.5</td>
<td>−1.8</td>
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<td>(59.3 to 66.4)</td>
<td>(−3.1 to −1.3)</td>
<td>(−4.5 to 1.3)</td>
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<tr>
<td>to nonavalent</td>
<td></td>
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<td>(−4.9 to 1.1)</td>
<td>(−5.0 to −1.1)</td>
<td>(−8.2 to −4.3)</td>
<td></td>
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</table>

* CIN = cervical intraepithelial neoplasia.
† Girls are vaccinated using the bivalent vaccine in years 0–4 and the quadrivalent thereafter (years >5).
‡ Girls are vaccinated using the bivalent vaccine in years 0–4 and the nonavalent thereafter (years >5).
§ Girls are vaccinated using the quadrivalent vaccine in years 0–4 and the bivalent thereafter (years >5).
|| Girls are vaccinated using the quadrivalent vaccine in years 0–4 and the nonavalent thereafter (years >5).
¶ Vaccine efficacy (VE) against HPV6 and -11 is assumed to be equal for quadrivalent and nonavalent (VE = 100%).
Increasing coverage not only improves the predicted population-level effectiveness of girls-only vaccination but also amplifies the absolute and relative differences between the bivalent, quadrivalent, and nonavalent vaccines (Figure 3, A and B). Using published type-specific efficacy against CIN2+, which has greater cross-protection than persistent infection, also increases differences between the bivalent and quadrivalent vaccines in terms of CIN2 and -3, but not SCC, prevention (Figure 3, C and D). This is because a higher proportion of CIN2 and -3 cases than SCC cases are caused by HPV31, -33, -45, -52, and -58 (cross-protective types). On the other hand, our model predicts that the bivalent and quadrivalent vaccines produce similar population-level effectiveness against CIN2 and -3 and SCC when duration of cross-protection is 10 years (Figure 3, C and D). Finally, reducing
vaccine-type efficacy from 100% to 95% has little impact on predictions (Figure 3, C and D).

Assumptions regarding duration of protection against vaccine types (HPV16 and -18) have a greater impact on differences in predicted population-level impact between the current vaccines than does cross-protection. For example, if the bivalent vaccine confers lifelong protection and the quadrivalent vaccine efficacy lasts for only 20 years (10 years for cross-protective types), our model predicts that the bivalent would prevent an additional 27% diagnosed CIN2 and -3 cases and 18% SCC cases at equilibrium (assuming 70% coverage; Figure 3, C and D).

Because there is no published information about the nonavalent vaccine’s efficacy, we examined which characteristics are required in order for the candidate vaccine to be more effective at the population-level than the existing vaccines. Our model suggests that the vaccine-type efficacy of the nonavalent vaccine must be greater than 80%–85% to produce higher population-level effectiveness against SCC than the bivalent and quadrivalent vaccines (assuming 100% vaccine-type efficacy, cross-protection, and lifelong protection for the first-generation vaccines and lifelong protection for the nonavalent [Figure 3, E and F]). Our model also predicts that a nonavalent vaccine with an average 30 years of vaccine-type protection would produce greater population-level effectiveness against CIN2 and -3 and SCC than bivalent and quadrivalent vaccines with lifelong vaccine protection (Figure 3, E and F).

Finally, the bivalent, quadrivalent, and nonavalent vaccines are predicted to substantially reduce adenocarcinoma and other HPV-related cancers (Figure 4). On the other hand, given that HPV16 and -18 (primarily HPV16) are present in more than 90% of vaginal, anal, and head and neck cancers attributed to HPV (7–9), there is little difference between HPV vaccines in terms of population-level effectiveness against these cancers (ie, differences in vaccine efficacy against HPV31, -33, -45, -52, and -58 have little impact on these cancers).

Discussion

Our modeling analysis indicates that differences between the bivalent and quadrivalent vaccines in preventing cervical and other HPV-related cancers will be relatively small and would only be observable decades after the start of vaccination programs. On the other hand, the quadrivalent vaccine is expected to substantially reduce AGW cases within the first decade of a girls-only vaccination program. Furthermore, even though the bivalent and quadrivalent vaccines are expected to substantially reduce HPV-related diseases, switching to a nonavalent vaccine (if proven efficacious) could produce substantial incremental gains in reduction of diagnosed lesions and cervical cancer but only marginal benefits in the prevention of other HPV-related diseases.

