Early release, published at www.cmaj.ca on December 8, 2014. Subject to revision.

Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study

Leah M. Smith MSc, Jay S. Kaufman PhD, Erin C. Strumpf PhD, Linda E. Lévesque PhD

Abstract

Background: Suboptimal human papillomavirus (HPV) vaccine coverage in some jurisdictions is partly attributed to fears that vaccination may increase risky sexual behaviour. We assessed the effect of HPV vaccination on clinical indicators of sexual behaviour among adolescent girls in Ontario.

Methods: Using Ontario's administrative health databases, we identified a population-based cohort of girls in grade 8 in the 2 years before (2005/06 and 2006/07) and after (2007/08 and 2008/09) implementation of Ontario's grade 8 HPV vaccination program. For each girl, we then obtained data on vaccine receipt in grades 8 and 9 and data on indicators of sexual behaviour (pregnancy and non–HPV-related sexually transmitted infections) in grades 10–12. Using a quasi-experimental method known as regression discontinuity, we estimated, for each outcome, the risk difference (RD) and relative risk (RR) attributable to vaccination and to program eligibility.

Results: The cohort comprised 260 493 girls, of whom 131 781 were ineligible for the program and 128 712 were eligible. We identified 15 441 (5.9%) cases of pregnancy and sexually transmitted infection and found no evidence that vaccination increased the risk of this composite outcome: RD per 1000 girls –0.61 (95% confidence interval [CI] –10.71 to 9.49) and RR 0.96 (95% CI 0.81 to 1.14). Similarly, we found no discernible effect of program eligibility: RD per 1000 girls –0.25 (95% CI –4.35 to 3.85) and RR 0.99 (95% CI 0.93 to 1.06). The findings were similar when outcomes were assessed separately.

Interpretation: We present strong evidence that HPV vaccination does not have any significant effect on clinical indicators of sexual behaviour among adolescent girls. These results suggest that concerns over increased promiscuity following HPV vaccination are unwarranted and should not deter from vaccinating at a young age.

Competing interests: None declared.

This article has been peer reviewed.

Correspondence to:
Leah Smith,
leah.smith3@mail.mcgill.ca

CMAJ 2014. DOI:10.1503/cmaj.140900

Infection with the human papillomavirus (HPV) is the most commonly diagnosed sexually transmitted infection in Canada and around the world.[1] Although most of these infections are transient and self-resolving, others persist and can cause important health outcomes, including cervical cancer and anogenital warts.

In 2006, Canada was among 49 countries to license Gardasil (Merck, Whitehouse Station, New Jersey), a quadrivalent HPV vaccine designed to protect against 4 types of HPV (6, 11, 16, 18) that cause 70% of cases of cervical cancer and most cases of anogenital warts.[2–4] As one of the first cancer-preventing vaccines, this vaccine received expedited approval in several countries and was the subject of intensive marketing, lobbying and public health campaigns around the world.[5] By 2012, it had been approved in almost 100 countries, many of which also implemented nationwide HPV vaccination programs aimed primarily at immunizing young girls before the onset of sexual activity.[6]

Despite the popularity of large-scale immunization programs, HPV vaccination has faced a great deal of controversy regarding unanswered questions about the real-world effects of this vaccine.[7,8] A major topic of public debate has been the possibility that HPV vaccination might lead to sexual disinhibition,[9] that is, that receipt of the vaccine might give women and girls a false sense of protection against *all* sexually transmitted infections and that this false sense of protection might lead them to engage in more risky sexual behaviours than they would otherwise (e.g., be more promiscuous or neglect to use condoms). Increases in these risky behaviours could have important clinical consequences, including increased risk of pregnancy and sexually transmitted infections. Although there is little empirical support for the notion that sexual health interventions promote risky sexual behaviours,[10,11] this possible unintended effect of the HPV vaccine would undermine its value for

reducing the burden of sexual health–related diseases. Moreover, parental fears of increased promiscuity following HPV vaccination have been reported as a major determinant of vaccine refusal,[12] which may help to explain suboptimal HPV vaccine coverage in some jurisdictions.[6,13] Evidently, both actual and perceived sexual disinhibition can have a negative effect on the potential health benefits of HPV vaccination. Therefore, we conducted a population-based, retrospective cohort study to assess the effect of HPV vaccination on clinical indicators of sexual behaviour among adolescent girls in Ontario.

Methods

This study was based in Ontario, Canada, which began offering all 3 doses of the quadrivalent HPV vaccine to grade 8 girls in September 2007, primarily through school-based clinics.[14] At that time, girls who were not eligible for the publicly funded program (e.g., in grade 8 before 2007) were able to receive the 3-dose series from their physician or local public health agency at a cost of about $400.

To carry out this study, we used 6 of Ontario's population-based administrative databases housed at the Institute for Clinical Evaluative Sciences. These databases, which are described in detail elsewhere (see Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140900/-/DC1),[15,16] were used to obtain individual-level information on sociodemographic characteristics, fee-for-service claims by physicians, hospital admissions, emergency department visits, same-day surgeries and vaccinations. Because each individual in these databases is represented by a unique identifier, anonymized, individual-level linkage of records across databases was possible.

Using these data, we identified a population-based cohort of all girls eligible for Ontario's grade 8 HPV vaccination program in the first 2 school years it was offered (i.e., 2007/08 and 2008/09). For the purpose of comparison, we also included girls who were in grade 8 in Ontario in the 2 years before the program began (i.e., 2005/06 and 2006/07), who were ineligible for publicly funded, school-based HPV vaccination. We did not have a direct measure of school grade; however, an estimated 96% of girls enter grade 8 at 13 years after their birth year,[17] so we identified all females born in 1992, 1993, 1994 and 1995 (to correspond with grade 8 years of 2005/06, 2006/07, 2007/08 and 2008/09, respectively) who were residing in Ontario on Sept. 1 of grade 8 (cohort entry) and whose vaccination records were available at the time of analysis. Cohort members were followed until the earliest of their date of death, occurrence of a study outcome or Mar. 31 of grade 12. To describe this cohort, we identified a number of baseline characteristics relating to sociodemographic characteristics, vaccination history, health service use and medical history.

For this comparison, we used the regression discontinuity design, a quasi-experimental method for assessing the causal effects of policy interventions in a way that accounts for observed and unobserved confounding.[18–20] Given the analogies between regression discontinuity design and randomization and the advantages it offers over standard regression adjustment, the regression discontinuity design is increasingly used in epidemiology to facilitate reliable causal inference in observational settings.[21,22] Here, we used the regression discontinuity design to exploit the quasi-experimental situation that arose because girls were "assigned" to Ontario's HPV vaccination program according to whether they were in grade 8 before or after program implementation (i.e., born Dec. 31, 1993, or earlier v. born Jan. 1, 1994, or later), which caused the probability of receiving the vaccine to jump discontinuously between eligibility groups at the eligibility cut-off (see Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140900/-/DC1). In this way, the factor influencing exposure to the intervention (known as the "forcing variable") was birth date. In the regression discontinuity design, a corresponding discontinuity in the risk of the outcome at the eligibility cut-off would reflect the causal effect of the intervention, whereas continuity would be suggestive of a null effect (Appendix 2).

Because the forcing variable in this study was based on birth date, the dates of Dec. 31, 1993, and Jan. 1, 1994, defined either side of the eligibility cut-off, and cohort members with birth dates earlier and later than these dates were represented with increasing distance from the cut-off on the ineligible and eligible sides, respectively. For the analyses, the forcing variable was collapsed into 3-month intervals, referred to as "birth year quarters" (Appendix 3, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140900/-/DC1).

Our primary outcome was a composite measure of incident pregnancy and non–HPV-related sexually transmitted infections occurring between Sept. 1 of grade 10 and Mar. 31 of grade 12 (Appendix 4, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140900/-/DC1). We also assessed each of these 2 clinical indicators of sexual behaviour separately. Cases were "incident" if they occurred following an event-free period of at least 365 days.

