

CIC 2014 CCI

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OTTAWA

**Canadian Immunization Conference
Conférence canadienne sur l'immunisation**

**The effect of HPV vaccination on clinical indicators
of sexual behaviour in a population-based cohort
of adolescent girls:
The Ontario Grade 8 HPV Vaccine Cohort Study**

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Erin C Strumpf, Linda E Lévesque

Disclosure Statement



- I have no affiliation (financial or otherwise) with a pharmaceutical, medical device or communications organization.

Press Embargo



- This study is scheduled for publication in the Canadian Medical Association Journal (CMAJ) December 8, 2014.
- The CMAJ has put this study under embargo until 12pm on the day of publication.
- No information from this presentation is allowed to be disseminated to the public until the embargo has lifted.

Thank you for respecting this embargo!

Quadrivalent HPV vaccine



- Designed to protect against 4 types of the human papillomavirus (HPV) that cause 70% of cervical cancer and >90% of anogenital warts (AGW)
- First available in 2006 (e.g., USA, Canada, Australia)
 - Indicated for use in young girls (e.g., aged 9-26 years), ideally before sexual debut
- Publicly funded HPV vaccination programs in Canada administered by individual provinces and territories

Ontario's Grade 8 HPV Vaccination Program

- Publicly funded, school-based program
- Began September 2007
- Offers all 3 doses to all Grade 8 girls



Similar programs offered across Canada and around the world.

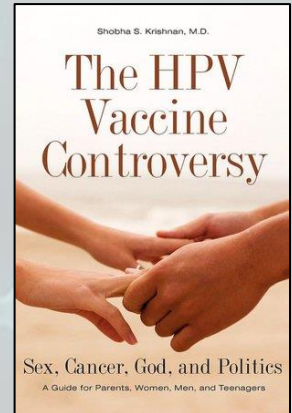
HPV Vaccine Controversy

**YOU COULD BECOME
1 LESS LIFE AFFECTED
BY CERVICAL CANCER.**



MACLEANS.CA

Our girls are not guinea pigs - Is an upcoming mass inoculation of a generation unnecessary and potentially dangerous? CATHY GULLI | August 27, 2007 |



Early release, published at www.cmaj.ca on August 1, 2007. Subject to revision.

COMMENTARY

Research

Human papillomavirus, vaccines and women's health: questions and cautions

Abby Lippman PhD, Ryan Melnychuk PhD, Carolyn Shimmin BJ, Madeline Boscoe RN DU

Influences sexual behaviour?

- **Public Health Implications:**
 - Parental concerns lead to decreased HPV vaccine coverage
 - Increases in teen pregnancy and non-HPV-related sexually transmitted infections (STIs) would undermine health benefits of HPV vaccination

