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Moving forward for better reduction of HPV-Related Diseases and Cancers in Canada

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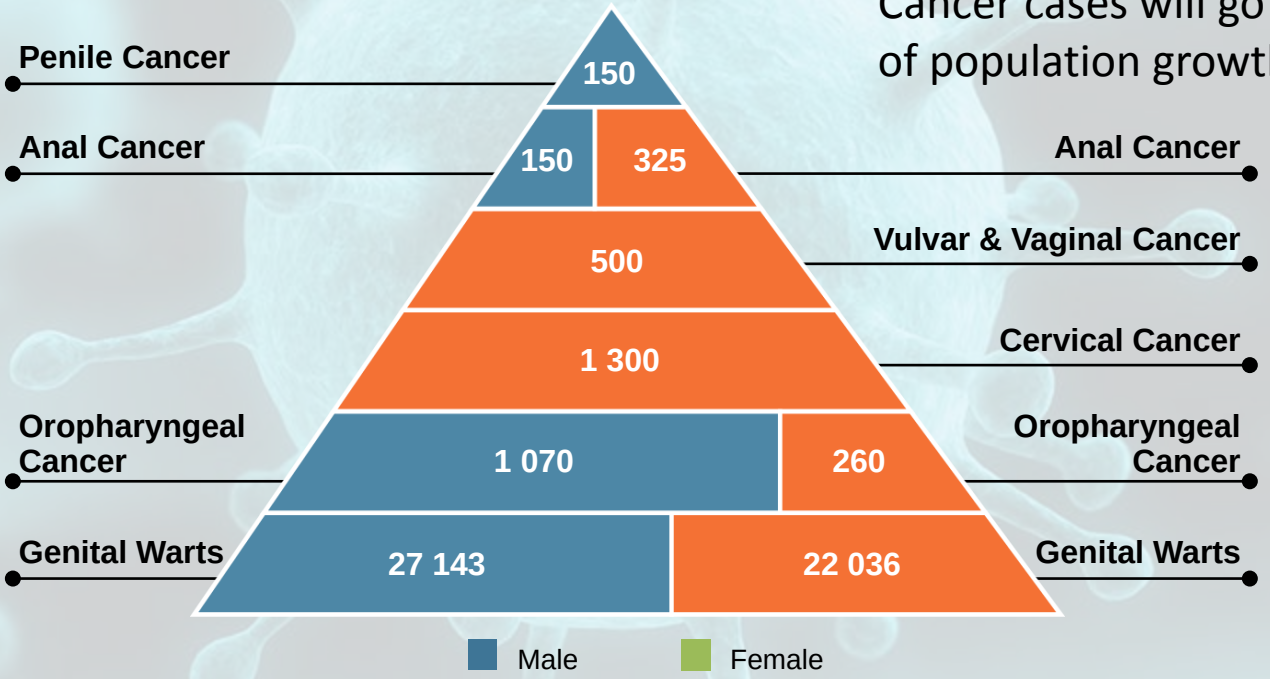
Objectives

- **Recognize the burden of HPV-related diseases and cancers in Canada**
- Summarize the impact of public health vaccination programs in the reduction of HPV related diseases in Canada
- Describe the Canadian efforts to further reduce the burden of HPV associated diseases and cancers
- Discuss the challenges of HPV vaccine public programs in the future in Canada
- Recognize the importance of cohorts and high risk groups not protected by public health program to further reduce the HPV burden

Annual Estimated Number of Cases



Cancer cases will go up because of population growth and aging

Cancer Incidence by Cancer Registry in Canada.

Canadian Cancer Statistics 2016. Special topic: HPV-associated cancers. Canadian Cancer Society, Government of Canada. October 2016.

Merck Canada Inc. 2015.

