

# **Evidence of Effective Delivery of the HPV Vaccine Through a Publicly Funded, School-Based Program: The Ontario Grade 8 HPV Vaccine Cohort Study**

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# Background

# Quadrivalent HPV Vaccine

- Protects against HPV-6, -11, -16, -18
  - 90% of anogenital warts
  - 70% of cervical cancers
- Highly efficacious
  - anogenital warts – 99% (95% CI: 96-100%)
  - pre-cancerous cervical lesions – 96% (95% CI: 91-98%)
    - Per protocol: three doses administered at 0, 2, and 6 months



<sup>1</sup>Future II. *BMJ*, 2010. 341: p. c3493

# HPV Vaccine in Canada

- July 2006: Approved in Canada
- March 2007: \$300 million federal immunization initiative
  - Ontario received \$117 million



# Ontario's Grade 8 HPV Vaccination Program

- Established September 2007
- Offers 3 free HPV vaccines to Grade 8 girls
- Administered by health units through school-based clinics

Dose 1	September/October	Month 0
Dose 2	November/December	Month 2
Dose 3	March/April	Month 6

*\*Programs are similar across Canada*

# Rationale

- No information on effectiveness of program delivery
- Number and timing of doses likely affect effectiveness of vaccine and impact of vaccination program on adolescent health

# Objectives

To assess HPV vaccine series completion and on-time dosing in Ontario's Grade 8 HPV vaccination program

# Methods



# Data Sources

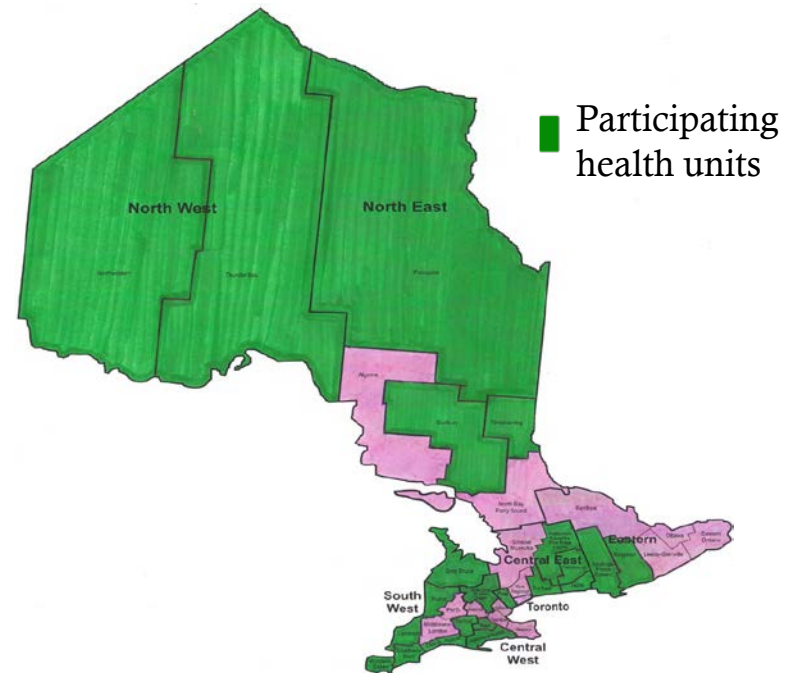
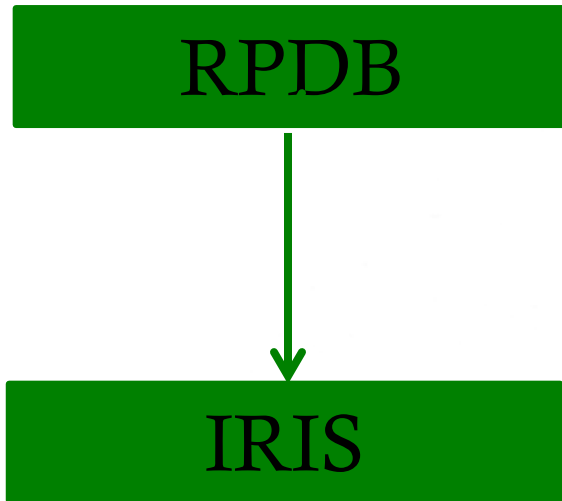
	RPDB	IRIS
Name	Registered Persons Database	Immunization Record Information System
Purpose	Population registry of everyone insured under Ontario Health Insurance Plan (OHIP)	Maintained by the 36 health units to track immunizations of school-aged children
Our use	Information on Ontario residency and socio-demographics	Information on vaccinations (including HPV vaccination)



High sensitivity (**99.8%**, 95% CI 99.3-99.9) and specificity (**97.7%**, 95% CI 96.3-98.7). **98.6%** dates were accurate.

