The Early Benefits of Human Papillomavirus Vaccination on Cervical Dysplasia and Anogenital Warts

Leah M. Smith, MSc, Erin C. Strumpf, PhD, Jay S. Kaufman, PhD, Aisha Lofters, MD, PhD, Michael Schwandt, MD, MPH, Linda E. Lévesque, BScPhm, PhD

**abstract**

**BACKGROUND:** Despite widespread promotion of quadrivalent human papillomavirus (qHPV) vaccination for young girls, there is limited information on the vaccine’s real-world effectiveness and none on the effectiveness of qHPV vaccination programs. We assessed the impact of the qHPV vaccine and Ontario’s grade 8 qHPV vaccination program on cervical dysplasia and anogenital warts (AGW).

**METHODS:** By using administrative health databases of Ontario, Canada, we identified a population-based retrospective cohort of girls in grade 8 before (2005/2006–2006/2007) and after (2007/2008–2008/2009) program implementation. Vaccine exposure was ascertained in grades 8 to 9 and outcomes in grades 10 to 12. A quasi-experimental approach known as regression discontinuity was used to estimate absolute risk differences (RDs), relative risks (RRs), and 95% confidence intervals (CIs) attributable to vaccination and program eligibility (intention-to-treat analysis).

**RESULTS:** The cohort comprised 131,781 ineligible and 128,712 eligible girls (n = 260,493). We identified 2,436 cases of dysplasia and 400 cases of AGW. Vaccination significantly reduced the incidence of dysplasia by 5.70 per 1000 girls (95% CI -9.91 to -1.50), corresponding to a relative reduction of 44% (RR 0.56; 95% CI 0.36 to 0.87). Program eligibility also had a significant protective effect on dysplasia: RD -2.32/1000 (95% CI -4.02 to -0.61); RR 0.79 (95% CI 0.66 to 0.94). Results suggested decreases in AGW attributable to vaccination (RD -0.83/1000, 95% CI -2.54 to 0.88; RR 0.57, 95% CI 0.20 to 1.58) and program eligibility (RD -0.34/1000, 95% CI -1.03 to 0.36; RR 0.81, 95% CI 0.52 to 1.25).

**CONCLUSIONS:** This study provides strong evidence of the early benefits of qHPV vaccination among girls aged 14 to 17 years, offering additional justification for not delaying vaccination.

WHAT’S KNOWN ON THIS TOPIC: Clinical trials of the quadrivalent human papillomavirus vaccine show it to be highly efficacious in preventing vaccine-type–specific cervical dysplasia and anogenital warts, but few studies have assessed its effects in the real world and none have done so at the program/population level.

WHAT THIS STUDY ADDS: This study provides strong evidence of the early benefits of quadrivalent human papillomavirus vaccination on reductions in cervical dysplasia and possible reductions in anogenital warts among girls aged 14 to 17 years, offering additional justification for not delaying vaccination until girls are older.
The human papillomavirus (HPV) is a sexually transmitted infection that affects most individuals at some point during their lives. Although the vast majority of these infections self-resolve without clinical sequelae, others can lead to important health consequences, including anogenital warts (AGW) and cancers of the cervix, anus, and penis. In 2006, Canada was among the first countries to license Gardasil (Merck, Whitehouse Station, NJ), a quadrivalent human papillomavirus (qHPV) vaccine that protects against 4 types of HPV that cause 70% of cases of cervical cancer and at least 90% of AGWs. As randomized controlled trials of the vaccine showed it to be highly efficacious in preventing vaccine-type-specific precancerous cervical lesions and AGW, the vaccine received a great deal of attention from the scientific and medical communities, as well as from the general public. Currently, the qHPV vaccine is available in >100 countries, many of which also have national qHPV immunization programs. These programs are generally aimed at immunizing young girls before the onset of sexual activity when the possibility of previous HPV infection is low (eg, ages 9–13 years). Despite widespread promotion of the vaccine and the popularity of large-scale qHPV vaccination programs, levels of vaccine uptake have been lower than expected in a number of jurisdictions. In part, low qHPV vaccine acceptance has been attributed to parental concerns about the effects of the vaccine, especially in the young age group targeted for vaccination. In addition, some parents are deciding to delay vaccination for their daughters until a later age, as they perceive their daughter’s likelihood of sexual activity as low. Given the tendency of parents to underestimate their child’s sexual experience, there are important concerns that delaying vaccination might result in missed opportunities for prevention. In addition, low vaccine coverage may jeopardize the expected public health benefits and cost-effectiveness of qHPV vaccine programs. As there are currently few studies on the real-world effects of the qHPV vaccine and none on the population-level impact of qHPV vaccine programs on the burden of disease, we undertook a population-based, retrospective cohort study to assess the impact of the qHPV vaccine and Ontario’s qHPV vaccination program on the incidence of cervical dysplasia and AGW among adolescent girls.