Canadian Cancer Statistics

2016

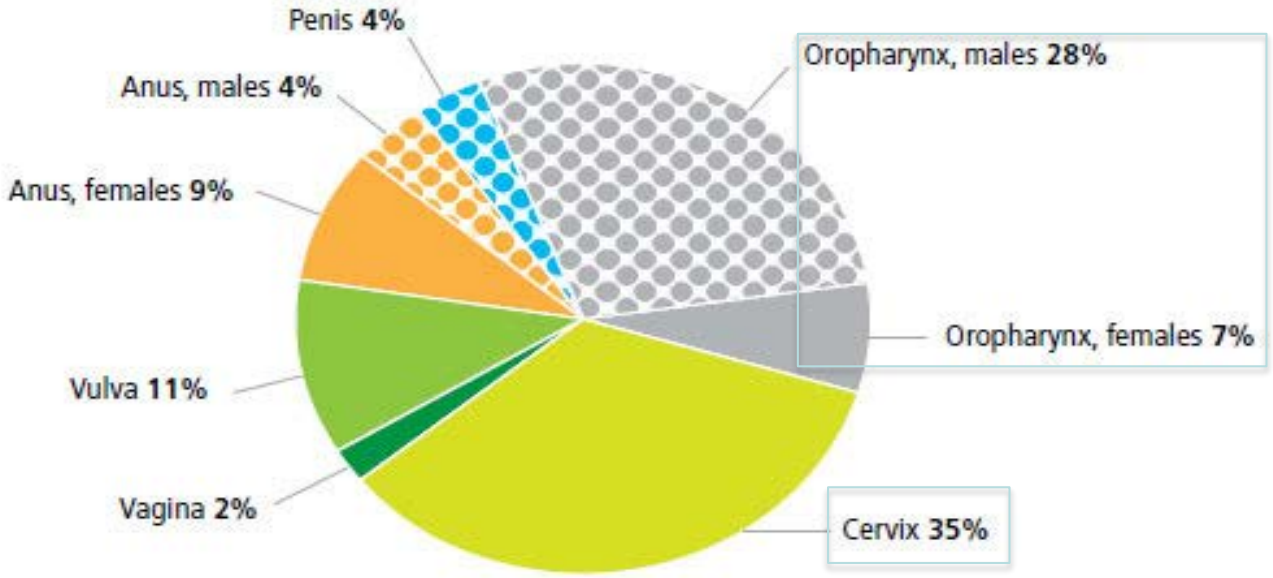
Special topic: HPV-associated cancers

Government of Canada / Gouvernement du Canada

Canadian Cancer Society / Société canadienne du cancer

Produced by Canadian Cancer Society, Statistics Canada,
Public Health Agency of Canada, Provincial/Territorial Cancer Registries
cancer.ca/statistics

FIGURE 7.1 Proportion (%) of new cases for selected HPV-associated cancers*, Canada, 2012†