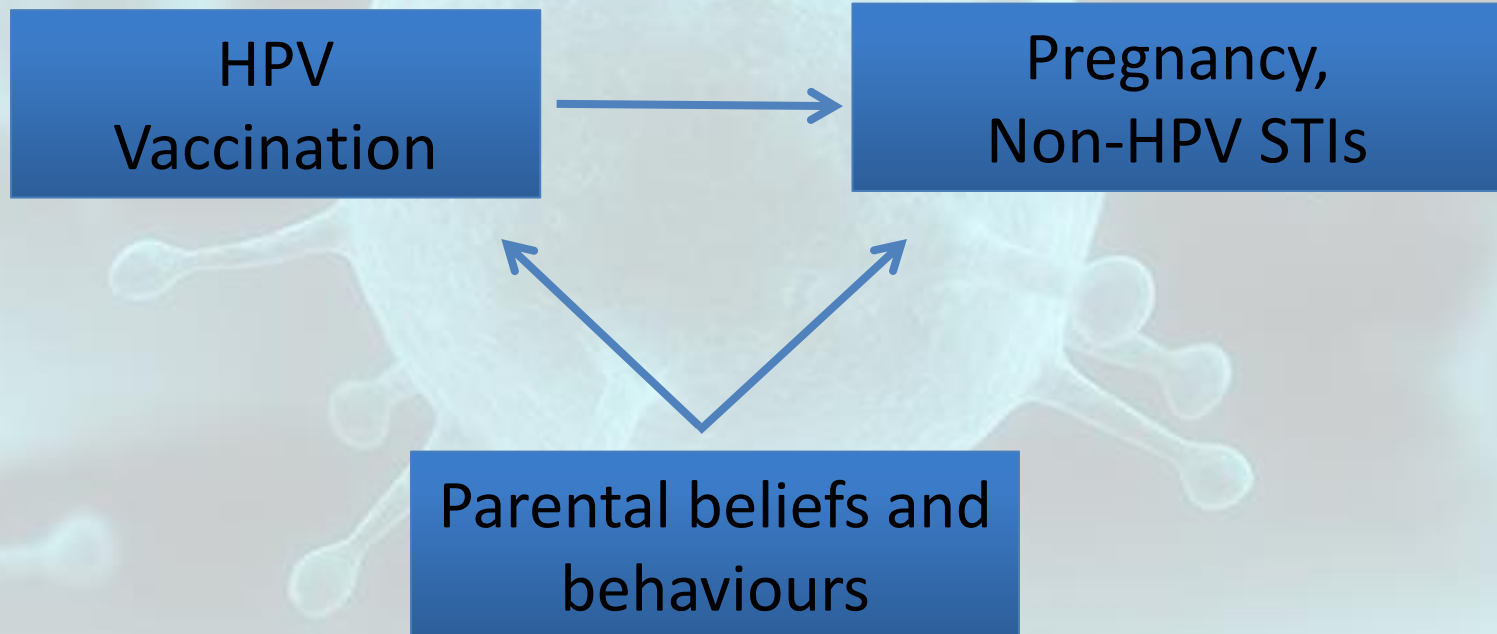


Objective



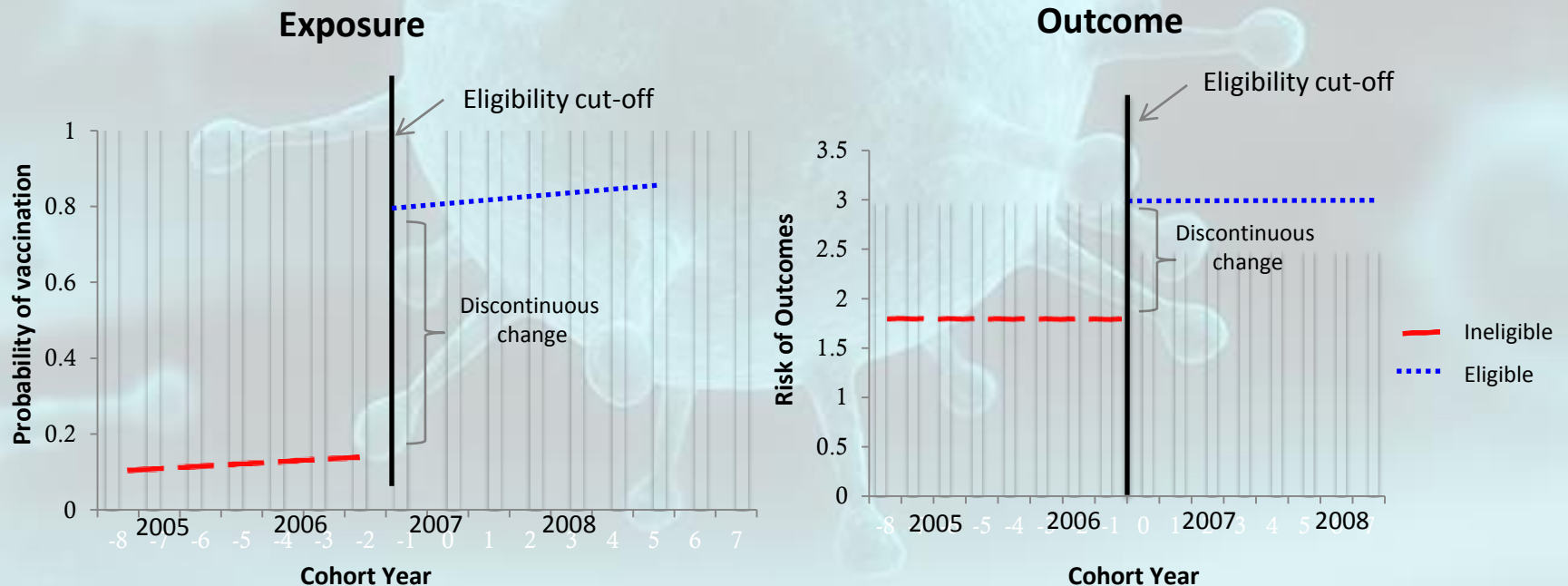
To assess the impact of the HPV vaccine and of Ontario's Grade 8 HPV vaccination program on clinical indicators of sexual behaviour among adolescent girls.