**METHODS**

This study was approved by the Research Ethics Boards of Queen’s University, McGill University, and Sunnybrook Health Sciences Centre.

**Study Setting**

Our study is based in Ontario, Canada’s most populous province, which began offering all 3 doses of the vaccine, free-of-charge, to all grade 8 girls in September of 2007. Doses are administered primarily through school-based immunization clinics, but girls also may receive the vaccine from a physician or at their health unit at no cost. Before September 2012, eligible girls had until the end of their grade 8 year to initiate the vaccine series and until the end of grade 9 to complete it. During our study period, girls who were not eligible for the school-based program (eg, in grade 8 before 2007) could obtain the vaccine series for $400.

**Data Sources**

Data for this study were obtained from Ontario’s population-based administrative health and immunization databases, which are housed at the Institute for Clinical Evaluative Sciences. We used (1) the Registered Persons Database (RPDB) for sociodemographics, (2) the Ontario Health Insurance Plan (OHIP) database for fee-for-service claims by physicians, (3) the Discharge Abstract Database for hospitalizations, (4) the Same-Day Surgery database for same-day surgeries, (5) the National Ambulatory Care Reporting System (NACRS) for emergency department visits, and (6) the Immunization Records Information System (IRIS) for vaccinations. In these databases, residents are represented by a unique, encrypted identifier, enabling anonymized, individual-level record linkage across databases and time. These databases are generated by Ontario’s universal health insurance programs and have been used extensively in health research, including in the postmarketing evaluation of drug and vaccine effects.
Measurement and Analysis

Approach

Observational studies of vaccine effects are notoriously vulnerable to confounding bias because individuals who opt for vaccination tend to have different health histories and behaviors than those who do not, and these characteristics are difficult to identify and quantify.\textsuperscript{31–34} To address this methodological challenge, we used the regression discontinuity design (RDD), a quasi-experimental approach for evaluating the causal effects of interventions in a way that accounts for this type of observed and unobserved confounding, thus facilitating reliable causal inference.\textsuperscript{35–37} The RDD has been used extensively in fields like health economics,\textsuperscript{37–39} and is becoming increasingly popular in epidemiology, given the advantages it offers over standard regression adjustment.\textsuperscript{40,41}

In this study, the RDD enabled us to exploit the fact that girls were eligible for free qHPV vaccination (ie, assigned to treatment) based on whether they were in grade 8 before or after the September 2007 program implementation date (ie, born December 31, 1993 or earlier versus January 1, 1994 or later), which induced discontinuity in the probability of qHPV vaccination at the eligibility cutoff (Supplemental Appendix 1A). As such, birth date acted as the forcing variable ("forcing variable") that influenced whether a girl was exposed to vaccination. Essentially, the goal of the RDD was to estimate any corresponding discontinuity in the probability of the outcomes between eligibility groups at the same cutoff (Supplemental Appendix 1B). The value of the RDD over more traditional designs relies on the assumption that because the program implementation date and eligibility criteria were based on administrative decisions, the exact location of the cutoff is random, making girls directly on either side of the cutoff similar with respect to measured and unmeasured confounders. In the RDD, this comparability is assumed to decrease with increasing distance from the cutoff, so this notion is taken into account in the analysis.

Forcing Variable

The forcing variable (ie, birth date) was categorized into 3-month intervals, referred to as "birth year quarters." Therefore, girls born October 1, 1993, to December 31, 1993, defined the "ineligible" side of the cutoff and girls born January 1, 1994, to March 31, 1994, defined the "eligible" side. Girls born earlier/later than these dates were represented with increasing distance from this cutoff on the ineligible/eligible sides (Supplemental Appendix 2).

Exposure

To evaluate the impact of the qHPV vaccination program, exposure status was based solely on program eligibility, thus providing an intention-to-treat definition of vaccination. To assess the impact of the vaccine on our outcomes, qHPV vaccine receipt also was taken into account. The qHPV vaccine exposure was defined as receipt of all 3 doses between September 1 of grade 8 and August 31 of grade 9.