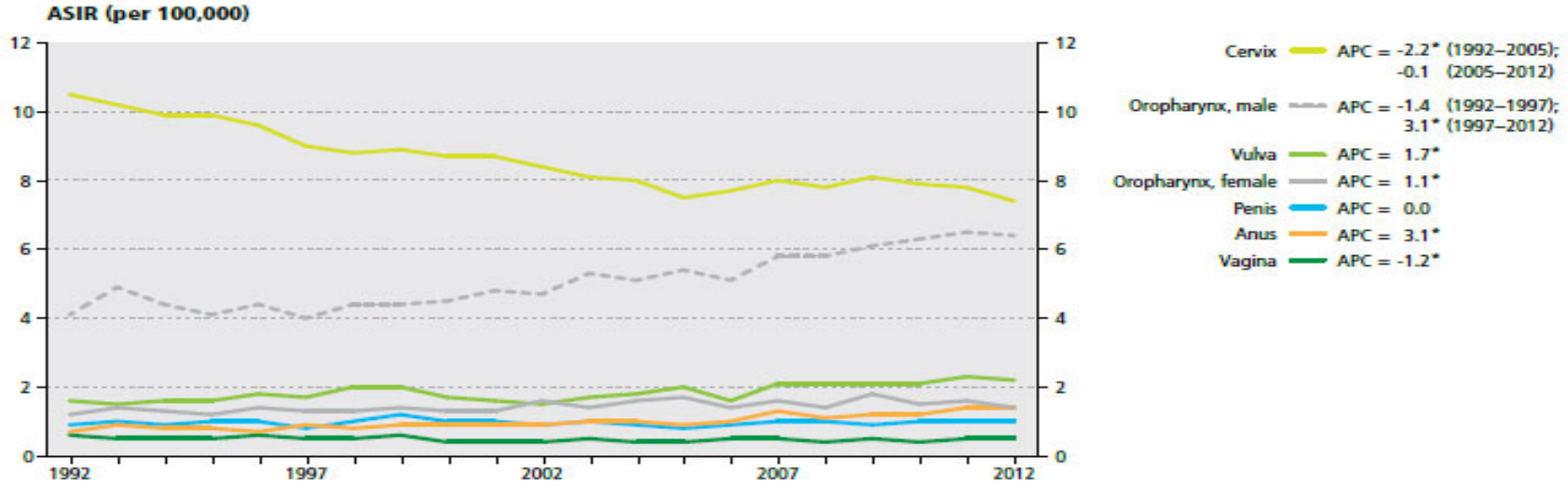


* Includes selected topographies and morphologies. Refer to Table A12 for definitions.

† Quebec data are from 2010.

Analysis by: Health Statistics Division, Statistics Canada
Data source: Canadian Cancer Registry database at Statistics Canada

FIGURE 7.3 Trends in age-standardized incidence rates (ASIR) and annual percent change (APC)[†] for HPV-associated cancers[‡], Canada, 1992–2012[§]



* Significant increase or decrease in APC, $p<0.05$

† APCs refer to 1992–2012 calendar years, unless there was a changepoint, in which case the applicable years are indicated.

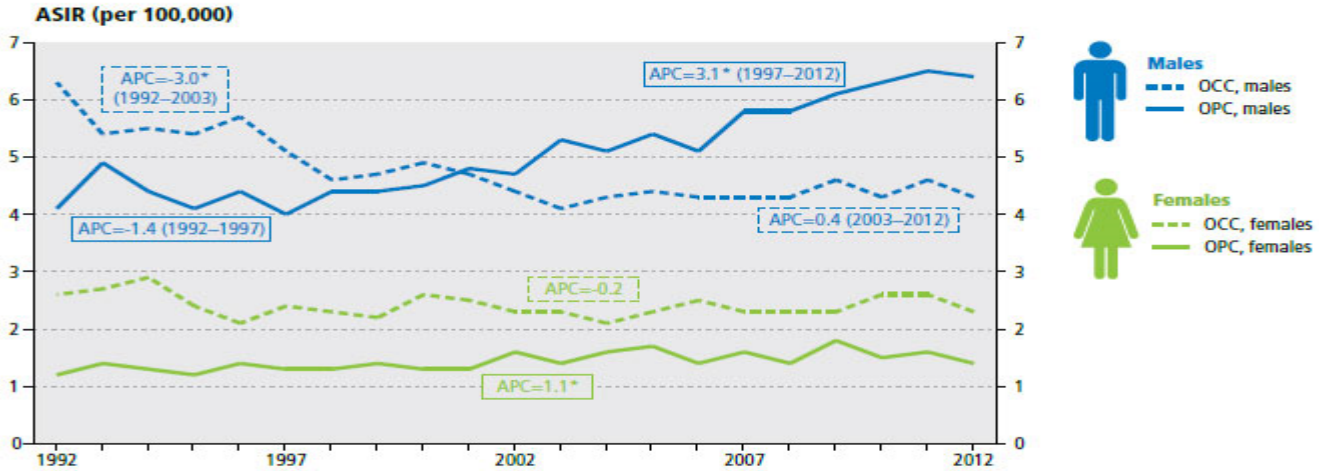
‡ Includes selected topographies and morphologies. Refer to Table A12 for definitions.

§ Actual incidence data were available to 2012 for all provinces and territories except Quebec, for which data were available to 2010 and carried forward thereafter.

Note: Rates are age-standardized to the 2011 Canadian population.

Analysis by: Health Statistics Division, Statistics Canada
Data source: Canadian Cancer Registry database at Statistics Canada

FIGURE 7.4 Trends in age-standardized incidence rates (ASIR) and annual percent change (APC)[†] for HPV-associated (OPC) and non-HPV-associated (OCC) head and neck cancers[‡], by sex, Canada, 1992–2012[§]



OPC=oropharyngeal cancer; OCC=oral cavity cancer

* Significant increase or decrease in APC, $p<0.05$

† APCs refer to 1992–2012 calendar years, unless there was a changepoint, in which case the applicable years are indicated.