To evaluate the program's effects, we used linear regression to model the association between program eligibility and outcomes. In this analysis,

exposure was defined on the basis of program eligibility, which thus provided an "intention-to-treat" estimate of vaccination. To evaluate the effect of the vaccine, actual receipt of vaccine was also taken into account; this was defined as receipt of all 3 doses between cohort entry and Aug. 31 of grade 9. In this analysis, we used 2-stage linear regression to estimate the association between program eligibility and vaccine exposure, in addition to the association between program eligibility and outcome. Analogously, we applied 1- and 2-stage log-binomial regressions to estimate the relative effect of program eligibility and vaccination on the outcomes. In all analyses, cohort members born in 1993 and 1994 were weighted twice as heavily as those born in 1992 and 1995 because individuals closest to the cut-off are the most comparable. Moreover, analyses were conditioned on birth timing (i.e., birth quarter) because we found that participants born early (or late) in the year were the most comparable across birth years (Appendix 5, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140900/-/DC1). We executed sensitivity analyses to test the robustness of our results.

This study was approved by the Institutional Review Board of McGill University's Faculty of Medicine, as well as by the Health Sciences Research Ethics Board of Queen's University. Data management was carried out using SAS statistical software, version 9.3 (SAS Institute Inc., Cary, North Carolina), and statistical analyses were executed using Stata version 13.1 (StataCorp, College Station, Texas). An expanded description of the methods used for this study is presented in Appendix 6 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140900/-/DC1).

Results

We identified a cohort of 260 493 girls, 49.4% of whom were eligible for publicly funded HPV vaccination (Figure 1). The mean age at cohort entry was 13.17 (standard deviation 0.28) years, and cohort members were followed for an average of 4.5 (standard deviation 0.3) years. Eligible and ineligible groups were similar, with the possible exception of small differences in neighbourhood income quintile, hepatitis B vaccination history and prevalence of some medical conditions (Table 1).

Although only 51% of eligible girls received all 3 doses of the HPV vaccine in grades 8 and 9, less than 1% of ineligible girls received the 3-dose series, which resulted in a clear discontinuity in HPV vaccine exposure at the eligibility cut-off (Figure 2). About 6% of cohort members had an outcome of interest between Sept. 1 of grade 10 and Mar. 31 of grade 12, 10 187 with pregnancies and 6 259 with a non–HPV-related sexually transmitted infection (Table 2). Figure 3, which depicts these risks by birth year quarter, shows that girls born during the first quarter of each year (January–March) were consistently at higher risk of these outcomes than girls born later in the year, which indicates the importance of controlling for birth timing in the analyses. Indeed, we observed no statistically significant increase in risk of the composite measure of indicators of sexual behaviour in relation to HPV vaccination, as evidenced on both the absolute and relative scales: risk difference (RD) per 1000 girls –0.61 (95% confidence interval [CI] –10.71 to 9.49) and relative risk (RR) 0.96 (95% CI 0.81 to 1.14). In addition, we identified no discernible effect of program eligibility: RD per 1000 girls –0.25 (95% CI –4.35 to 3.85) and RR 0.99 (95% CI 0.93 to 1.06). The

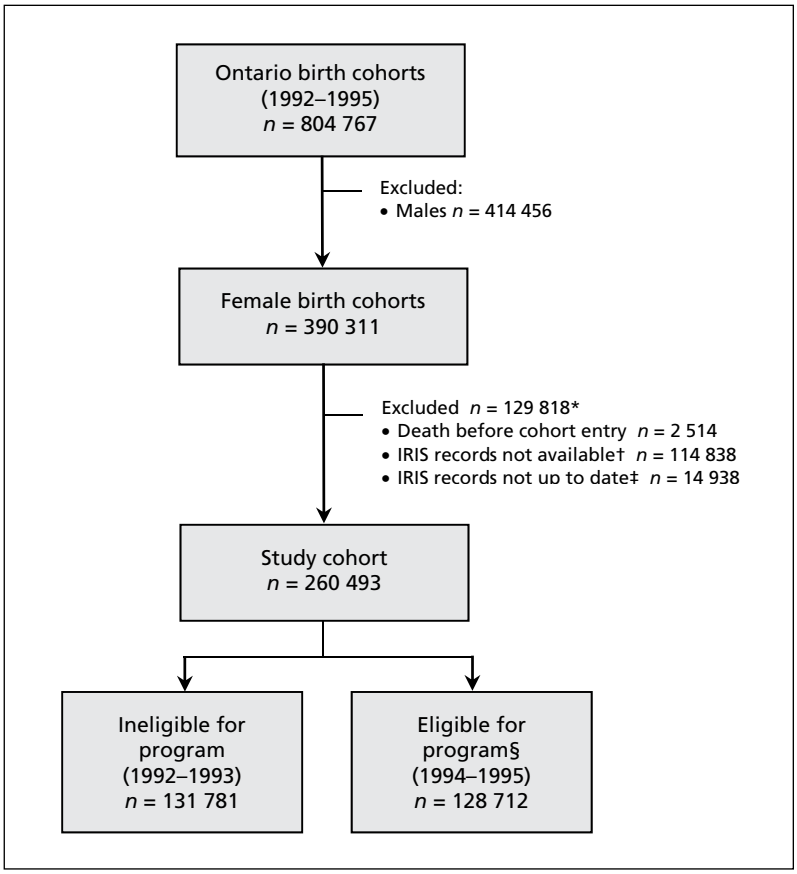


Figure 1: Cohort flow diagram. *The total number of exclusions at this stage is less than the sum of exclusions listed because some girls were excluded for more than one reason. †At the time of this study, 2 of Ontario's 36 Immunization Records Information System (IRIS) databases, representing about 22% of Ontario's population, had not yet been transferred to the Institute for Clinical Evaluative Sciences and were therefore unavailable for use. IRIS records were also unavailable for girls who emigrated from Ontario before starting kindergarten or immigrated to Ontario after completing high school. ‡A girl's IRIS record was defined as "up to date" if it had been modified 30 days before cohort entry or later. Otherwise, it was assumed that the girl had moved out of our study area before cohort entry. §Eligible for Ontario's publicly funded, school-based human papillomavirus vaccination program.

findings were similar when pregnancy and non–HPV-related sexually transmitted infections were assessed separately (Table 3). These results were robust to sensitivity analyses.

Interpretation

In this large population-based cohort study, we found no evidence that publicly funded HPV vaccination had any significant effect on clinical indicators of sexual behaviour. In particular, we found that neither HPV vaccination nor program eligibility increased the risk of pregnancy and non–HPV-related sexually transmitted infections among females aged 14–17 years.

To date, only one other study has reported on the association between HPV vaccination and clinical indicators of risky sexual behaviour. Bednarczyk and colleagues[23] compared sexual behaviour–related outcomes between vaccinated and unvaccinated females and reported that HPV

Table 1: Baseline characteristics of the eligibility groups in the study cohort

Characteristic	Program eligibility group; % of eligibility group*		Characteristic	Program eligibility group; % of eligibility group*	
	Ineligible (*n* = 131 781)	Eligible (*n* = 128 712)		Ineligible (*n* = 131 781)	Eligible (*n* = 128 712)
Sociodemographic†			**Health services use**†††**		
Age, yr, mean ± SD	13.17 ± 0.28	13.17 ± 0.28	Hospital admission		
Birth quarter			0	98.0	98.2
Jan.–Mar.	24.3	24.2	≥ 1	2.0	1.8
Apr.–June	26.1	26.1	LOS, d, mean ± SD	7.4 ± 15.6	8.0 ± 18.2
July–Sept.	25.7	25.8	Same-day surgery		
Oct.–Dec.	23.9	23.9	0	97.7	97.8
Residency			≥ 1	2.4	2.2
Urban	85.3	85.8	Emergency department visits		
Rural	14.0	13.5	0	70.7	71.1
Missing‡	0.7	0.6	1	18.1	17.8
Income quintile			≥ 2	11.2	11.1
1 (lowest)	16.6	15.0	Outpatient visits		
2	18.4	17.8	0 or 1	22.6	22.8
3	20.6	21.1	2–5	27.4	26.9
4	22.0	23.1	6–12	25.1	24.5
5 (highest)	21.4	22.1	≥ 13	25.0	25.8
Missing‡	1.0	0.9	**Medical history**		
Vaccination history§			Cancer**	0.7	0.7
Measles–mumps–rubella¶	97.9	98.2	Mental health diagnosis**	9.5	9.7
Diphtheria, tetanus and pertussis¶	98.0	98.3	Sexual health indicators**‡‡	0.7	0.7
Hepatitis B¶	84.1	82.0	Down syndrome	0.5	0.5
All 3 vaccines	83.0	81.1	Congenital malformations	12.4	11.8
			Intellectual disability§	0.7	0.7

Note: LOS = length of stay, SD = standard deviation.
*Except where indicated otherwise.
†At cohort entry.
‡Because of missing or inaccurate postal code.
§Between birth and cohort entry.
¶At least one dose.
**In the 2 years before cohort entry.
††Categories determined on the basis of the frequency distribution.
‡‡Composite of sexually transmitted infections, cervical dysplasia, Papanicolaou smear and pregnancy.

vaccination was not associated with these outcomes (RD 1.6 per 100 person-years, 95% CI –0.03 to 3.24; RR 1.29, 95% CI 0.92 to 1.80). Their article has been frequently cited as evidence of a lack of association between HPV vaccination and risky sexual behaviours. However, their study was limited by a small sample size (n = 1398), which is especially important given that the point estimates were suggestive of a potential increased risk. Moreover, because their study directly compared vaccinated and unvaccinated females, the results may have been confounded by health beliefs and behaviours affecting the probability of both the outcome and vaccination.