Methodological Challenge



Methodological Solution

- Regression Discontinuity Design (RDD)
 - Quasi-experimental, instrumental variable-based approach
 - Used to assess the causal impact of interventions and policies



Data Sources

Acronym	Name	Data	Uses
IRIS	Immunization Information Recording System	Vaccinations	<ul style="list-style-type: none"> • Cohort formation, • HPV vaccine exposure • Covariates
RPDB	Registered Persons Database	Demographics	<ul style="list-style-type: none"> • Cohort formation • Covariates
OHIP	Ontario Health Insurance Plan	Physician Services	<ul style="list-style-type: none"> • Outcomes • Covariates
DAD	Discharge Abstract Database	Hospital stays	
NACRS	National Ambulatory Care Database	Emergency Room Visits	
SDS	Same-Day Surgery Database	Outpatient surgeries	

Study Design and Population

- Study Design
 - Population-based retrospective cohort
- Study Population
 - Girls in Grade 8 in 2005/06 to 2008/09

	Grade 8 Cohort
Ineligible	2005/06
	2006/07

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	Grade 8 Cohort
Ineligible	2005/06
	2006/07
Eligible	2007/08
	2008/09

Eligibility
cut-off
←

Study Follow-Up

- *Cohort entry:* September 1 of Grade 8
- *Cohort exit:* March 31 of Grade 12

	Grade 8 Cohort	School Year							
		05/06	06/07	07/08	08/09	09/10	10/11	11/12	12/13
Ineligible	2005/06	Gr. 8	Gr. 9	Gr. 10	Gr. 11	Gr. 12			
	2006/07		Gr. 8	Gr. 9	Gr. 10	Gr. 11	Gr. 12		
Eligible	2007/08			Gr. 8	Gr. 9	Gr. 10	Gr. 11	Gr. 12	
	2008/09				Gr. 8	Gr. 9	Gr. 10	Gr. 11	Gr. 12

Exposure Ascertainment



(1) Program eligibility

- In Grade 8 2005/06-2006/07 vs. 2007/08-2008/09
 - “Intention-to-treat” (ITT) definition
 - Used to estimate *program impact*

(2) QHPV vaccine receipt

- 3 doses between Sept 1 of Grade 8 and Aug 31 of Grade 9)
 - Used to estimate *vaccine impact*

Outcome Definition



- Composite endpoint of 2 clinical proxies of sexual behaviour
 - Pregnancy
 - Sexually transmitted infections (excluding anogenital warts)
- Ascertained September 1 of Grade 10 to March 31 of Grade 12
- Incident case = no diagnosis/treatment in previous year