‡ Includes selected topographies and morphologies. Refer to Table A12 for definitions.

§ Actual incidence data were available to 2012 for all provinces and territories except Quebec, for which data were available to 2010 and carried forward thereafter.

Note: Rates are age-standardized to the 2011 Canadian population.

Analysis by: Health Statistics Division, Statistics Canada
Data source: Canadian Cancer Registry database at Statistics Canada

Morbidity and Mortality Weekly Report

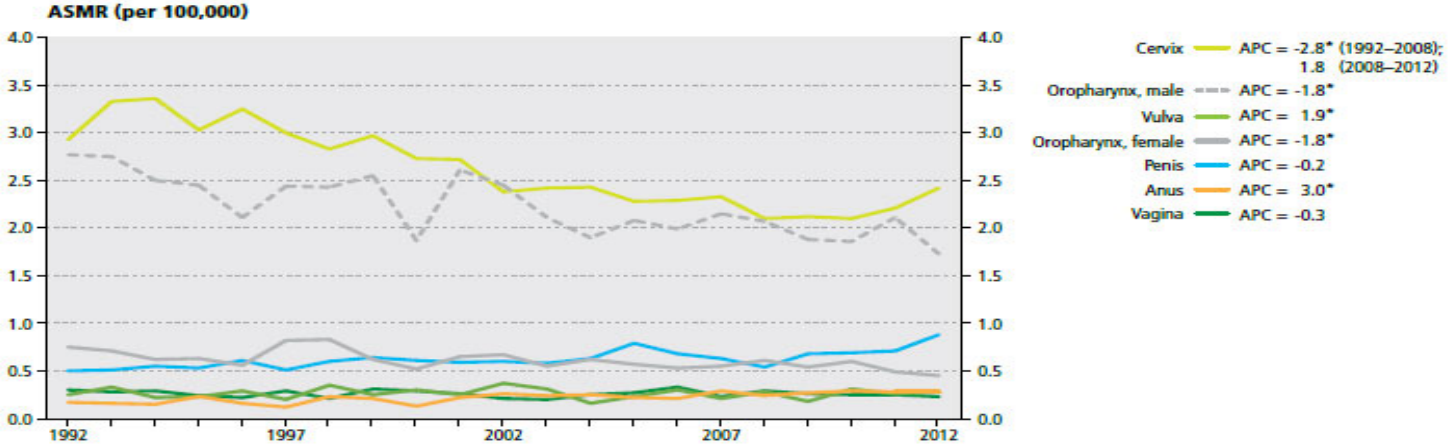
Trends in Human Papillomavirus–Associated Cancers — United States, 1999–2015

Elizabeth A. Van Dyne, MD[1,2]; S. Jane Henley, MSPH[2]; Mona Saraiya, MD[2]; Cheryll C. Thomas, MSPH[2]; Lauri E. Markowitz, MD[3]; Vicki B. Benard, PhD[2]

- *Oropharyngeal squamous cell carcinoma is now the most common HPV-associated cancer.*
- *During 1999–2015*
  - *cervical carcinoma incidence rates decreased 1.6% per year,*
  - *and oropharyngeal SCC incidence rates increased*
    - *2.7% per year among men and*
    - *0.8% per year among women*

MMWR Sept 2018.. https://www.cdc.gov/mmwr/volumes/67/wr/pdfs/mm6733a2-H.pdf.

FIGURE 7.5 Age-standardized mortality rates (ASMR) and annual percent change (APC)[†] for HPV-associated cancer types[‡], Canada, 1992–2012