Outcomes

Incident cases of detected cervical dysplasia and AGW were identified between September 1 of grade 10 and March 31 of grade 12. Cases were “incident” if they occurred after at least 730 days (cervical dysplasia) or 365 days (AGW) event-free. Because algorithms for ascertaining these outcomes have not been validated, we created 3 definitions of each (broad, possible, and probable) in consultation with substantive experts in the field to reflect different degrees of potential misclassification (Supplemental Appendices 3 and 4).

Baseline Characteristics

We identified a number of characteristics relating to sociodemographics, vaccination history, health service use, and medical history. These were compared between eligibility groups and across levels of the forcing variable.

Statistical Analyses

To assess program impact, local linear regression was used to estimate the association between program eligibility and each outcome of interest.\textsuperscript{35,36} Specifically, regression functions were estimated on each side of the eligibility cutoff, and the difference/discontinuity between intercepts represented the absolute impact of program eligibility on the outcome. To assess vaccine impact, a second stage was added to also estimate the association between program eligibility and qHPV vaccine exposure. The absolute effect of the vaccine was determined based on the ratio of the 2 discontinuities: eligibility-outcome and eligibility-vaccine. This 2-stage analysis is analogous to an instrumental variable approach.\textsuperscript{35} Similarly, 1- and 2-stage log-binomial regression models were used to estimate the relative impact of program eligibility and vaccination on each outcome. Finally, the “number needed to treat” (NNT) of each outcome was estimated based on the reciprocal of the absolute risk difference (RD) and 95% confidence limits.\textsuperscript{42} All analyses were based on the entire study cohort; however, girls born in 1993 and 1994 were weighted twice as heavily as girls born in 1992 and 1995 because girls closest to the cutoff are most comparable (ie, lower potential for confounding). Similarly, we controlled for birth quarter because we found that girls born early (or late) in the year were most comparable between birth years (Supplemental Appendix 5). A number of sensitivity analyses were performed to evaluate the robustness of our results, including...
one that modified the “exposed” definition to include girls who received only 2 doses of the vaccine, as 2 doses may be sufficient to provide immunity. The other assumptions of the RDD were tested quantitatively or qualitatively and were found to hold.

SAS statistical software version 9.3 (SAS Institute, Inc, Cary, NC) was used for data management and Stata version 12 (StatCorp, College Station, TX) for analyses.

RESULTS

We identified a cohort of 260,493 girls, of whom almost half were eligible for free, school-based qHPV vaccination (Fig 1). Girls were 12.7 to 13.7 years old at cohort entry and were followed for an average of 4.6 years. Eligibility groups were similar with respect to a number of baseline characteristics, including frequency of outpatient physician visits and previous receipt of the measles-mumps-rubella and diphtheria, tetanus, and pertussis vaccines. There were small differences in such characteristics as neighborhood income quintile, hepatitis B vaccination, and indicators of previous sexual behavior (Table 1). Of the 75,848 cohort members who received at least 1 dose of the qHPV vaccine in grades 8 to 9, 88% completed the 3-dose series. As expected, program eligibility had a major impact on this exposure. Specifically, 50.6% of eligible girls were classified as qHPV vaccine exposed compared with <1% of ineligible girls. Figure 2 illustrates the discontinuity in qHPV vaccination between groups.

We identified 2436 (0.94%) cohort members with incident cervical dysplasia (Table 2). Although there was no apparent discontinuity at the eligibility cutoff when assessed across birth year quarters (Fig 3A), collapsing into birth years revealed a clear drop in risk between groups (Fig 3B), demonstrating the importance of controlling for birth quarter in the analyses. Indeed, the primary analysis (which adjusted for birth timing) revealed a statistically significant reduction in detected dysplasia attributable to program eligibility: RD $\pm$ 2.32 cases per 1000 girls, 95% confidence interval (CI) $\pm$ 4.02 to $\pm$ 0.61. An even stronger effect was observed for the vaccine: RD $\pm$ 5.70 per 1000 girls, 95% CI $\pm$ 9.91 to $\pm$ 1.50. These results indicate that 1 case of cervical dysplasia was prevented for every 431 (95% CI 248 to 1639) girls eligible for publicly funded vaccination and for every 175 (95% CI 101 to 667) girls who received the vaccine. The absolute RDs corresponded to a 21% (95% CI 6% to 34%) and 44% (95% CI 13% to 64%) relative risk (RR) reduction for eligibility and vaccination, respectively. RR reductions were similar for possible dysplasia and probable dysplasia, whereas absolute RDs decreased and NNTs increased with increasing specificity of the dysplasia definition (Table 3).