Our results have important implications for clinicians and policymakers. They provide evidence of the comparative population-level benefits of the bivalent and quadrivalent vaccines in the short- to long-term. To put our results into perspective, in Canada (30 million individuals; approximately one-tenth of the US population), a quadrivalent vaccination program of 12-year-old girls with 70% coverage is predicted to prevent 1.9 million diagnosed AGW cases in men and women, 560100 diagnosed CIN2 and -3 cases, and 20800 SCC cases over 70 years. Switching from the quadrivalent to the bivalent vaccine would produce a rebound in diagnosed AGW cases (increase cases by 1.8 million) but would prevent an additional 42600 diagnosed CIN2 and -3 cases and 1400 SCC cases over the same period. Given the long time-lag between the age at vaccination and disease, the full benefit in prevention of CIN2 and -3 and cervical cancer by switching from a quadrivalent to a bivalent vaccine is not expected for 20–40 years after the start of the vaccination programs. It should be pointed out that these predictions assumed lifelong vaccine protection (vaccine and cross-protective types). If the duration of cross-protection is shorter (eg, 10 years) for both vaccines, then the bivalent and quadrivalent vaccines are predicted to produce very similar vaccine effectiveness against HPV-related cancers. On the other hand, important incremental benefits are predicted if the bivalent vaccine confers substantially greater duration of protection than the quadrivalent vaccine. Clearly, an important priority for future research is to better understand whether the higher immunogenicity measured for the bivalent vs the quadrivalent vaccine has implications on long-term vaccine protection (16,17).

The relatively small incremental benefit of the bivalent vaccine over the quadrivalent vaccine, when duration of protection is similar, can be explained by the fact that more than 70%–80% of cervical cancers (6) and 90% of other HPV-related cancers are due to HPV16 and -18 (7–9) (HPV16 mostly for noncervical sites), against which both vaccines are highly efficacious. Furthermore,
the additional type-specific vaccine efficacy provided by the bivalent vs the quadrivalent vaccine is mainly limited to HPV31, -33, and -45 (Table 1).

If the nonavalent HPV vaccine proves to be safe and effective, policy makers will have to decide whether or not to introduce the second-generation vaccine. In Canada, changing from a quadrivalent to a nonavalent vaccine is predicted to prevent an additional 171,200 diagnosed CIN2 and -3 cases and 4,700 SCC cases over 70 years assuming 100% vaccine efficacy, 70% coverage, and vaccination of 12-year-old girls. The success of this second-generation vaccine will depend on whether high HPV16 and -18 vaccine efficacy will be achieved and maintained, and the level and duration of cross-protection produced by the current HPV vaccines. Our model predicts that vaccine efficacy against the vaccine types would have to be greater than 80%–85% and duration of protection longer than 30 years for the nonavalent vaccine to produce incremental gains compared with a perfect bivalent or quadrivalent vaccine (100% vaccine efficacy and lifelong protection). Given the importance of protecting against HPV16 and -18 infection and disease, it is unlikely that the nonavalent would be used if its efficacy against these types is shown to be lower than the current HPV vaccines. However, a point of uncertainty that will likely remain when decisions are made regarding the nonavalent vaccine will be its relative duration compared with the current vaccines.

The study has several methodological strengths. We developed HPV-ADVISE, the first HPV microsimulation model that fully integrates the various levels of heterogeneity across the HPV-related disease control spectrum—sexual behavior, health-seeking behavior (vaccination and screening), type-specific natural history of infection and disease, and vaccine efficacy. Second, the model was calibrated to highly stratified data on sexual behavior, natural history, and cervical cancer screening to identify multiple good-fitting parameter sets. Using multiple parameter sets is important to 1) capture uncertainty in key parameters because type-specific and age-specific empirical data on the natural history of HPV infection and disease are incomplete (26,45,59,60) and 2) increase the robustness of predictions to changes in our understanding of the biology and epidemiology of HPV (eg, natural immunity) (61). Finally, the impact of vaccination was estimated by modeling HPV types individually using the most recent type-specific estimates of vaccine cross-protection (10,12–14,29). Previous modeling studies that have examined the impact of cross-protection have grouped multiple non-HPV16 and -18 types and used combined estimates of vaccine efficacy from clinical trials (eg, efficacy against HPV31, -33, -45, -52, and -58 infection or CIN2+ lesions). It has been shown that grouping multiple types should be avoided when modeling HPV vaccine effectiveness because it produces a fictional “super bug,” which can lead to biased predictions (26). Using vaccine efficacy against grouped HPV types can also lead to biased results (29). This is because grouped vaccine efficacy is dependent on the efficacy against each individual type and the relative distribution of these types in the clinical trial population may differ from the distribution in the population that is modeled.