# Data Access – ICES

- Institute for Clinical Evaluative Science (ICES)
  - Individual-level record linkage



# Cohort Information

- Study Design
  - Retrospective, population-based cohort study
- Study Population
  - Girls eligible for Ontario's Grade 8 HPV vaccination program in 2007/08, 2008/09, and 2009/10 who initiated the vaccination series
- Study Follow-Up
  - *Cohort entry*: September 1 of Grade 8
  - *Study end*: March 31, 2011

# HPV Vaccine Use



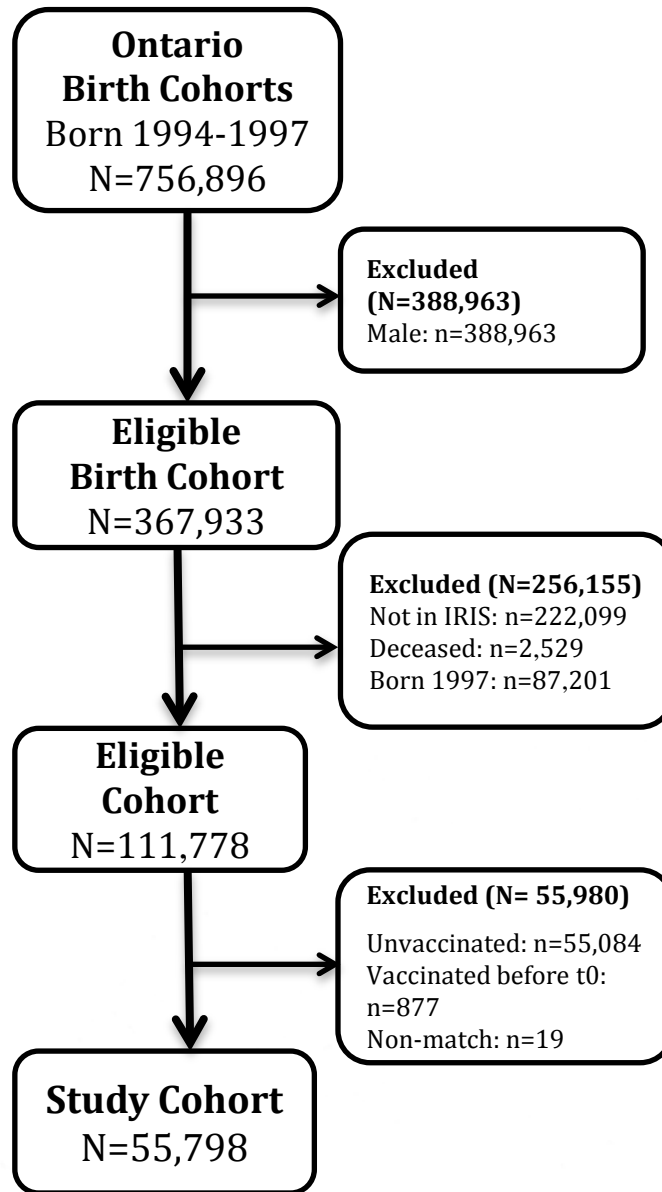
- Number of HPV vaccine doses
- Time windows
  - *Grade 8 eligibility*: Sept 1-Aug 31 of Grade 8
  - *Program eligibility*: Sept 1 of Grade 8 – Aug 31 of Grade 9
- Series Completion
  - *Incomplete*: 1-2 doses
  - *Complete*:  $\geq 3$  doses
    - Analysis: Proportion by eligibility period – overall & by program year