We ascertained 400 cases of AGW (Table 2). Figure 4 A and B depict this risk by birth year quarter and by birth year, respectively. The results suggested reductions in detected AGW attributable to program eligibility and vaccination, both on the absolute scale (RD $\pm$ 0.34 per 1000, 95% CI $\pm$ 1.03 to 0.36; RD $\pm$ 0.83, 95% CI $\pm$ 2.54 to 0.88) and the relative scale (RR 0.81, 95% CI 0.52 to 1.25; RR 0.57, 95% CI 0.20 to 1.58); however, these results were not statistically significant. Findings indicated even greater RR reductions for more specific outcome definitions of AGW, whereas absolute risk reductions were similar across definitions (Table 3). Results for both cervical dysplasia and AGW were robust in sensitivity analyses, including analyses that adjusted for additional baseline characteristics (Supplemental Appendix 6), defined HPV vaccine exposure based on

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**Figure 1**

Cohort flow diagram. *At the time of this study, 2 of Ontario’s 36 IRIS databases (representing approximately 22% of Ontario’s population) had not yet been transferred to the Institute for Clinical Evaluative Sciences and were therefore unavailable for use in this study. IRIS records also were unavailable if the girl emigrated from Ontario before starting kindergarten or immigrated to Ontario after completing high school. 1A girls IRIS record was defined as “up to date” if it had been modified 30 days before cohort entry or later. Otherwise, it was assumed the girl had moved out of our study area before cohort entry.

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**Table 1**

Baseline characteristics of study cohort and by eligibility group.

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>12.6 (12.5–12.7)</td>
<td>12.6 (12.5–12.7)</td>
</tr>
<tr>
<td>Household income quintile</td>
<td>1 (1–3)</td>
<td>1 (1–3)</td>
</tr>
<tr>
<td>School location</td>
<td>Urban</td>
<td>Suburban</td>
</tr>
</tbody>
</table>

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**Table 2**

Relative and absolute risk reductions for incident cervical dysplasia and AGW.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Absolute Risk Reduction (RD)</th>
<th>Relative Risk Reduction (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical dysplasia</td>
<td>21% (95% CI 6% to 34%)</td>
<td>0.81 (95% CI 0.52 to 1.25)</td>
</tr>
<tr>
<td>AGW</td>
<td>44% (95% CI 13% to 64%)</td>
<td>0.57 (95% CI 0.20 to 1.58)</td>
</tr>
</tbody>
</table>
DISCUSSION

This is the first observational study of the benefits of the qHPV vaccine to use a methodological approach that permits causal inference, providing new, strong evidence of the positive health impact of qHPV vaccination on health outcomes. In particular, our analyses revealed a protective effect of the qHPV vaccine program on cervical dysplasia among girls aged 14 to 17 years and, although imprecise, we also observed apparent reductions in the incidence of AGW. Estimates of vaccine impact for both outcomes were even stronger than those of program impact. All results speak to the value of offering qHPV vaccination to young girls through a population-based program.

Our use of the RDD enabled us to evaluate the intention-to-treat effects of qHPV vaccination for the first time outside of clinical trials. These analyses have particular public health value, as they provide measures of the population-level impact of the qHPV vaccine program on cervical dysplasia and AGW. Importantly, our findings revealed that despite relatively low qHPV vaccine coverage in Ontario (~50% among eligible girls), meaningful benefits were nevertheless observed in this young age group at the population level. These results are promising for other jurisdictions across Canada and beyond that have also struggled with low HPV vaccine coverage.

Nevertheless, estimates of program impact were considerably weaker than estimates of vaccine impact. For example, we observed almost 2.5 times greater absolute reductions in cervical dysplasia attributable to the vaccine compared with the program. Given that the benefits of the program impact are largely dependent on the proportion of girls vaccinated, these differences were not surprising, and they help demonstrate the important implications of vaccine coverage on reducing the burden of HPV-related health effects.
diseases in the population. Indeed, a thorough appreciation of the interplay between the program- and vaccine-level effects in any region will be crucial to improving qHPV vaccine policy and practice in ways that maximize the health and economic benefits of this vaccine.