Analyses

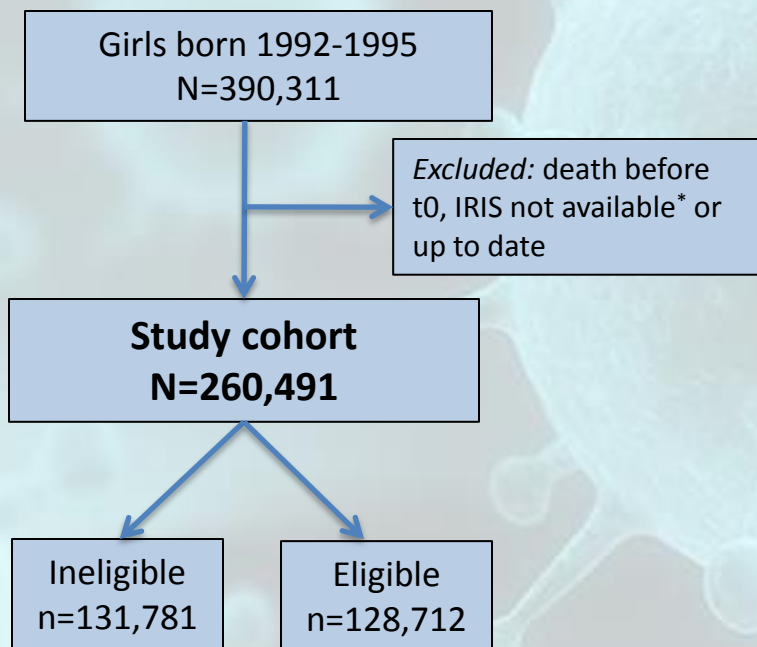
Absolute Risks – Local Linear Regression

- 1-stage – Program Impact
 - Intention-to-treat estimate
- 2-stage – Vaccine Impact

Relative Risks – Log Binomial Regression

- 1-stage – Program Impact
 - Intention-to-treat estimate
- 2-stage – Vaccine Impact