Our study has limitations. First, estimates of type-specific efficacies against nonvaccine HPV types for both vaccines were derived from clinical trials with different populations and designs (10,12,14), which could partly explain the differences in cross-protection estimates between the vaccines. However, we performed a systematic literature review to select similar vaccine efficacy outcomes extracted from the most comparable populations (ie, HPV-naive females) (29). Second, similarly to other studies (23,28), the natural history of noncervical HPV-related cancers was not modeled explicitly. Instead, model predictions of the reduction in type-specific HPV prevalence at equilibrium were imputed to the distribution of these types within the different HPV-related cancers. Because HPV16 and -18 are the cause of most noncervical HPV-related cancers, including more complex natural histories is unlikely to influence our conclusion that the effectiveness against other HPV-related cancers will be very similar between the HPV vaccines (assuming equal vaccine-type efficacy and duration). Third, similar to the majority of HPV vaccination modeling studies (21,62–64), only heterosexual transmission was included. Given that the probability of transmission and prevalence of HPV is very high and that the population of men who have sex with men is estimated to be small [3%–5% (34)], men who have sex with men are unlikely to influence overall HPV transmission at the population-level. Therefore, including men who have sex with men in our model is expected to have little impact on our predictions of the relative impact of girls-only bivalent, quadrivalent, and candidate nonavalent vaccination programs. Fourth, similarly to all other dynamic models of HPV vaccination in industrialized countries, we did not model HIV as a potential modifying factor of HPV natural history or vaccine efficacy because HIV prevalence is too low (65) to influence the population-level effectiveness of girls-only HPV vaccination. Finally, similar to the other HPV dynamic modeling studies (21,62–64), we assume that sexual behavior remains constant over time. Population-level data from North America suggest that age at sexual debut, having multiple partners, and condom use have remained relatively stable in the past 15–20 years (73–75). However, even if sexual behavior changes in the next decades, this is unlikely to impact our model conclusions given that our main outcomes are comparisons in relative population-level effectiveness across HPV vaccines (rather than absolute differences). To considerably modify the relative effectiveness between the HPV vaccines, changes in sexual activity would have to differentially impact acquisition of the different HPV types (eg, HPV16 and -18 versus HPV31, -33, -45, -52, and -58) and thus substantially influence the distribution of types among cervical lesions, which is unlikely. However, if sexual activity changes substantially, absolute differences in population-level effectiveness for vaccination versus no vaccination would increase or decrease in parallel and could also affect the relative impact of the different HPV vaccines.

Although HPV-ADVISE was calibrated to Canadian data, our main conclusions are relevant to other developed countries given similarities in sexual behavior (34,66), HPV type distribution (15,67,68), age profile of HPV prevalence (69), and cervical cancer incidence and mortality rates between industrialized countries (70). However, our results must be extrapolated to resource-poor settings with caution due to differences in sexual behavior (34,66), HPV epidemiology (69,70) and potential cofactors of HPV infection and disease, such as high HIV prevalence (71).

This is the first modeling paper to provide evidence on 1) the potential comparative population-level effectiveness of the bivalent and quadrivalent HPV vaccines, taking into account the most...
recent type-specific cross-protective efficacy estimates and herd immunity, 2) the impact of switching HPV vaccines within ongoing programs, and 3) the potential additional benefits of a candidate nonavalent vaccine. Population-level effectiveness is only one of several important criteria in decisions regarding vaccination (72). Although outside the scope of this study, future research should aim at examining the cost-effectiveness of the bivalent and quadrivalent vaccines and the price differential in order for both vaccines to be deemed equally cost effective. Although previous models suggest that the bivalent vaccine needs to be cheaper than the quadrivalent vaccine to produce equal cost-effectiveness results, these studies did not incorporate either type-specific cross-protection or herd immunity (20–23,25). Future research should also focus on identifying which outcome (persistent infection, CIN2+ including or excluding coinfected lesions with HPV16 and/or -18) is the most important, estimating the duration of vaccine protection.

In summary, our model shows that HPV vaccines can substantially reduce HPV-related diseases. Based on the higher cross-protective efficacy reported in the current clinical trials, the bivalent vaccine is expected to be slightly more effective at preventing diagnosed cervical precancerous lesions and cervical cancer in the longer term, whereas the quadrivalent vaccine will substantially reduce AGW cases. Finally, the candidate nonavalent vaccine has the potential to produce substantial incremental benefits.

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the model. E. Franco, E. Kliewer, F. Coutlée, and M.-H. Mayrand provided the data necessary for model calibration and validation and provided comments on the model structure. N. Van de Velde, M. Brisson, M. Drolet, T. Malagón, and J.-F. Laprise performed the analysis. N. Van de Velde, M. Brisson, and M. Drolet drafted the manuscript. All authors contributed to the interpretation of results, critically revised the manuscript for important intellectual content, and approved the final version submitted for publication. The funders had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

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