To date, observational studies of cervical dysplasia and AGW have reported estimates of vaccine effectiveness based on analyses comparing vaccinated and unvaccinated girls. Our results of vaccine impact are generally consistent with previous research on cervical dysplasia.17–20 Although all observational studies have reported more conservative estimates than randomized controlled trials,7 this is not surprising given that trials estimated treatment effects under ideal conditions. This does, however, highlight the importance of observational studies in determining the real-world effectiveness of this vaccine. The only nonecologic observational study of AGW reported an effect greater than reported here; however, the estimates generally fell within our CIs.21 The difference in results between studies may be partly attributable to residual confounding between vaccinated and unvaccinated groups in the earlier study. Regardless, given the low risk of diagnosed AGW in our study’s young age group and the resulting imprecision of our estimates, additional studies are needed to further elucidate these findings.

A major strength of this study is the use of population-based administrative databases, which enabled us to conduct a large cohort study with limited potential for selection, recall, or response biases. An additional benefit is that our HPV vaccination data were highly sensitive (99.8%; 95% CI 99.3 to 99.9) and specific (97.7%; 95% CI 96.3 to 98.7) to girls’ vaccination status,44 meaning the impact of any exposure misclassification was likely negligible among eligible girls. Conversely, it is possible that we were missing information on HPV vaccines obtained by ineligible girls through private means. Although we expect this percentage to be low, it would nevertheless have caused us to underestimate the impact of the vaccine on our outcomes. The potential for herd immunity among ineligible girls would also have underestimated the benefits of the vaccine in this study. However, given the young age group and limited follow-up time of the study population, as well as the difference in calendar years of follow-up between eligibility groups, this effect was likely negligible.

Another limitation is the potential for outcome misclassification, as measures of cervical dysplasia and AGW have not been validated. To assess this potential for error, we created 3 levels of each outcome to reflect increasing levels of outcome sensitivity. Indeed, the fact that the RR of broad AGW was biased toward the null compared with the more sensitive definitions suggests the broad definition was misclassified. This is not surprising, as this definition included a diagnostic code that also could be used to capture warts on other body sites. On the other hand, the consistency in relative estimates across definitions of dysplasia and between definitions of possible and probable AGW suggests that most of our outcome definitions did not result in misclassification. Another limitation of our data are...
they detected only outcomes of girls who followed up with their physician after an abnormal screening result or girls who received care for AGWs through physicians reimbursed through OHIP. As such, some incident cases may have been missed. Because this underascertainment would have affected both groups equally, it would not have affected our relative estimates; however, our absolute estimates of effect are likely conservative. Another limitation is that we could not distinguish between dysplasia and cervical ectropion/erosion in the OHIP database. Because any resulting misclassification would have affected eligibility groups equally, it would have caused us to underestimate the magnitude of reductions. Also, although we could not report on the stage of dysplasia, given the young age of the study cohort and the long latency between HPV infection and cervical cancer,45 it is safe to assume the vast majority of cases of dysplasia represent atypical squamous cells or low-grade squamous intraepithelial lesions (ie, mild dysplasia). Future studies are needed to monitor for progression to high-grade lesions and cancer.

Although the RDD addresses confounding by factors affecting an individual’s decision to receive the vaccine, it is conceptually vulnerable to confounding by factors that might have differentially affected eligibility groups, such as changes in cervical cancer screening practice or changes in sexual behavior caused by the implementation of the vaccination program. However, a recent study in this population provided strong evidence against changes in sexual behavior,29 and screening practices likely did not change in Ontario until January 1, 2013, when physicians were no longer reimbursed for screening girls younger than 21.