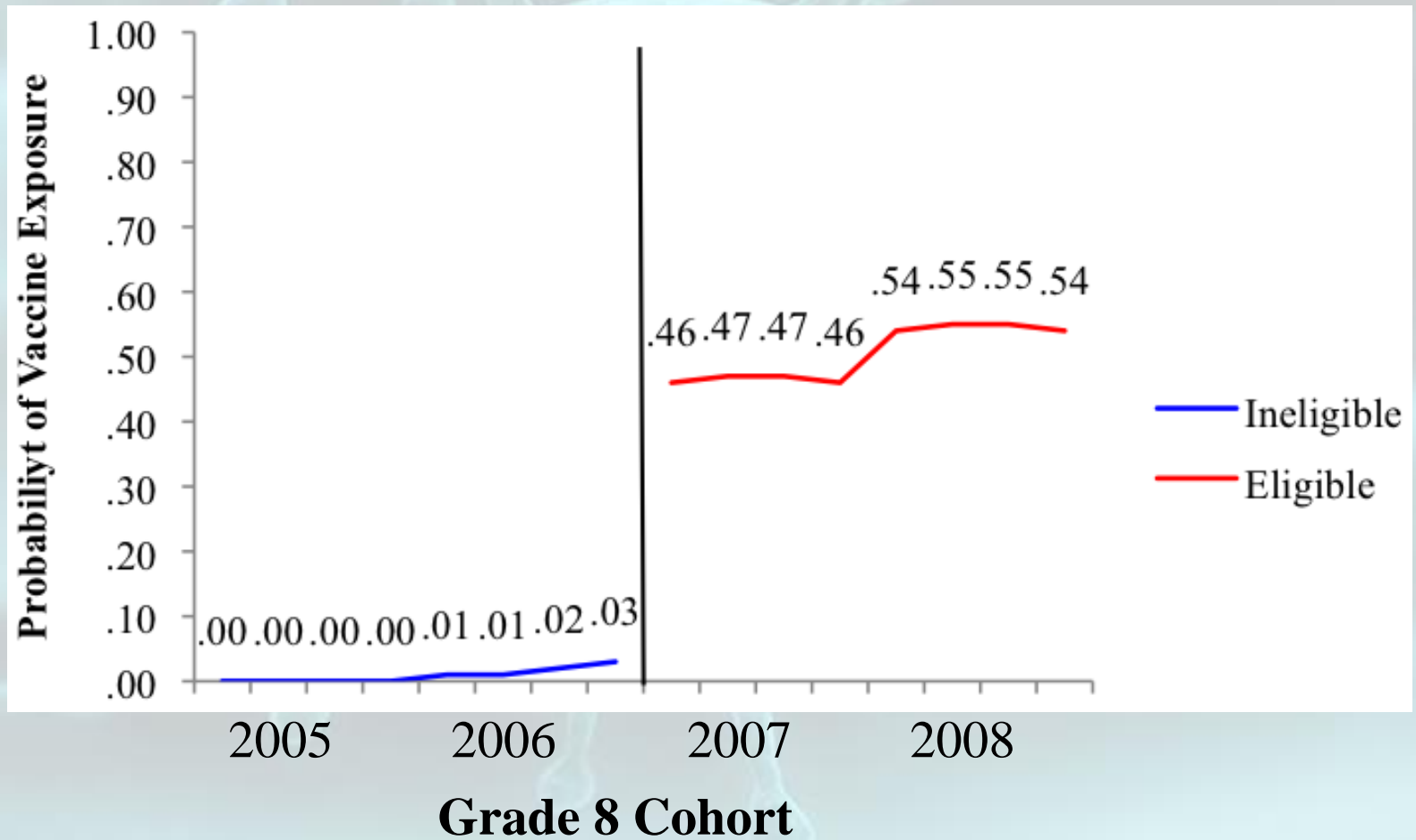
Study Cohort



Selected Baseline Characteristics	Ineligible n=131,781	Eligible n=128,712
Mean age (years), SD	13.2, 0.3	13.2, 0.3
Mean follow-up (years), SD	4.6, .12	4.6, .12
Income Quintile		
1 st (lowest)	16.6 %	15.0 %
3 rd	20.6%	21.1%
5 th	21.4%	22.1%
Prior sexual health-related outcome	0.68%	0.73%
Prior MMR & DTP vaccination	97.3%	97.8%

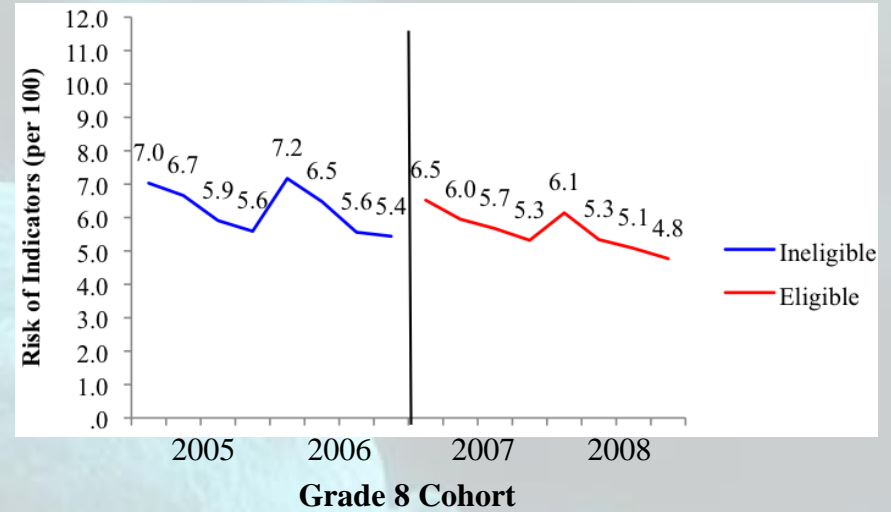
*At the time of this study, we had access to data from 34/36 health regions (~80% of the population)