The few additional studies on this topic have focused on perceptions of risk following vaccination, rather than actual risk,[24,25] or have relied on self-reports of sexual behaviour,[26,27] which are vulnerable to recall, response and social desirability biases.[28,29] Furthermore, all were based on small samples (range 193–1243 females). Our study, which was based on a sample of 260 493 girls, provides strong evidence against a meaningful risk increase. Our findings are also consistent with studies assessing the effect of school-based sexual health interventions on adolescents' behaviour, which have indicated that programs aimed at improving access to condoms and sexual health education for teens do not increase sexual activity.

A major strength of our study was the use of a methodologic approach that enabled us to avoid the potential for confounding bias that arises when vaccinated and unvaccinated individuals are directly compared.[30,31] Circumventing this type of bias is particularly important when studying factors related to risky sexual behaviour, because these outcomes are likely strongly associated with the same unmeasured and unidentifiable health beliefs and behaviours that influence HPV vaccine decision-making.[12,32,33] Theoretically, residual confounding could have arisen in the presence of an intervention that differentially affected eligibility groups, such as a sexual health education program being paired with the HPV vaccination program. However, no such program was implemented in Ontario and, to the best of our knowledge, any sex education provided through the Ontario school system was offered similarly across birth cohorts. Another advantage of using the regression discontinuity design is that it permits assessment of the population-level effect of the vaccination program (i.e., the intention-to-treat effect), in addition to the effect of receiving the vaccine. The consistency of our results between these 2 measures provides additional support for our conclusions. Finally, our study benefited from validated HPV vaccination data,[17] which minimized the potential for exposure misclassification.

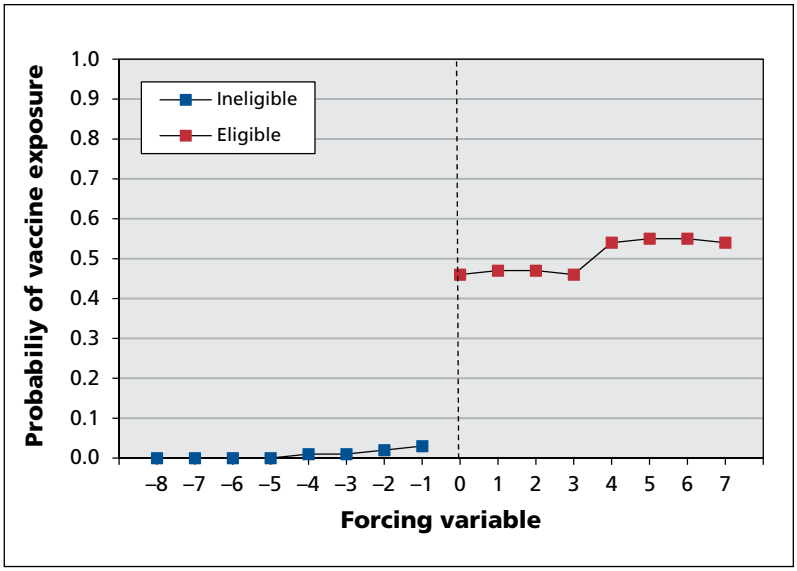


Figure 2: Probability of exposure to the quadrivalent human papillomavirus vaccine according to birth year quarter (the forcing variable) and program eligibility. See Appendix 3 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140900/-/DC1) for a description of how the forcing variable was operationalized.

Table 2: Cumulative risk of outcomes, according to eligibility for Ontario's quadrivalent human papillomavirus vaccination program and birth year

	Program eligibility; birth year; no. (%) of participants				
	Ineligible		Eligible		
Clinical indicator of sexual behaviour	1992 (n = 66 653)	1993 (n = 65 128)	1994 (n = 64 818)	1995 (n = 63 894)	Total (n = 260 493)
Composite outcome	4 203 (6.3)	4 032 (6.2)	3 801 (5.9)	3 405 (5.3)	15 441* (5.9)
Pregnancy	2 854 (4.3)	2 658 (4.1)	2 476 (3.8)	2 199 (3.4)	10 187 (3.9)
STIs	1 609 (2.4)	1 653 (2.5)	1 541 (2.4)	1 456 (2.3)	6 259 (2.4)

STI = sexually transmitted infection.
*This number is smaller than the sum of the 2 subsequent rows (for pregnant participants and those with sexually transmitted infections not related to human papillomavirus) because some cohort members had both outcomes.

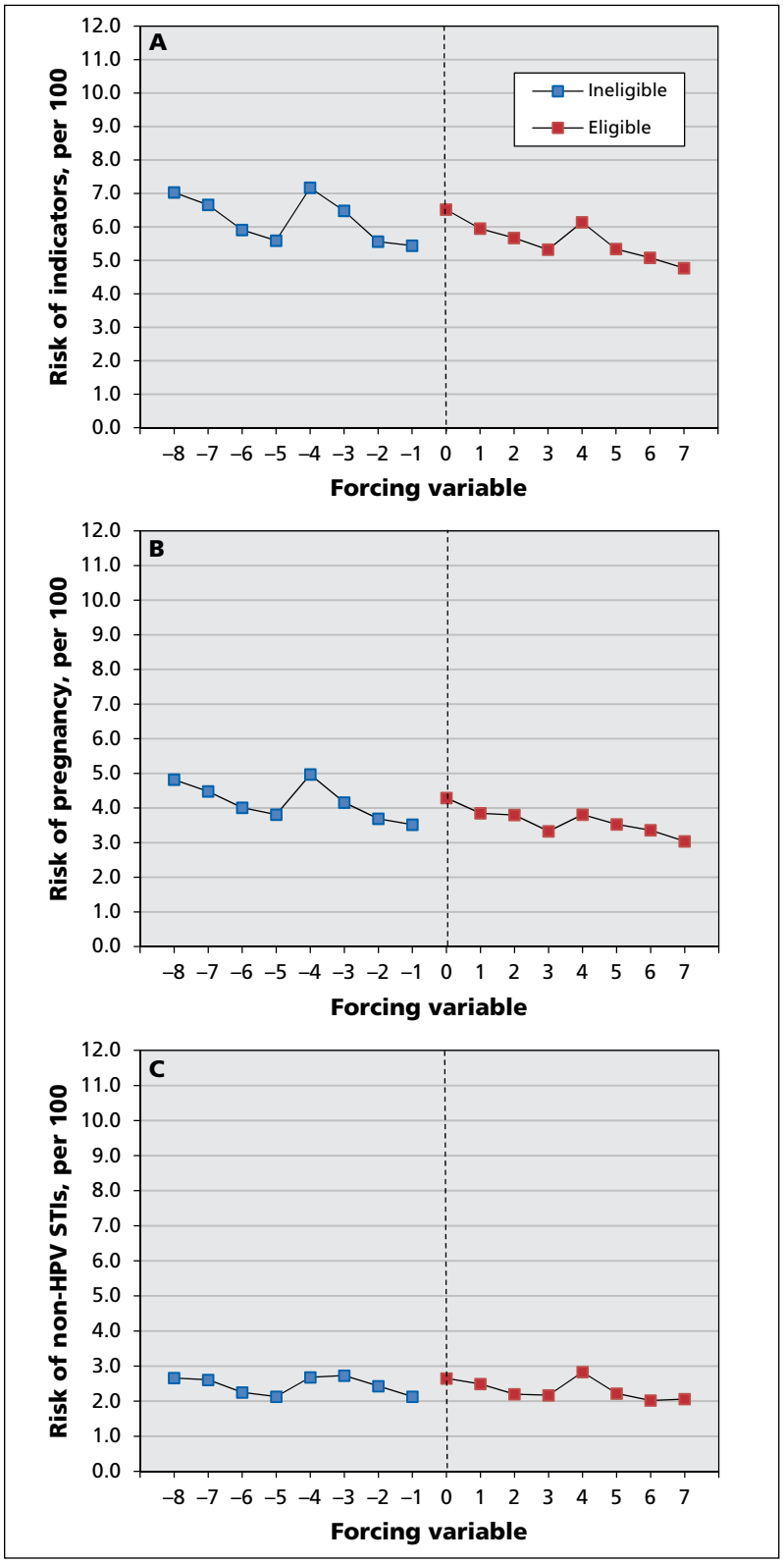


Figure 3: Risk of clinical indicators of sexual behaviour (ascertained for the period between Sept. 1 of grade 10 and Mar. 31 of grade 12), according to birth year quarter (the forcing variable) and eligibility for the human papillomavirus (HPV) vaccination program. (A) Composite outcome of pregnancy and non–HPV-related sexually transmitted infections (STIs). (B) Pregnancy. (C) Non–HPV-related STIs. See Appendix 3 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140900/-/DC1) for a description of how the forcing variable was operationalized.