* Significant increase or decrease in APC, $p<0.05$

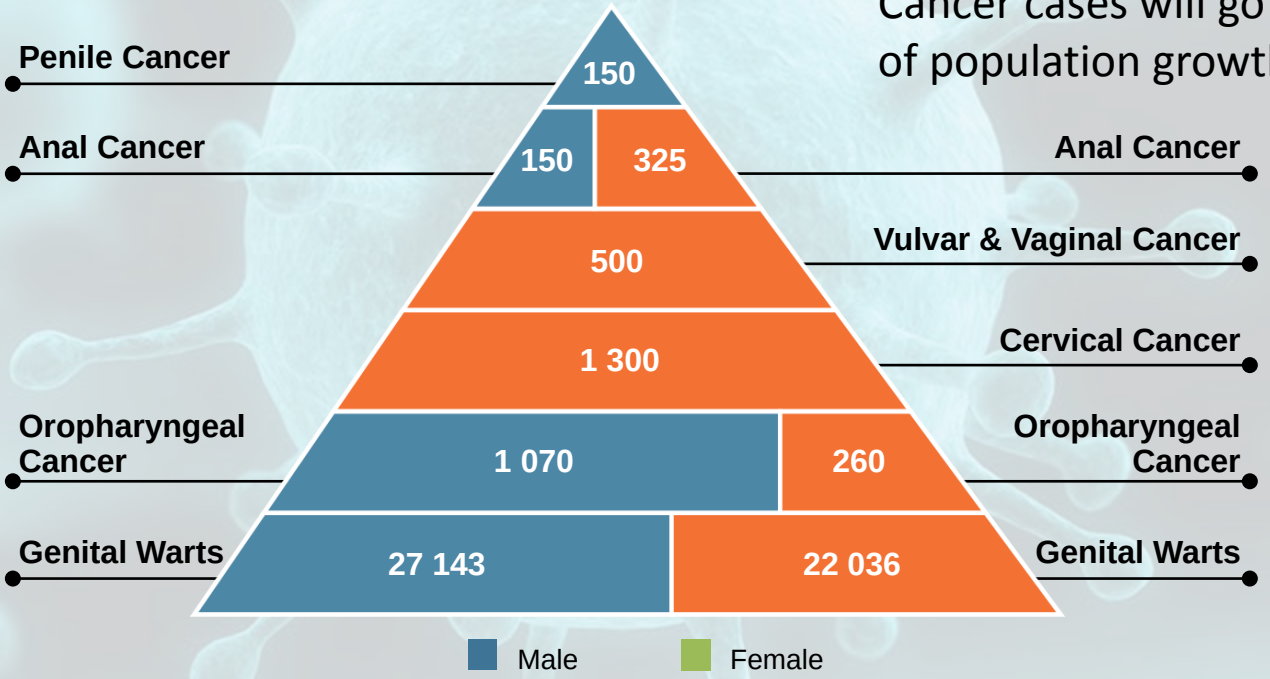
[†] APCs refer to 1992–2012 calendar years, unless there was a changepoint, in which case the applicable years are indicated.

[‡] Refer to Table A13 for definitions. As morphology data were not available for deaths, these include both HPV-associated and non–HPV-associated cancers of each cancer type.

Note: Rates are age-standardized to the 2011 Canadian population.

Analysis by: Surveillance and Epidemiology Division, CCDP, Public Health Agency of Canada
Data source: Canadian Vital Statistics death database at Statistics Canada

Annual Estimated Number of Cases



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Merck Canada Inc. 2015.

AGW in Québec province drug plan patients

- 24,267 persons were diagnosed with at least one episode between 1998 and 2007.
  - ~ 59,000 cases for the total province
- 10% more than one episode
  - 12% of ♂ and 8% of ♀ had more than one episode

Steben M, Ouhoummane N, Rodier C, Brassard P. Temporal Trends in Genital Warts Among Individuals Covered by the Public Prescription Drug Insurance Plan in the Province of Quebec. Canada, From 1998 to 2007. Journal of Lower Genital Tract Disease: April 2013 - Volume 17 - Issue 2 - p 147–153

Genital warts and cost of care in England

Sarika Desai, Sally Wetten, Sarah C Woodhall, Lindsey Peters, Gwenda Hughes, Kate Soldan