# Dose Timing

Category*	Dosing Interval (days)		
	D1 – D2	D2 – D3	D1 – D3
<b>Too short</b>	<30 days	<90 days	D1-D3 <120 days <i>or</i> D2-D3 <90 days
<b>On schedule</b>	30-90 days	≥90 days	D1-D3 120-240 days <i>and</i> D2-D3 ≥90 days
<b>Acceptable</b>	N/A	N/A	241-365 days
<b>Too Long</b>	>90 days	N/A	>365 days

\*created based on the dosing schedule (and 'flexibility period') specified in the Gardasil® product monograph ([http://www.merck.ca/assets/en/pdf/products/GARDASIL-PM\\_E.pdf](http://www.merck.ca/assets/en/pdf/products/GARDASIL-PM_E.pdf))

# Results



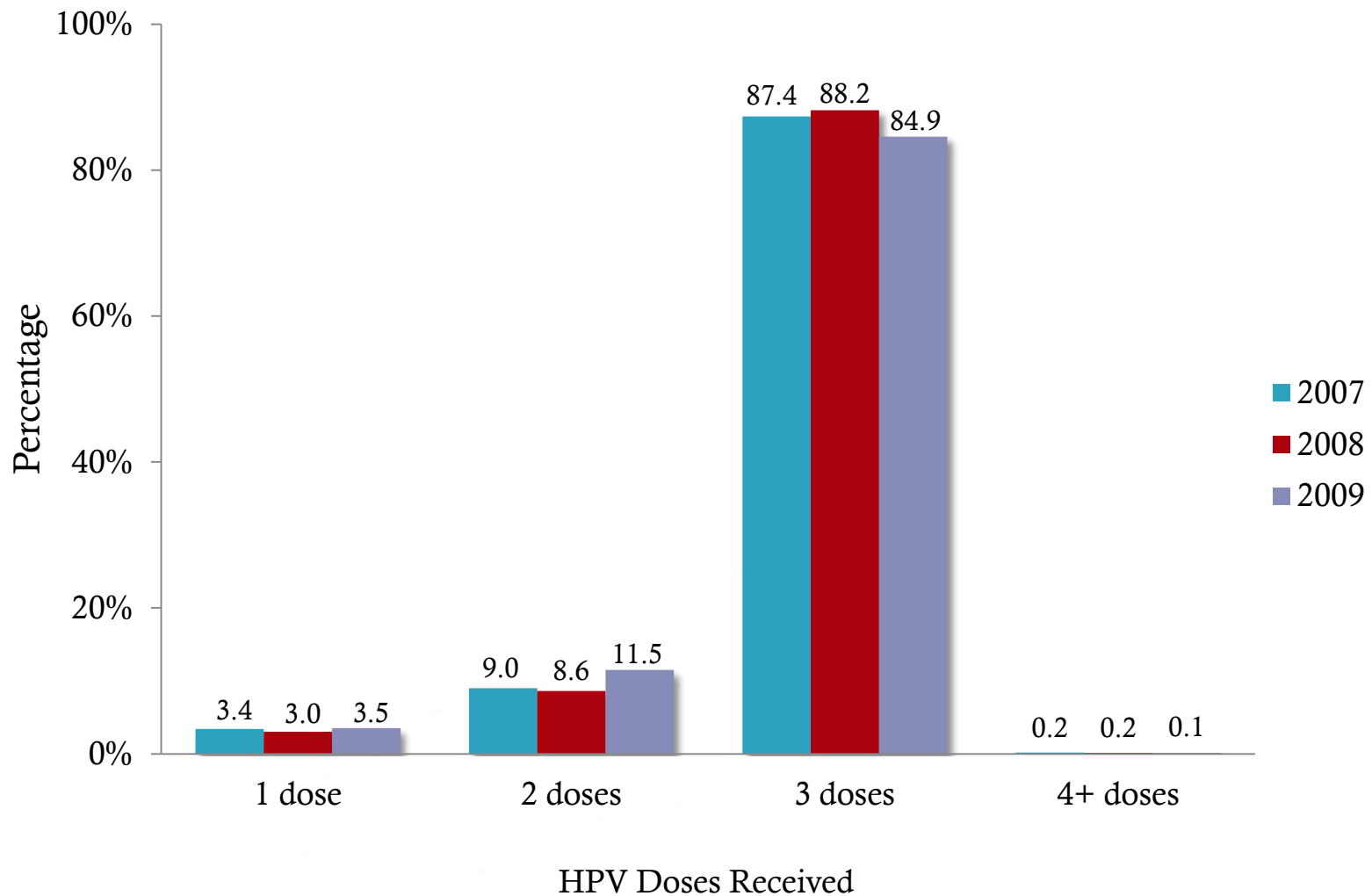
50% of eligible girls initiated the vaccination series and comprised our study cohort (N=55,798)