Limitations

One limitation of our study is the lack of validation of our outcome measures. Importantly, although we did not intend to capture anogenital warts in our definition of non–HPV-related sexually transmitted infections, it is likely that some cases of anogenital warts were coded as "other venereal diseases." Given that both the vaccine and the HPV vaccination program are intended to reduce the risk of anogenital warts, and given that such reductions have been reported for other jurisdictions,[34,35] this misclassification would explain why our point estimates for this outcome were slightly below the null. Consequently, we believe that pregnancy is the more valid indicator of sexual behaviour.

A second limitation is the likelihood of underascertainment of our outcomes (e.g., not all pregnancies reported to physicians). Consequently, the absolute risk estimates reported here are likely underestimates, and the risk differences are likely biased toward the null. However, such underascertainment would have affected eligible and ineligible groups equally, and so would not have affected our relative estimates.

Also, we did not have the direct measures of sexual behaviour (e.g., number of sexual partners, condom use) that have been the focus of public controversy. Instead, we used pregnancy and sexually transmitted infections, as these outcomes represent direct measures of the health consequences of risky sexual behaviour. Although these outcomes do not encompass all facets of disinhibition, they are nonetheless objective measures of certain manifestations of risky sexual behaviour that are not susceptible to the biases that affect more direct measures.[24,25] Moreover, from a public health perspective, changes in rates of pregnancy and sexually transmitted infections are arguably of equal, if not greater, importance, given their direct effect on the health of adolescents and the use of health care services.

Finally, the generalizability of our results to other populations and jurisdictions is not yet known. However, the consistency of our findings with the existing evidence provides support for the absence of sexual disinhibition following HPV vaccination in a range of populations.

Conclusion

In this large, population-based cohort study, we found strong evidence that HPV vaccination does not have any significant effect on clinical indicators of risky sexual behaviour among adolescent girls. These findings suggest that fears of increased risky sexual behaviour following HPV vaccination are unwarranted and should not be a

Table 3: Effect of quadrivalent human papillomavirus vaccination on clinical indicators of sexual behaviour*

Outcome	No. of excess cases per 1000 girls (95% CI)	RR (95% CI)	Adjusted† RR (95% CI)
Effect of vaccine			
Composite outcome	–0.61 (–10.71 to 9.49)	0.96 (0.81 to 1.14)	0.98 (0.84 to 1.14)
Pregnancy	0.70 (–7.57 to 8.97)	0.99 (0.79 to 1.23)	1.00 (0.83 to 1.21)
STIs	–4.92 (–11.49 to 1.65)	0.81 (0.62 to 1.05)	0.81 (0.63 to 1.04)
Effect of program			
Composite outcome	–0.25 (–4.35 to 3.85)	0.99 (0.93 to 1.06)	1.00 (0.93 to 1.07)
Pregnancy	0.29 (–3.07 to 3.64)	1.00 (0.92 to 1.09)	1.01 (0.93 to 1.10)
STIs	–2.00 (–4.67 to 0.67)	0.92 (0.83 to 1.03)	0.92 (0.83 to 1.03)

Note: CI = confidence interval, RR = relative risk, STIs = sexually transmitted infections.
*To address the effect of birth timing that we observed, we used the entire bandwidth of data (i.e., all observations in the 1992 to 1995 birth cohorts) and included birth quarter as a covariate in the model. In all analyses, the birth cohorts closest to the cut-off (1993 and 1994) were weighted twice as heavily as those furthest from the cut-off (1992 and 1995).
†In this sensitivity analysis, we adjusted for neighbourhood income quintile, hepatitis B vaccination and history of sexual health–related indictor, as well as for birth quarter.

barrier to vaccinating at a young age. The results of this study can be used by physicians, public health providers and policy-makers to address public and parental concerns about HPV vaccination and promiscuity.

References

1. Trottier H, Franco EL. The epidemiology of genital human papillomavirus infection. *Vaccine* 2006;24 Suppl 1:S1-15.
2. Parry J. Vaccinating against cervical cancer. *Bull World Health Organ* 2007;85:89-90.
3. Muñoz N, Bosch FX, Castellsague X, et al. Against which human papillomavirus types shall we vaccinate and screen? The international perspective. *Int J Cancer* 2004;111:278-85.
4. Lacey CJ, Lowndes CM, Shah KV. Chapter 4: Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. *Vaccine* 2006;24 Suppl 3:S3/35-41.
5. Haas M, Ashton T, Blum K, et al. Drugs, sex, money and power: an HPV vaccine case study. *Health Policy* 2009; 92:288-95.
6. Markowitz LE, Tsu V, Deeks SL, et al. Human papillomavirus vaccine introduction — the first five years. *Vaccine* 2012;30 Suppl 5:F139-48.
7. Haug CJ. Human papillomavirus vaccination — reasons for caution. *N Engl J Med* 2008;359:861-2.
8. Lippman A, Melnychuk R, Shimmin C, et al. Human papillomavirus, vaccines and women's health: questions and cautions. *CMAJ* 2007;177:484-7.
9. Forster A, Wardle J, Stephenson J, et al. Passport to promiscuity or lifesaver: press coverage of HPV vaccination and risky sexual behavior. *J Health Commun* 2010;15:205-17.
10. Kirby D. The impact of schools and school programs upon adolescent sexual behavior. *J Sex Res* 2002;39:27-33.
11. Mueller TE, Gavin LE, Kulkarni A. The association between sex education and youth's engagement in sexual intercourse, age at first intercourse, and birth control use at first sex. *J Adolesc Health* 2008;42:89-96.
12. Brewer NT, Fazekas KI. Predictors of HPV vaccine acceptability: a theory-informed, systematic review. *Prev Med* 2007; 45:107-14.
13. Colucci R, Hryniuk W, Savage C. HPV vaccination programs in Canada: Are we hitting the mark? Report card on cancer in Canada. Toronto: Cancer Advocacy Coalition of Canada; 2008. p. 7-10.
14. Ontario's HPV vaccination program. Toronto: Ministry of Health and Long-Term Care; 2013. Available: www.health.gov.on.ca/en/ms/hpv/ (accessed 2014 Mar. 13)
15. *ICES data dictionary.* Toronto: Institute of Clinical Evaluative Sciences; 2014. Available: https://datadictionary.ices.on.ca/Applications/DataDictionary/Default.aspx (accessed 2014 Mar. 6).
16. Appendix 4: Data sources and population health indicators limitations. An appendix to the initial report on public health (2009). Toronto: Ministry of Health and Long-Term Care, Public Health Division; 2009. Available: www.health.gov.on.ca/en/public/publications/pubhealth/init_report/pdfs/appendix4.pdf (accessed 2014 Mar. 6)
17. Smith LM, Lévesque LE, Nasr M, et al. Validity of the Immunization Record Information System (IRIS) database for epidemiologic studies of the human papillomavirus (HPV) vaccine. *Can J Clin Pharmacoepidemiol* 2010;17:e90-127.
18. Cook TD. ''Waiting for life to arrive'': a history of the regression-discontinuity design in psychology, statistics and economics. *J Econom* 2007;142:636-54.
19. Imbens GW, Lemieux T. Regression discontinuity designs: a guide to practice. *J Econom* 2008;142:615-35.
20. Lee H, Munk T. Using regression discontinuity design for program evaluation. In: *Proceedings of the 2008 Joint Statistical Meeting*; 2008 Aug. 3–7; Denver. Alexandria (VA): American Statistical Association; 2008. p. 1675-82. Available: www.amstat.org/sections/srms/proceedings/y2008/Files/301149.pdf (accessed 2014 Oct. 21).
21. Bor J, Moscoe E, Mutevedzi P, et al. Regression discontinuity designs in epidemiology: causal inference without randomized trials. *Epidemiology* 2014;25:729-37.
22. O'Keeffe AG, Geneletti S, Baio G, et al. Regression discontinuity designs: an approach to the evaluation of treatment efficacy in primary care using observational data. *BMJ* 2014; 349:g5293.
23. Bednarczyk RA, Davis R, Ault K, et al. Sexual activity–related outcomes after human papillomavirus vaccination of 11- to 12-year-olds. *Pediatrics* 2012;130:798-805.
24. Mullins TL, Zimet GD, Rosenthal SL, et al. Adolescent perceptions of risk and need for safer sexual behaviors after first human papillomavirus vaccination. *Arch Pediatr Adolesc Med* 2012;166:82-8.
25. Mather T, McCaffery K, Juraskova I. Does HPV vaccination affect women's attitudes to cervical cancer screening and safe sexual behaviour? *Vaccine* 2012;30:3196-201.
26. Liddon NC, Leichliter JS, Markowitz LE. Human papillomavirus vaccine and sexual behavior among adolescent and young women. *Am J Prev Med* 2012;42:44-52.
27. Forster AS, Marlow LA, Stephenson J, et al. Human papillomavirus vaccination and sexual behaviour: cross-sectional and longitudinal surveys conducted in England. *Vaccine* 2012; 30:4939-44.
28. Fenton KA, Johnson AM, McManus S, et al. Measuring sexual behavior: methodological challenges in survey research. *Sex Transm Infect* 2001;77:84-92.
29. Clark LR, Brasseux C, Richmond D, et al. Are adolescents accurate in self-report of frequencies of sexually transmitted diseases and pregnancies? *J Adolesc Health* 1997;21:91-6.
30. Chen RT, Davis RL. RHodes PH. Special methodological issues in pharmacoepidemiology studies of vaccine safety. In: Strom BL, editor. *Pharmacoepidemiology*. 4th ed. Chichester (UK): John Wiley & Sons; 2005. p. 455-85.