**TABLE 3** Impact of qHPV Vaccination on the Risk of Cervical Dysplasia and AGWs (n = 260,493)

<table>
<thead>
<tr>
<th>Dysplasia</th>
<th>RDs, per 1000 Girls (95% CI)</th>
<th>Risk Ratio (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Program impact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broad</td>
<td>−2.32 (−4.02 to −0.61)</td>
<td>0.79 (0.66 to 0.94)</td>
<td>431 (248 to 1639)</td>
</tr>
<tr>
<td>Possible</td>
<td>−1.70 (−3.08 to −0.32)</td>
<td>0.76 (0.61 to 0.95)</td>
<td>588 (325 to 3125)</td>
</tr>
<tr>
<td>Probable</td>
<td>−0.79 (−1.74 to −0.16)</td>
<td>0.76 (0.56 to 1.05)</td>
<td>1266 (575 to ≤ NNH 6250)</td>
</tr>
<tr>
<td>Vaccine impact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broad</td>
<td>−5.70 (−9.91 to −1.50)</td>
<td>0.56 (0.37 to 0.85)</td>
<td>175 (101 to 267)</td>
</tr>
<tr>
<td>Possible</td>
<td>−4.19 (−7.59 to −0.80)</td>
<td>0.50 (0.30 to 0.82)</td>
<td>239 (132 to 1250)</td>
</tr>
<tr>
<td>Probable</td>
<td>−1.94 (−4.28 to 0.39)</td>
<td>0.51 (0.23 to 1.12)</td>
<td>515 (234 to ≤ NNH 2564)</td>
</tr>
<tr>
<td>AGWs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Program impact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broad</td>
<td>−0.34 (−1.03 to 0.36)</td>
<td>0.81 (0.52 to 1.25)</td>
<td>2941 (971 to ≤ NNH 2778)</td>
</tr>
<tr>
<td>Possible</td>
<td>−0.34 (−0.81 to 0.13)</td>
<td>0.60 (0.31 to 1.15)</td>
<td>2941 (1255 to ≤ NNH 7892)</td>
</tr>
<tr>
<td>Probable</td>
<td>−0.29 (−0.74 to 0.16)</td>
<td>0.63 (0.32 to 1.24)</td>
<td>3448 (1351 to ≤ NNH 6250)</td>
</tr>
<tr>
<td>Vaccine impact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broad</td>
<td>−0.83 (−2.54 to 0.08)</td>
<td>0.57 (0.24 to 1.35)</td>
<td>1205 (394 to ≤ NNH 1138)</td>
</tr>
<tr>
<td>Possible</td>
<td>−0.84 (−1.99 to 0.31)</td>
<td>0.31 (0.07 to 1.41)</td>
<td>1190 (503 to ≤ NNH 3226)</td>
</tr>
<tr>
<td>Probable</td>
<td>−0.72 (−1.82 to 0.38)</td>
<td>0.34 (0.05 to 2.14)</td>
<td>1389 (348 to ≤ NNH 2632)</td>
</tr>
</tbody>
</table>

NNT, number needed to treat; NNH, number needed to harm. To address the effect of birth timing we observed, we used the entire bandwidth of data (ie, all observations in the 1992 to 1995 birth cohorts), and included birth timing as a covariate in the model. In all analyses, the birth cohorts closest to the cutoff (1993 and 1994) were weighting twice as heavily as those farthest from the cutoff (1992 and 1995). When absolute RDs are not statistically significant, the limits of the CI for the NNT reflect both the possibility of benefit (NNT) and the possibility of harm (NNH). Moreover, the NNT is infinite (∞) when the absolute RD is 0. To convey the continuity of the CI, Altman42 suggests that both the NNT and the NNH be represented in 1 interval and that 0 be represented by infinity.

**FIGURE 3**

Before that date, physicians typically made prescriptions for the oral contraceptive pill contingent on undergoing annual screening, meaning a large proportion of sexually active teenage girls received Papanicolaou tests. Because the vast majority of follow-up time was complete by January 2013, this policy change would not have had a meaningful impact on our results.

We provide absolute measures of effect given their importance in determining the public health and economic impact of this intervention, but because absolute differences are a function of the underlying baseline risk, their generalizability to other populations is unclear. Therefore, our analyses should be repeated in a range of settings and over time, and readers should use the relative measures when comparing our results to other studies. It is also important to recognize that our intention-to-treat estimates were influenced by the relatively low qHPV vaccine coverage in Ontario, meaning estimates of program impact are likely be of greater magnitude in jurisdictions with higher coverage. Conversely, the relative measures of vaccine impact take into account actual vaccine exposure and are therefore likely more generalizable to other jurisdictions offering free qHPV vaccination to girls who are largely sexually naive.

CONCLUSIONS
This study provides new, strong evidence of the impact of qHPV vaccination on reductions in cervical dysplasia among adolescent girls. Although imprecise, we also observed apparent reductions in AGWs. The fact that these benefits were observed in such a young age group strengthens current recommendations that vaccination should occur at an early age. As such, policy makers and physicians can use these findings to substantiate arguments that delaying vaccination may result in missed opportunities for prevention. In addition, cost-effectiveness studies should be updated to incorporate real-world estimates of program- and vaccine-level effectiveness and coverage to provide more accurate assessments of the value of qHPV vaccination.
potential conflict of interest: the authors have indicated they have no potential conflicts of interest to disclose.

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