**Figure 1. Cohort Flow Diagram**

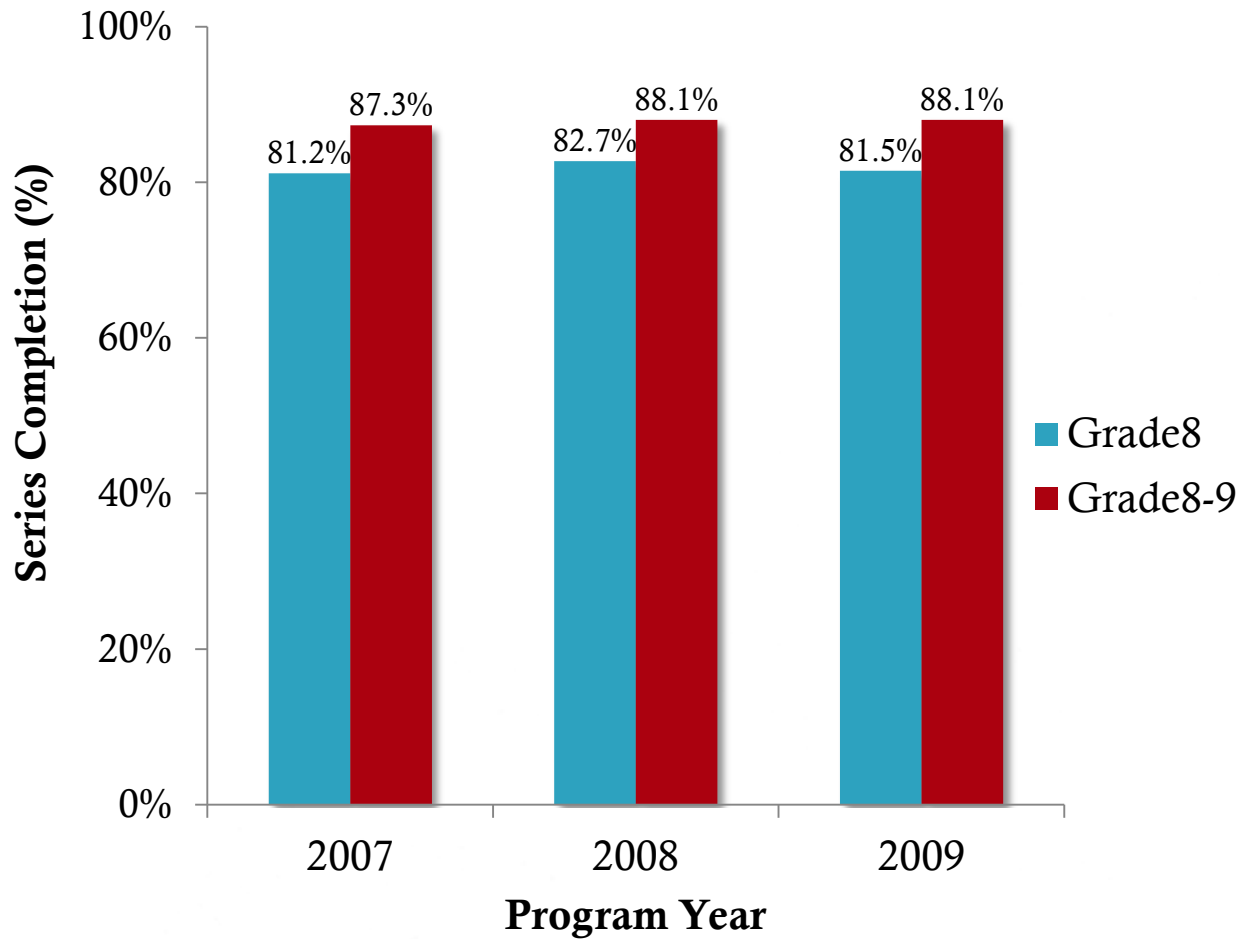
**Table 1. Characteristics of study cohort (N=55,798)**