31. Nelson JC, Jackson ML, Weiss NS, et al. New strategies are needed to improve the accuracy of influenza vaccine effectiveness estimates among seniors. *J Clin Epidemiol* 2009;62:687-94.
32. Rosenthal SL, Rupp R, Zimet GD, et al. Uptake of HPV vaccine: demographics, sexual history and values, parenting style, and vaccine attitudes. *J Adolesc Health* 2008;43:239-45.
33. Kessels SJ, Marshall HS, Watson M, et al. Factors associated with HPV vaccine uptake in teenage girls: a systematic review. *Vaccine* 2012;30:3546-56.
34. Leval A, Herweijer E, Ploner A, et al. Quadrivalent human papillomavirus vaccine effectiveness: a Swedish national cohort study. *J Natl Cancer Inst* 2013;105:469-74.
35. Ali H, Donovan B, Wand H, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. *BMJ* 2013; 346:f2032.

Affiliations: Department of Epidemiology, Biostatistics, and Occupational Health (Smith, Kaufman, Strumpf), McGill University, Montréal, Que.; Department of Public Health Sciences (Lévesque), Queen's University, Kingston, Ont.

Contributors: Leah Smith was involved in acquiring study data, played a major role in the conception, design and interpretation of the study, carried out the statistical analyses and drafted the manuscript. Erin Strumpf and Jay Kaufman played a major role in the conception, design, analysis and interpretation of the study and critically reviewed the manuscript. Linda Lévesque played the principal role in acquiring the study data, played a major role in the conception, design, analysis and interpretation of the study, and critically reviewed the manuscript. All authors were involved in obtaining funding for this study, have given final approval of the manuscript and agree to be accountable for all aspects of the work.

Funding: This study was funded by a grant from the Canadian Institutes of Health Research (CIHR MOP 130339). The funder had no role in the design or conduct of this study; the collection, analysis or interpretation of the data; the preparation, review or approval of the manuscript; or the decision to submit the manuscript for publication.

This study was also supported by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred.

Leah Smith is supported by a CIHR Fredrick Banting and Charles Best Canada Graduate Scholarships Doctoral Award; Jay Kaufman by the Canada Research Chairs program; Erin Stumpf by a Chercheure Boursier Junior 1 from the Fonds de recherche du Québec–Santé and the Ministère de la Santé et des Services sociaux du Québec; and Linda Lévesque by the Canadian Foundation for Innovation – Leaders Opportunity Fund.

Appendix 1 (as supplied by the authors): Description of Databases

Database	Description	Original Source	Data elements	Diagnostic record
Registered Persons' Database (RPDB)	Basic information about anyone who has ever been covered by Ontario health insurance	MOHLTC	• Demographic information (e.g., sex, date of birth, income quintile) • Geographic information (e.g., city/town, urban/rural) • Data of death (if applicable)	• N/A
Ontario Health Insurance Plan (OHIP)	Record of services from health care providers that claim under OHIP	MOHLTC	• Clinical data (e.g. diagnoses, procedures) • Administrative data (e.g. date of admission, fee paid) • Physician information (e.g., specialty)	• 1 diagnosis per visit • 1 fee code per visit • 3-digit diagnosis code (variant of ICD-9) • physician specialty
Discharge Abstract Database (DAD)	Record on inpatient hospital activity	CIHI	• Clinical data (e.g. diagnoses, procedures) • Administrative data (e.g. date of admission, date of discharge)	• 1-25 diagnoses per admission • 3-4 character ICD-9 codes (before 2002) • 3-4 character ICD-10 codes (2002 onward)
Same-Day-Surgeries (SDS)	Record on same-day surgeries	CIHI	• Clinical data (e.g. procedures) • Administrative data (e.g. date of admission, date of discharge)	• 1-16 diagnoses per admission • 3-4 character ICD-9 codes (before 2002) • 3-4 character ICD-10 codes (2002 onward)
National Ambulatory Care Reporting System (NACRS)	Record on patient visits to emergency departments	CIHI	• Clinical data (e.g. diagnoses, procedures) • Administrative data (e.g. date of admission)	• 1-10 diagnoses per consultation • 3-4 character ICD-9 codes • 3-4 character ICD-10 codes

Appendix to: Smith LM, Kaufman JS, Strumpf EC, et al. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study. *CMAJ* 2014. DOI:10.1503/cmaj.140900.

Immunization Records Information System (IRIS)	Record of the immunizations of school-aged children	LPHAs*	• Demographic information (e.g. health region) • Vaccine data (e.g., type, date)	• N/A

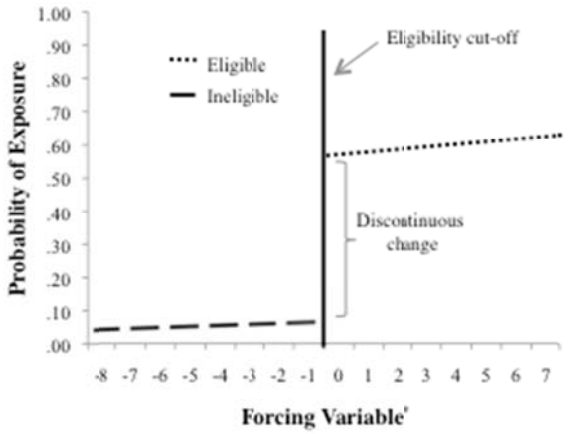
MOHLTC: Ministry of Health and Long-Term Care; CIHI: Canadian Institutes of Health Information; LPHA: Local Public Health Agency; ICD: International Classification of Diseases; N/A: Not applicable

*At the time of this study, IRIS data from 34 of Ontario's 36 LPHAs were available for our use.