HPV Vaccine Exposure

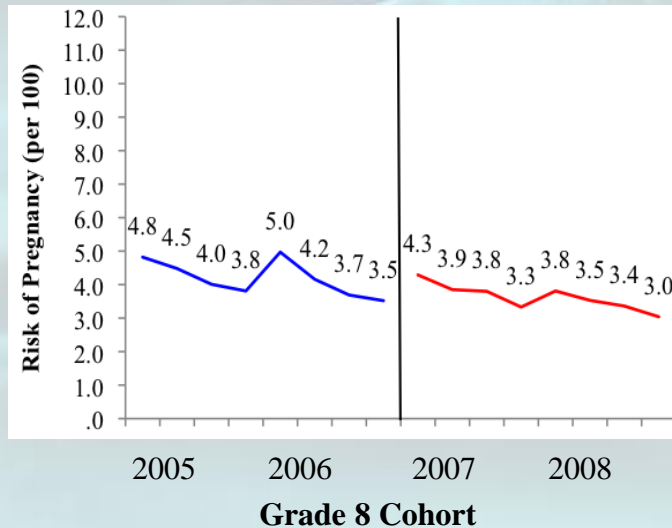


OUTCOMES

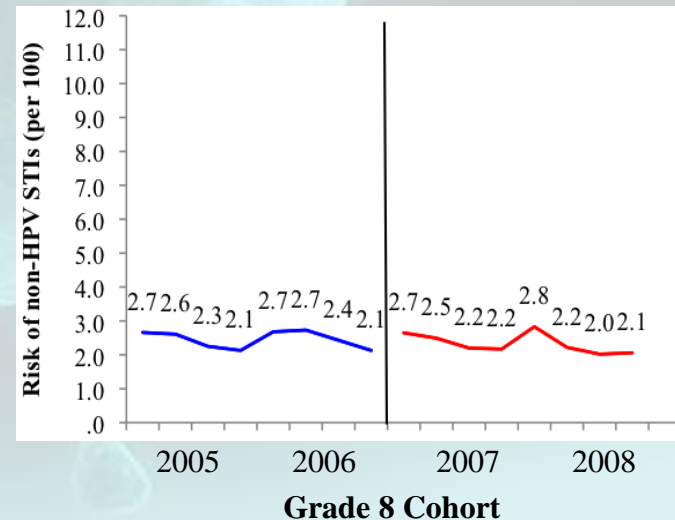
Composite Endpoint (N=15,441)



Pregnancy (N=10,187)



STIs (N=6,269)



Effect of Program and Vaccine

	Risk Difference, per 1000 (95% CI)	Risk Ratio (95% CI)
Program Impact (ITT)		
Composite endpoint	-0.25 (-4.35, 3.85)	0.99 (0.93, 1.06)
Pregnancy	-0.29 (-3.07, 3.64)	1.00 (0.92, 1.09)
Non-HPV-STI	-2.00 (-4.67, 0.67)	0.92 (0.83, 1.03)
Vaccine Impact		
Composite endpoint	-0.61 (-10.71, 9.49)	0.96 (0.83, 1.11)
Pregnancy	-0.70 (-7.57, 8.97)	0.99 (0.80, 1.21)
Non-HPV-STI	-4.92 (-11.49, 1.65)	0.80 (0.63, 1.04)

Results provide evidence against any meaningful association between the HPV vaccination program or the HPV vaccine and clinical indicators of sexual behaviour

Smith LM, Kaufman JS, Strumpf EC, Lévesque LE. The effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent females: The Ontario Grade 8 HPV Vaccine Cohort Study. *CMAJ*. In Press. (UNDER EMBARGO UNTIL DEC 8, 2014)

Discussion



Strengths

- Quasi-experimental approach that permits causal inference
- Large population-based cohort
- Validated HPV vaccination data

Limitations

- Outcome definitions not validated
 - Non-HPV-related STIs might be misclassified (i.e., include anogenital warts)
- Did not have direct measures of sexual behaviour (e.g., condom use)

Conclusions



- First study of health effects of publicly funded HPV vaccination in Canada
- Strong evidence HPV vaccination does not affect clinical indicators of sexual behaviour
- Suggests fears of increased promiscuity are unsubstantiated

Acknowledgements

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THANK YOU!

REMINDER: This study is under embargo by the CMAJ until 12pm Monday, December 8, 2014

Comparison with Research

Bednarczyk et al. (*Pediatrics* 2012)

- Location: United States
- Small sample size (N=1,398)
- Analysis: Vaccinated vs. unvaccinated
- Results suggestive of potential increase in risk

- RD = **1.6 per 100** person-years; 95% CI -0.03, 3.24
- RR=**1.29**; 95% CI 0.92, 1.80