<b>Characteristic</b>	<b>Percent (%)</b>
<b>Socio-demographics</b>	
<i>Age (years), mean (SD)</i>	13.2 (0.3)
<i>Follow-up (years), mean (SD)</i>	2.6 (0.8)
<i>Deaths during follow-up</i>	0.02
<i>Place of residence</i>	
Urban	84.5
Rural	15.5
Missing	0.1
<i>Income Quintile</i>	
1 (low)	14.4
2	18.7
3	22.7
4	22.9
5 (high)	21.0
Missing	0.4
<b>Vaccination History</b>	
<i>Mandatory Vaccines</i>	
Mandatory Vaccines	98.7
Measles, mumps, rubella (MMR)	99.1
Diphtheria, tetanus, pertussis (DTP)	99.1
<i>Optional Vaccines</i>	
Optional Vaccines	74.4
Hepatitis B	86.7
Meningococcal C	79.2
<i>Mandatory and optional vaccines</i>	73.8

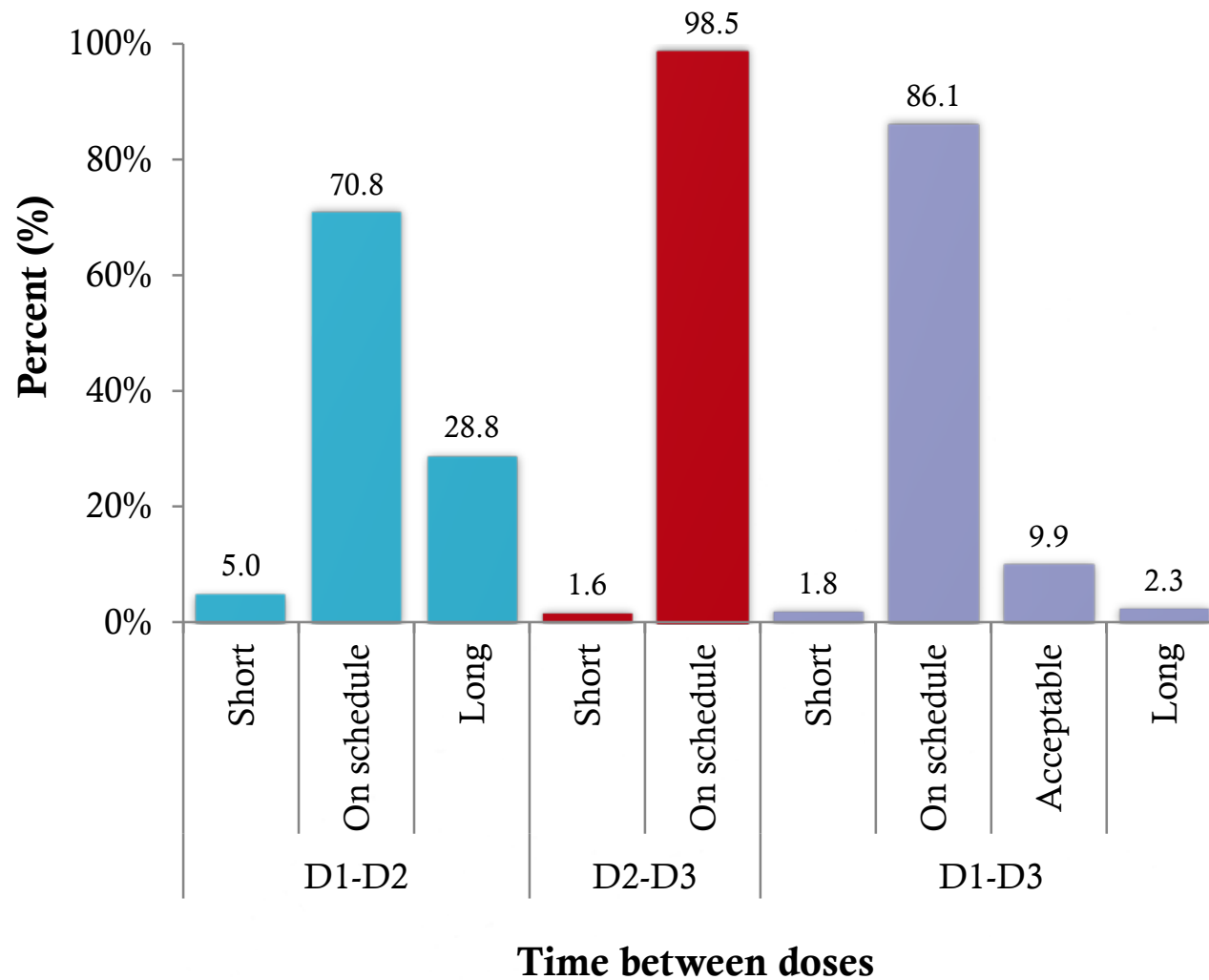




**Figure 2. Number of doses received during the program eligibility period (Grades 8-9), stratified by program year**



**Figure 3. Completion of the three-dose schedule across program year, stratified by eligibility period.**



**Figure 4. Compliance with recommended dosing intervals**

**Table 2. On-time dosing by program year**

Dose 1-2			
<i>Short</i>	0.2	0.2	1.0
<i>On schedule</i>	85.7	82.1	43.5
<i>Long</i>	14.2	17.6	55.4
Dose 2-3			
<i>Short</i>	1.2	0.5	3.9
<i>On schedule</i>	89.8	89.0	79.1
Dose 1-3			
<i>Short</i>	1.2	0.5	3.9
<i>On schedule</i>	89.8	89.0	79.1
<i>Acceptable</i>	7.4	7.2	15.4
<i>Long</i>	1.7	3.4	1.6
Overall			
<i>All on schedule</i>	85.6	80.6	42.1
<i>Not on schedule</i>	14.4	19.4	57.9