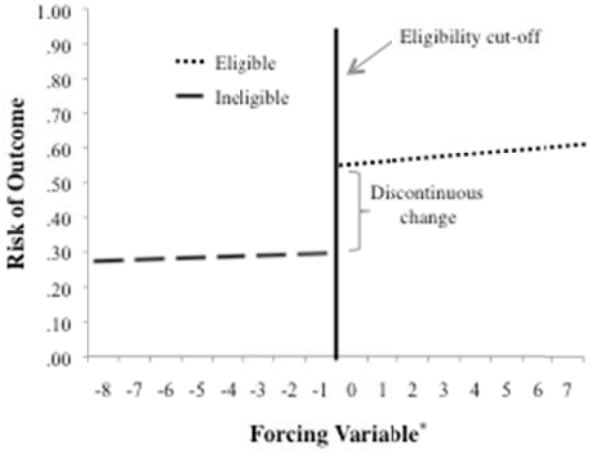
Appendix to: Smith LM, Kaufman JS, Strumpf EC, et al. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study. *CMAJ* 2014. DOI:10.1503/cmaj.140900.

Appendix 2 (as supplied by the authors): Hypothetical depictions of RDD scenarios*

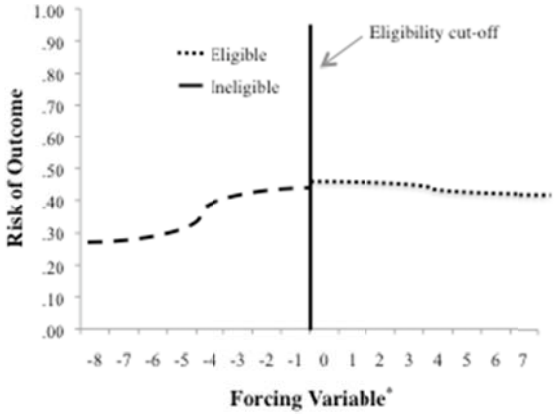
A.



B.



C.



A. Discontinuity in the probability of exposure at the eligibility cut-off

B. Discontinuity in the risk of the outcome at the eligibility cut-off

C. Continuity in the risk of the outcome at the eligibility cut-off

Note: RDD = regression discontinuity design.

*In these examples, the forcing variable was based on date of birth, which was collapsed into three-month categories and assigned a numerical value. For example, the value of the forcing variable was -1 for cohort members born October 1, 1993 to December 31, 1993 and 0 for cohort members born January 1, 1994 to March 31, 1994.

Appendix to: Smith LM, Kaufman JS, Strumpf EC, et al. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behavior among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study. *CMAJ* 2014. DOI:10.1503/cmaj.140900.

Appendix 3 (as supplied by the authors): Operationalization of Forcing Variable

	Birth Year	Birth Quarter	Birth Date	Value of Forcing Variable
Ineligible	1992	Q1	Mar 1992 – Jan 1992	-8
		Q2	Jun 1992 – Apr 1992	-7
		Q3	Sept 1992 – Jul 1992	-6
		Q4	Dec 1992 – Oct 1992	-5
	1993	Q1	Mar 1993 – Jan 1993	-4
		Q2	Jun 1993 – Apr 1993	-3
		Q3	Sept 1993 – Jul 1993	-2
		Q4	Dec 1993 – Oct 1993	-1
Eligible	1994	Q1	Jan 1994 – Mar 1994	0
		Q2	Apr 1994 – Jun 1994	1
		Q3	Jul 1994 – Sept 1994	2
		Q4	Oct 1994 – Dec 1994	3
	1995	Q1	Jan 1995 – Mar 1995	4
		Q2	Apr 1995 – Jun 1995	5
		Q3	Jul 1995 – Sept 1995	6
		Q4	Oct 1995 – Dec 1995	7

Appendix to: Smith LM, Kaufman JS, Strumpf EC, et al. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behavior among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study. *CMAJ* 2014. DOI:10.1503/cmaj.140900.

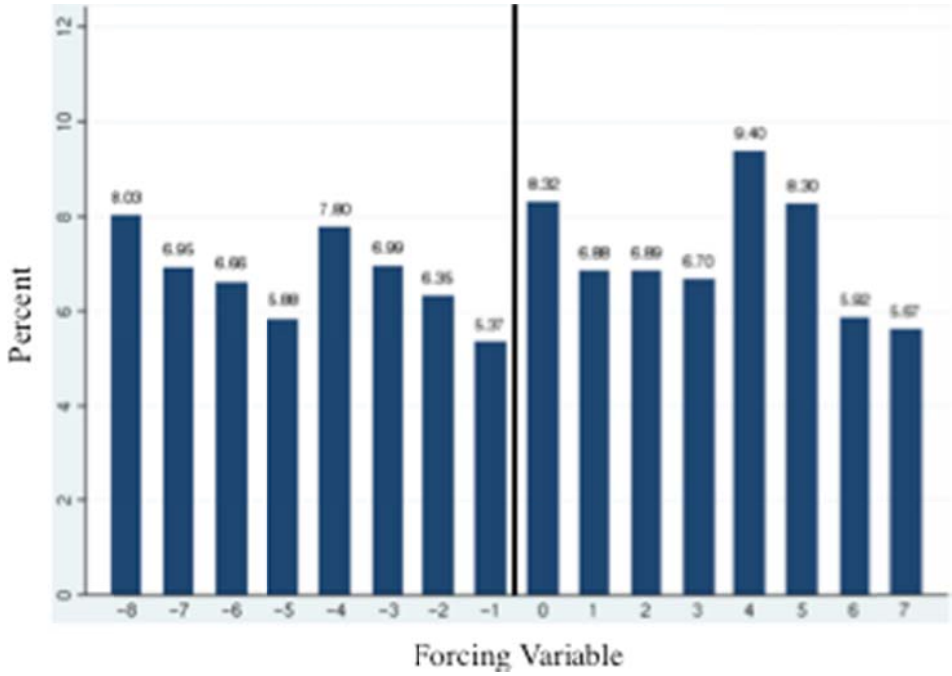
Appendix 4 (as supplied by the authors): Outcome Definition

Outcome		OHIP codes	ICD-10 codes	Description
Clinical indicators of sexual behaviour	**Non-HPV-related STIs**	097, 098, 099	A51-A60, A638, A64	Syphilis, gonococcal infections, or "other" venereal diseases (e.g., herpes, chlamydia, trichomoniasis)
	Pregnancy	632-635, 640-646, 650-653, 656, 658, 660-662	000-008, 010-048, 060, 080-084	Pregnancy, spontaneous abortion, therapeutic abortion, or delivery

OHIP: Ontario Health Insurance Plan; ICD-10 = International Classification of Diseases, version 10; STIs: sexually transmitted infections

Appendix to: Smith LM, Kaufman JS, Strumpf EC, et al. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behavior among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study. *CMAJ* 2014. DOI:10.1503/cmaj.140900.

Appendix 5 (as supplied by the authors): Percent of cohort with pregnancy, sexually transmitted infection, or cervical cancer screening in the two years before cohort entry, by forcing variable.



Appendix to: Smith LM, Kaufman JS, Strumpf EC, et al. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behavior among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study. *CMAJ* 2014. DOI:10.1503/cmaj.140900.

Appendix 6 (as supplied by the authors): Methods — Extended Version

This study was approved by the Institutional Review Board of McGill University's Faculty of Medicine, as well as by the Health Sciences Research Ethics Board of Queen's University.

Ontario's Grade 8 HPV Vaccination Program

Ontario's grade 8 HPV vaccination program began in September 2007. This publicly funded program offers the three recommended doses of the vaccine, free-of-charge, to all grade 8 girls in the province.[1] The program is primarily delivered through school-based immunization clinics administered by the province's 36 public health units, but eligible girls also have the option of receiving the vaccine at the their local health unit or through their family physician at no cost. During our study period, eligible females had until the end of their grade 8 school year to initiate the vaccine series and until the end of grade 9 to complete it under the publicly funded program. Prior to September 2012, no catch-up program was offered; therefore, females who were not eligible for the program (e.g., completed grade 8 before September 2007) would have had to pay for the vaccine at a cost of approximately $150 per dose.