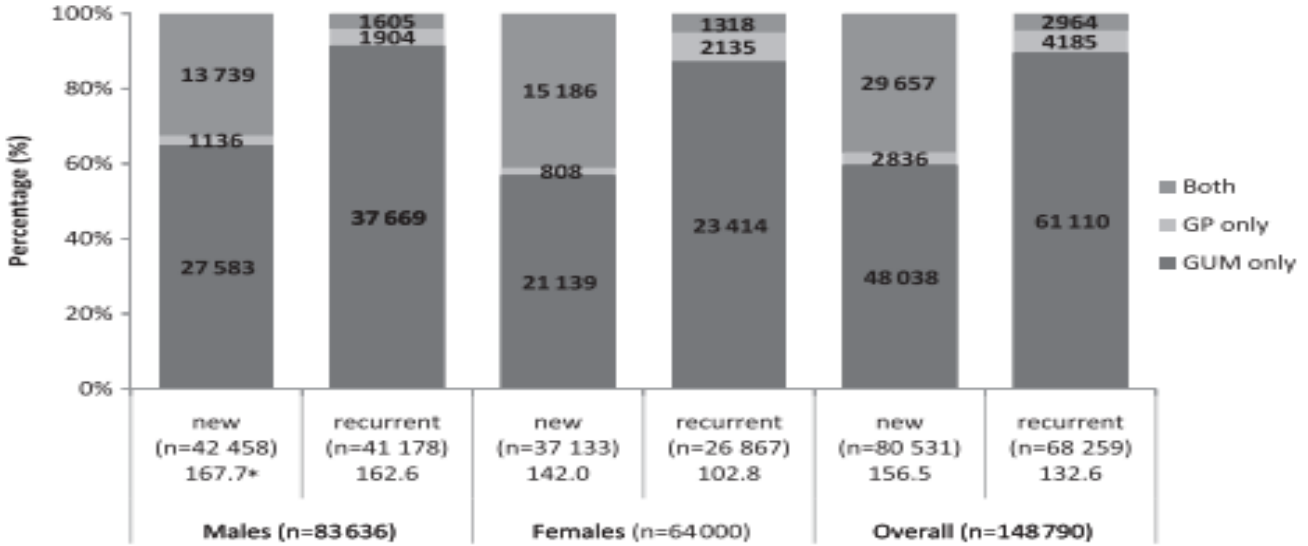
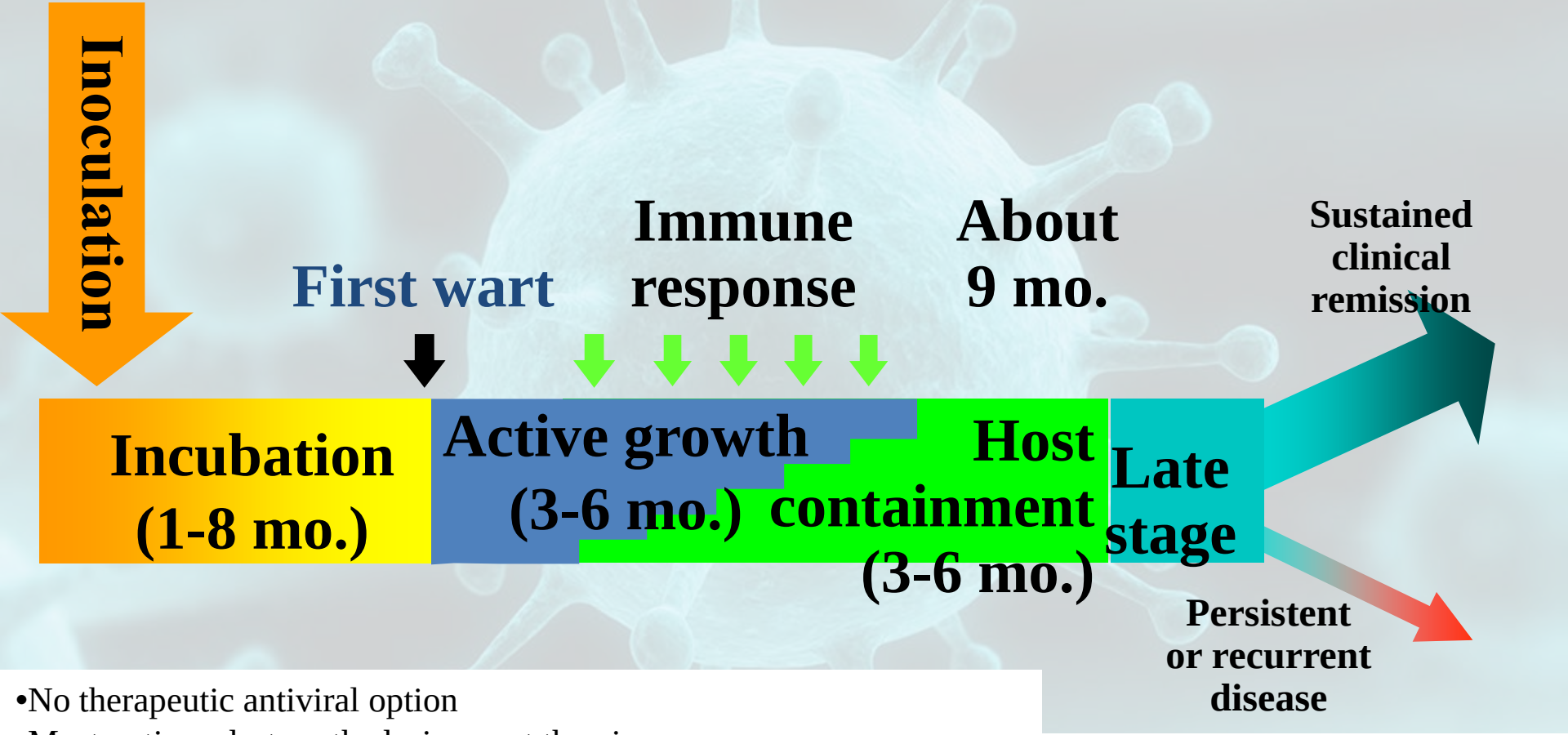