# Discussion

# Interpretation

- Series completion has consistently been high (~90%)
  - Highest completion reported to date<sup>1-4</sup>
- On-time dosing was also good
  - Previous research (in public systems) reported poorer dose-timing<sup>5,6</sup>
- Exception: delays in dose 2 in the 2009/10 program year
  - Corresponds with H1N1 immunization

(1) Hirth, J.M., et al., *Cancer*, 2012. 118(22): p. 5623-9. (2) Chou, B., et al., *Obstet Gynecol*, 2011. 118(1): p. 14-20. (3) Brotherton, J., et al., *Communicable Diseases Intelligence Quarterly Report*, 2011. 35(2): p. 197-201 (4) Niccolai, L.M., N.R. Mehta, and J.L. Hadler, *Am J Prev Med*, 2011. 41(4): p. 428-33. (5) Sheridan, A. and J. White. *Annual HPV vaccine coverage in England in 2009/2010*. 2012 March 4, 2013 (5) Tan, W., et al., *Vaccine*, 2011. **29**(14): p. 2548-54. (6) Dorell, C.G., et al., *Vaccine*, 2012. **30**(3): p. 503-5.

# Limitations

- Losses to follow-up
- Incomplete follow-up time for 2009 cohort
  - Truncated at March 31 of their Grade 9 year
- Generalizability

# Future Studies

- Generalizability
- Clinical implications of:
  - Excess doses
  - Off-schedule dose timing



# Conclusion

Delivery of the HPV vaccine through a publicly funded, school-based program is enabling the vast majority of girls who initiate the vaccination series to successfully complete it as recommended.

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Thank You!