Data Sources

Data for this study were obtained from Ontario's population-based administrative databases, which are generated by the province's universal health insurance programs and were housed at the Institute for Clinical Evaluative Sciences (ICES). Specifically, we used the following databases: (1) Registered Persons Database (RPDB), Ontario's population registry of insured persons, for information on socio-demographics, (2) Ontario Health Insurance Plan (OHIP) database for information on fee-for-service claims

Appendix to: Smith LM, Kaufman JS, Strumpf EC, et al. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study. *CMAJ* 2014. DOI:10.1503/cmaj.140900.

by physicians, (3) Discharge Abstract Database (DAD) for information on hospitalizations, (4) Same-Day Surgery (SDS) database for information on procedures carried out during same-day surgeries, and (5) National Ambulatory Care Reporting System (NACRS) for information on emergency department visits. These databases have been used extensively in health research, including in the post-marketing evaluation of drug and vaccine effects.[2–6] Details on these databases are available elsewhere (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140900/-/DC1).[7–11]

We also used the Immunization Records Information System (IRIS) for information on vaccinations, including HPV vaccinations.[11] IRIS databases are maintained by each of Ontario's 36 health units to record and track the immunization status of all school-aged children in their jurisdiction. Although these databases were originally developed for the six designated diseases (diphtheria, tetanus, polio, measles, mumps and rubella) for which immunization is prescribed by the Minister of Health and Long-Term Care (*Immunization of Schools Pupils Act, 1982*), they are currently used for other vaccines as well, particularly those that are publicly funded. Prior to centralizing the IRIS databases ICES, we validated the HPV vaccination data of a medium-sized health unit and found that it captured HPV vaccination status with near-perfect sensitivity (99.8%, 95% confidence interval [CI] 99.3 to 99.9) and high specificity (97.7%, 95% CI 96.3 98.7). Moreover, 98.6% of HPV vaccination dates were accurate.[12] Due to the rigorous and standardized procedures that have developed as a result of the requirements in the *Immunization of Schools Pupils Act*, we expect the HPV vaccine data of other health units to be of similarly high quality.

Appendix to: Smith LM, Kaufman JS, Strumpf EC, et al. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study. *CMAJ* 2014. DOI:10.1503/cmaj.140900.

All data were accessed through the ICES satellite unit at Queen's University. Since residents of Ontario are represented in these databases by a unique encrypted identifier, individual-level record linkage is possible across databases and over time.

Study Population and Cohort Formation

We identified a population-based cohort of all girls eligible for Ontario's grade 8 HPV vaccination program in the first two school years it was offered (i.e., 2007/08 and 2008/09). For the purpose of comparison, we also included girls who were in grade 8 in Ontario in the two years before the program (i.e., 2005/06 and 2006/07), who were therefore ineligible for publicly funded, school-based HPV vaccination. Although we did not have a direct measure of school grade, Ontario school entry practices are such that children typically enter school (Kindergarten) in September of the calendar year during which they turn 5, meaning the vast majority of children in a given grade have the same birth year.[13] Since this means girls in grade 8 typically turn 13 by December 31 of that school year, we identified a cohort of all females born in 1992, 1993, 1994, and 1995 to correspond with grade 8 years of 2005, 2006, 2007, and 2008, respectively. We then restricted the cohort to girls who were alive and residing in Ontario on September 1 of their grade 8 year (cohort entry) and whose immunization records were available at the time of the analysis. Although using birth year to determine grade 8 year misclassifies cohort members who were held back or advanced a grade, we found that this approach correctly identified 96.4% of girls eligible for the program's first two years (i.e., 2007/08 and 2008/09).[14] Cohort members were followed until the earliest of their date of death, occurrence of a study outcome, or March 31 of grade 12 (i.e., March 31 of 2010, 2011, 2012, or 2013, depending on the girl's birth year).

Appendix to: Smith LM, Kaufman JS, Strumpf EC, et al. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study. *CMAJ* 2014. DOI:10.1503/cmaj.140900.

Measurement and Analysis

The Regression Discontinuity Design – To address our objectives, we used the regression discontinuity design (RDD), a quasi-experimental approach that was specifically created to evaluate the causal effects of interventions.[15–19] The RDD is used in situations when assignment to an intervention (e.g., HPV vaccine program) is determined by the value of an observed continuous factor (e.g., birth date), referred to as the "forcing variable", being on one side of a fixed eligibility cut-off or the other, causing the probability of receiving the intervention (e.g., HPV vaccine) to increase discontinuously at this cut-off. In terms of Ontario's grade 8 HPV vaccination program, assignment to the intervention was based on whether individuals were in grade 8 before or after the September 2007 program implementation date (i.e., born December 31, 1993 or earlier *vs*. January 1, 1994 or later), causing the probability of receiving the vaccine to jump at the eligibility cut-off (Appendix 2A, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140900/-/DC1). RDD analyses are used to measure any corresponding discontinuous change in the probability of the outcome at the same eligibility cut-off (Appendix 2B), which is interpreted as the causal effect of the intervention. Correspondingly, a null effect is reflected by *continuity* in the outcome across the cut-off (Appendix 2C).

The major advantage of the RDD rests on the notion that the eligibility criteria and implementation date, which determine the assignment cut-off, are based on administrative decisions, meaning the exact location of the eligibility cut-off is random with respect to the characteristics of cohort members. Consequently, individuals falling directly on either side of the cut-off are comparable with respect to all measured and

Appendix to: Smith LM, Kaufman JS, Strumpf EC, et al. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study. *CMAJ* 2014. DOI:10.1503/cmaj.140900.

unmeasured confounders; the only factor that differentiates them is their probability of receiving the vaccine. This type of design is particularly valuable in studies of vaccine effects because individuals who opt for vaccination tend to have different health beliefs and behaviours than those who do not. Since health beliefs and behaviours are strongly associated with health outcomes and are difficult to identify and quantify, traditional methods of analysis that directly compare vaccinated and unvaccinated individuals are prone to confounding bias.[20–23] Conversely, by controlling for this type of observed and unobserved confounding, the RDD facilitates reliable causal inference.[15–17]

Forcing variable and cut-off – As mentioned above, our study design exploits the fact that girls were eligible for the HPV vaccination program based on when they were in grade 8. Since school grade was estimated based on birth date, females born January 1 1992 to December 31, 1993 (corresponding with the 2005/06 and 2006/07 grade 8 calendar years) were ineligible for the HPV vaccination program, whereas females born January 1, 1994 to December 31, 1995 (corresponding with the 2006/07 and 2007/08 grade 8 years) were eligible for this program. Accordingly, the forcing variable was based on birth date and December 31, 1993 *vs*. January 1, 1994 defined either side of the eligibility cut-off. For the purposes of analysis, the forcing variable was collapsed into three-month intervals (referred to as "birth year quarters"), meaning cohort members born October 1, 1993 to December 31, 1993 were directly on the ineligible side of the cut-off and cohort members born January 1, 1994 to March 31, 1994 were directly on the eligible side. Cohort members born earlier/later than those dates were represented with increasing distance from the cut-off on the ineligible/eligible sides (Appendix 3, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140900/-/DC1).

Appendix to: Smith LM, Kaufman JS, Strumpf EC, et al. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study. *CMAJ* 2014. DOI:10.1503/cmaj.140900.

Exposure Ascertainment – Two levels of exposure were analyzed. First, to evaluate the impact of the vaccination program, exposure was based solely on program eligibility. Therefore, cohort members who were in grade 8 in the 2005/06 and 2006/07 school years were classified as *ineligible* and those in grade 8 in the 2007/08 and 2008/09 were classified as *eligible*. This approach is analogous to an "intention-to-treat" (ITT) definition of exposure. Second, to assess the impact of vaccination, actual HPV vaccine receipt was also taken into account. A girl was classified as *vaccinated* if she received three doses of the vaccine between September 1 of grade 8 and August 31 of grade 9, which is the program vaccination period; otherwise, she was considered *unvaccinated*. The use of three doses for the primary exposure definition was based on the fact that this vaccine is administered as a three-dose series in Ontario. However, we also conducted sensitivity analyses based on receipt of at least one dose to assess whether the act of vaccination may have been sufficient to induce disinhibition. Similarly, we defined HPV vaccination status based on two doses in light of recent evidence that suggests two doses provide adequate protection.[24,25]

Outcome Ascertainment – Our primary outcome was a composite measure of incident non-HPV-related STIs and pregnancy (Appendix 4, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140900/-/DC1). We also assessed each endpoint separately. We excluded anogenital warts (an STI caused by HPV) from our measure of STIs because a decrease in this endpoint is an intended effect of the program and the vaccine. To ensure fixed follow-up time with equal probability of the outcomes for all cohort members, outcomes were ascertained between September 1 of grade 10 and

Appendix to: Smith LM, Kaufman JS, Strumpf EC, et al. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study. *CMAJ* 2014. DOI:10.1503/cmaj.140900.

March 31 of grade 12. A case was defined as incident if there was no indication of that event (STI or pregnancy) in the previous 365 days.

Baseline Characteristics – To describe the study cohort, we identified a number of baseline characteristics relating to socio-demographics, vaccination history, health service use, and medical history.