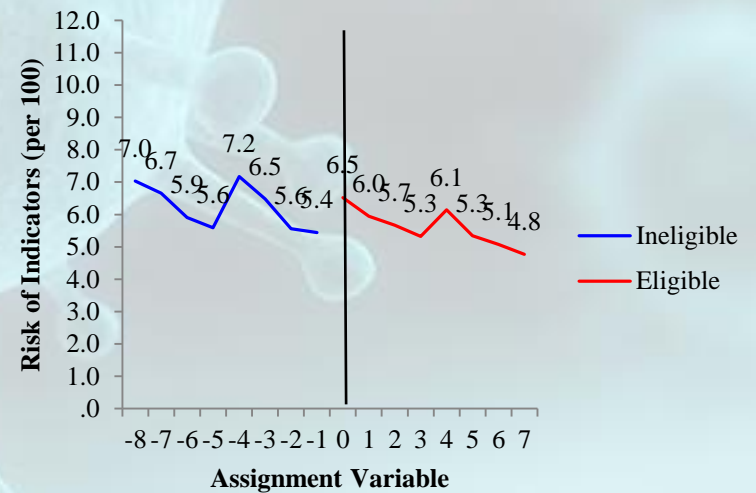
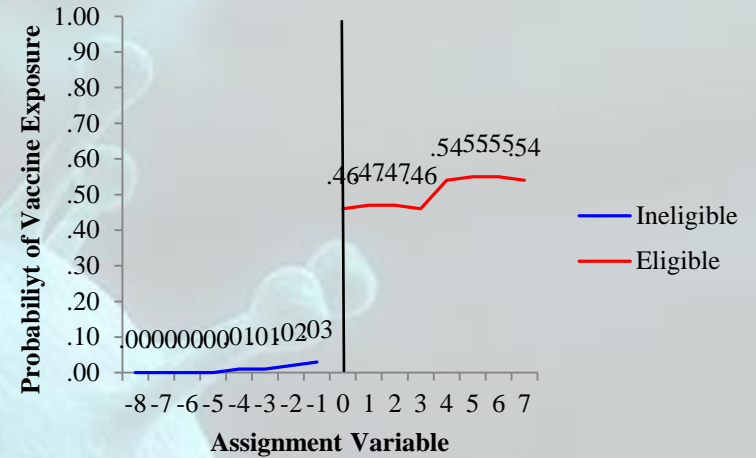
This study (*CMAJ* 2014)

- Location: Ontario, Canada
- Large sample size (N=260,493)
- Analysis: Quasi-experimental approach
- Results provide no evidence of increase in risk

- RD = **-0.061 per 100** girls; 95% CI -1.07, 0.95
- RR=**0.96**; 95% CI 0.81, 1.14
- $RR_{\text{preg}} = 0.99; 0.80, 1.21$

Bednarczyk RA, Davis R, Ault K, Orenstein W, Omer SB. Sexual activity-related outcomes after human papillomavirus vaccination of 11- to 12-year-olds. *Pediatrics* 2012;130(5):798-805.

	Grade 8 Year	Birth Year	Birth Date	Assignment Variable
Ineligible	2005/06	1992	Mar 92 – Jan 92	-8
			Jun 92 – Apr 92	-7
			Sept 92 – Jul 92	-6
			Dec 92 – Oct 92	-5
	2006/07	1993	Mar 93 – Jan 93	-4
			Jun 93 – Apr 93	-3
			Sept 93 – Jul 93	-2
			Dec 93 – Oct 93	-1
Eligible	2007/08	1994	Jan 94 – Mar 94	0
			Apr 94 – Jun 94	1
			Jul 94 – Sept 94	2
			Oct 94 – Dec 94	3
	2008/09	1995	Jan 95 – Mar 95	4
			Apr 95 – Jun 95	5
			Jul 95 – Sept 95	6
			Oct 95 – Dec 95	7



Validity of IRIS Database*

- Vaccination Status
 - Sensitivity: 99.8%, 95% CI 99.3-99.9
 - Specificity: 97.7%, 95% CI 96.3-98.7
- Vaccination dates
 - 98.6% accurate to the day
- Cohort definition
 - Correctly identified 96.4% eligible girls

*References

(1) 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. *Can J Clin Pharmacol* Vol 17(1) Winter 2010:e90-e127; March 26, 2010.

(2) Lévesque LE*, Smith LM, Perry AG, Nasr M, Hogan ML, Martin A, Monreal M. The Ontario Grade 8 HPV Vaccine Cohort Study: A Feasibility and Validity Evaluation. *Vaccine Sciences Symposium*, Toronto, Ontario (November 24, 2011).