# Back-Up Slides

# Cohort Definition

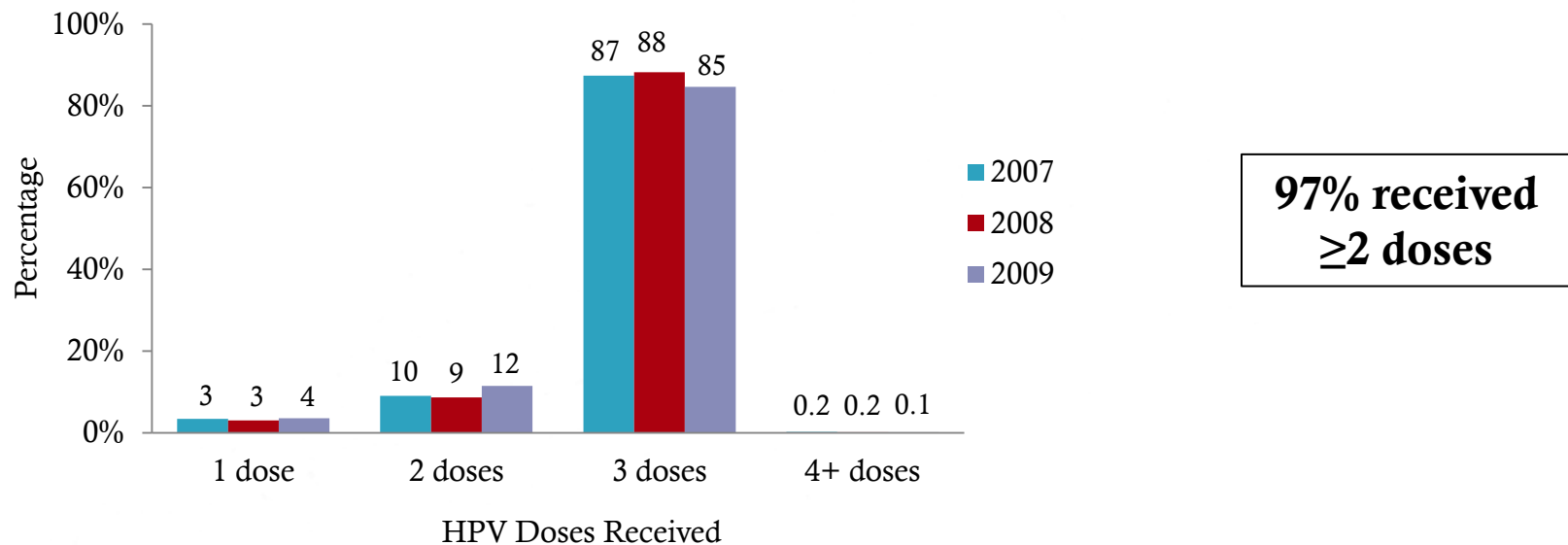
<b>Conceptual Definition: Grade 8 Year</b>	<b>Operational Definition: Birth Year</b>
<b>2007-08</b>	<b>1994</b>
<b>2008-09</b>	<b>1995</b>
<b>2009-10</b>	<b>1996</b>

**Accuracy: 96.4%**

# Two doses may be enough!

Dobson SM, 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): 1793-1802.

Kreimer, AR, et al., *Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine*. Journal of the National Cancer Institute, 2011. **103**(19): 1444-51.



# Description of Dose Intervals

<b>Statistic (days)</b>	<b>Interval</b>		
	<b>Dose 1 to Dose 2</b>	<b>Dose 2 to Dose 3</b>	<b>Dose 1 to Dose 3</b>
<b>Mean (SD)</b>	84.3 (43.9)	126.4 (48.8)	206.5 (60.5)
<b>Median</b>	72.0	119.0	196.0
<b>Mode</b>	63.0	91.0	203.0

## Characteristics of cohort members (N=55,798)

Characteristic	n (%)
<b>Socio-demographics</b>	
<i>Age (years), mean (SD)</i>	13.2 (0.3)
<i>Follow-up (years), mean (SD)</i>	2.6 (0.8)
<i>Deaths during follow-up</i>	13 (0.02)
<i>Place of residence</i>	
Urban	47,130 (84.5)
Rural	8630 (15.5)
Missing	38 (0.1)
<i>Income Quintile</i>	
1 (low)	8,054 (14.4)
2	10,428 (18.7)
3	12,648 (22.7)
4	12,767 (22.9)
5 (high)	11,698 (21.0)
Missing	203 (0.4)
<b>Vaccination History</b>	
<i>Mandatory Vaccines</i>	
Measles, mumps, rubella (MMR)	55,272 (99.1)
Diphtheria, tetanus, pertussis (DTP)	55,316 (99.1)
<i>Optional Vaccines</i>	
Hepatitis B	48,393 (86.7)
Meningococcal C	44,181 (79.2)
<i>Mandatory and optional vaccines</i>	41,158 (73.8)