Statistical Analyses – To evaluate the program impact (i.e., intention-to-treat effect), linear regression was used to model the association between program eligibility and the outcome. To evaluate the vaccine impact, two-stage linear regression was used to estimate the association between program eligibility and the outcome *and* the association between program eligibility and HPV vaccine exposure. In the two-stage analysis, the estimate of interest was the ratio of coefficients from the two regressions, which represents the absolute impact of HPV vaccination on the outcome. Similarly, one- and two-stage log-binomial regressions were used to estimate the relative impact of program eligibility and vaccination on the outcomes of interest. In all analyses, cohort members born in 1993 or 1994 (i.e., closest to the cut-off) were weighted twice as heavily as those born in 1992 and 1995 because individuals closest to the cut-off are the most comparable. Moreover, analyses were conditioned on birth timing (i.e., birth quarter) because we found that, across birth years, females born early (or late) in the year were the most comparable (Appendix 5, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140900/-/DC1). Similar effects of relative age have been found in other studies as well.[26–28]

Sensitivity analyses were executed to test the robustness of our results to our various assumptions. For example, we assessed the impact of using different weights for

birth year. Also, as previously mentioned, vaccination status was re-defined based on receipt of at least one and a least two doses. In addition, exposure and outcome ascertainment windows were altered to ascertain vaccine exposure in grade 8 (since this is when most girls are vaccinated) and outcomes in grades 9 to grade 12. Furthermore, we conducted sensitivity analyses that controlled for neighbourhood income quintile, hepatitis B vaccination, and a recent sexual health-related outcome (i.e., pregnancy, diagnosis of an STI, or cervical cancer screening) in addition to birth quarter.

Data management was carried out using SAS statistical software version 9.3 (SAS Institute Inc., Cary, North Carolina), and statistical analyses were executed using Stata version 13.1 (StataCorp, College Station, Texas).

References

1. Ministry of Health and Long-Term Care. Ontario's HPV Vaccination Program. 2013. (Accessed March 13, 2014, at http://www.health.gov.on.ca/en/ms/hpv/.)
2. Lipscombe LL, Gomes T, Levesque LE, Hux JE, Juurlink DN, Alter DA. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. *JAMA* 2007;298(22):2634-43.
3. Lipscombe LL, Levesque L, Gruneir A, Fischer HD, Juurlink DN, Gill SS, et al. Antipsychotic drugs and hyperglycemia in older patients with diabetes. *Arch Intern Med* 2009;169(14):1282-9.
4. Kwong JC, Tanuseputro P, Zagorski B, Moineddin R, Chan KJ. Impact of varicella vaccination on health care outcomes in Ontario, Canada: effect of a publicly funded program? *Vaccine* 2008;26(47):6006-12.

Appendix to: Smith LM, Kaufman JS, Strumpf EC, et al. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study. *CMAJ* 2014. DOI:10.1503/cmaj.140900.

5. Juurlink DN, Stukel TA, Kwong J, Kopp A, McGeer A, Upshur RE, et al. Guillain-Barre syndrome after influenza vaccination in adults: a population-based study. *Arch Intern Med* 2006;166(20):2217-21.

6. Smith LM, Brassard P, Kwong JC, Deeks SL, Ellis AK, Levesque LE. Factors associated with initiation and completion of the quadrivalent human papillomavirus vaccine series in an ontario cohort of grade 8 girls. *BMC Public Health* 2011;11:645.

7. Iron K. Moving toward a better health data system for Ontario. *ICES Investigative Report*. Toronto: Institute for Clinical Evaluative Sciences, 2006.

8. Iron K, Zagorski BM, Sykora K, Manuel DG. Living and dying in Ontario: An opportunity for improved health information. *ICES Investigative Report*. Toronto: Institute for Clinical Evaluative Sciences, 2008.

9. Improving health care data in Ontario. *ICES Investigative Report*. Toronto: Institute for Clinical Evaluative Sciences, 2005.

10. Juurlink D, Preyra C, Croxford R, Chong A, Austin P, Tu J, et al. Canadian Institute for Health Information Discharge Abstract Database: A Validation Study. Toronto: Institute for Clinical Evaluative Sciences, 2006.

11. Ministry of Health and Long-Term Care. Data sources and population health indicators limitations (An appendix to the Initial Report on Public Health). 2009. (Accessed March 6, 2014, at http://www.health.gov.on.ca/en/public/publications/pubhealth/init_report/pdfs/appendix4.pdf.)

Appendix to: Smith LM, Kaufman JS, Strumpf EC, et al. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study. *CMAJ* 2014. DOI:10.1503/cmaj.140900.

12. Smith LM, Lévesque LE, Nasr M, Perry AG. Validity of the Immunization Record Information System (IRIS) database for epidemiologic studies of the human papillomavirus (HPV) vaccine. *Canadian Journal of Clinical Pharmacoepidemiology* 2010;17(1):e90-e127.

13. Teach in Ontario. Accessed July 4, 2014 at http://www.teachinontario.ca/tio/en/structure.htm)

14. Lévesque LE, Smith LM, Perry AG, Nsar M, Hogan ML, Martin A, et al. The Ontario Grade 8 HPV Vaccine Cohort Study: A Feasibility and Validity Evaluation. *Ontario Vaccine Sciences Symposium*. Toronto, ON, 2011.

15. Cook TD. ''Waiting for Life to Arrive'': A history of the regression-discontinuity design in Psychology, Statistics and Economics. *Journal of Econometrics* 2007;142:636-54.

16. Hahn J, Todd P, Van der Klaauw W. Identification and Estimation of Treatment Effects with a Regression-Discontinuity Design. *Econometrica* 2001;69(1):201-09.

17. Imbens GW, Lemieux T. Regression discontinuity designs: A guide to practice. *Journal of Econometrics* 2008;142:615-35.

18. Lee H, Munk T. Using Regression Discontinuity Design for Program Evaluation. Section on Survey Research Methods - Joint Statistical Meeting; 2008; 1675-1682 (Denver, Colorado).

19. Zuckerman IH, Lee E, Wutoh AK, Xue Z, Stuart B. Application of regression-discontinuity analysis in pharmaceutical health services research. *Health Serv Res* 2006;41(2):550-63.

Appendix to: Smith LM, Kaufman JS, Strumpf EC, et al. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study. *CMAJ* 2014. DOI:10.1503/cmaj.140900.

20. Fine PE, Chen RT. Confounding in studies of adverse reactions to vaccines. *Am J Epidemiol* 1992;136(2):121-35.

21. Chen RT, Davis RL, RHodes PH. Special Methodological Issues in Pharmacoepidemiology studies of vaccine safety. In: Strom BL, editor. *Pharmacoepidemiology*. Fourth ed: John Wiley & Sons, Ltd, 2005:455-85.

22. Jackson LA, Jackson ML, Nelson JC, Neuzil KM, Weiss NS. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. *Int J Epidemiol* 2006;35(2):337-44.

23. Nelson JC, Jackson ML, Weiss NS, Jackson LA. New strategies are needed to improve the accuracy of influenza vaccine effectiveness estimates among seniors. *J Clin Epidemiol* 2009;62(7):687-94.

24. Dobson SR, McNeil S, Dionne M, Dawar M, Ogilvie G, Krajden M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. *JAMA* 2013;309(17):1793-802.

25. Herweijer E, Leval A, Ploner A, Eloranta S, Simard JF, Dillner J, et al. Association of varying number of doses of quadrivalent human papillomavirus vaccine with incidence of condyloma. *JAMA* 2014;311(6):597-603.

26. Buckles KS, Hungerman DM. Season of Birth and Later Outcomes: Old Questions, New Answers. *The review of economics and statistics* 2013;95(3):711-24.

27. Hancock DJ, Adler AL, Cote J. A proposed theoretical model to explain relative age effects in sport. *Eur J Sport Sci* 2013;13(6):630-7.

Appendix to: Smith LM, Kaufman JS, Strumpf EC, et al. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study. *CMAJ* 2014. DOI:10.1503/cmaj.140900.

28. Morrow RL, Garland EJ, Wright JM, Maclure M, Taylor S, Dormuth CR. Influence of relative age on diagnosis and treatment of attention-deficit/hyperactivity disorder in children. *CMAJ* 2012;184(7):755-62.

Appendix to: Smith LM, Kaufman JS, Strumpf EC, et al. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study. *CMAJ* 2014. DOI:10.1503/cmaj.140900.