Figure 1 Estimated annual number of genital wart (GW) diagnoses and rate per 100 000 population in each setting by episode type and sex. Numbers are extrapolated to England using Office of National Statistics population data by sex, while overall numbers are age adjusted and do not equal sum of male and female patients. *Rates are per 100 000 population. GP, general practice; GUM, genitourinary medicine.

SF cohorts attack rate acquiring HPV 6-11

- Women
- The 36-month cumulative genital warts incidence was 64.2%

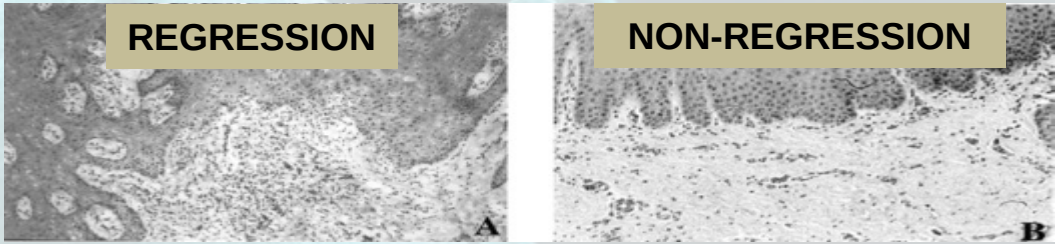
- Men
- The 24-month cumulative genital wart incidence was 57.9%



- No therapeutic antiviral option
- Most options destroy the lesions not the virus
- Immune stimulation may be better treatment?

Modified from Cox then Stanley

Events leading to disapearance of AGW



- 125 patients
- Spontaneous regression in 14 patients
- Biopsies demonstrated a cellular type immune reaction with activation markers
- Conclusion: treatment that would reproduce this reaction would heighten the efficacy of immuno- intervention against HPV infection the genital tract level

Coleman N,Birley HD,Renton AM,Hanna NF,et al. Immunological events in regressing genital warts. (PMID:7801889) American Journal of Clinical Pathology[1994, 102(6):768-774]

Research Article

Cancer Epidemiology, Biomarkers & Prevention

Incidence, Duration, and Reappearance of Type-Specific Cervical Human Papillomavirus Infections in Young Women

Ralph P. Insinga[1], Gonzalo Perez[2], Cosette M. Wheeler[3], Laura A. Koutsky[4], Suzanne M. Garland[5], Sepp Leodolter[6], Elmar A. Joura[6], Daron G. Ferris[7], Marc Steben[8], Darron R. Brown[9], Elamin H. Elbasha[1], Jorma Paavonen[10], and Richard M. Haupt[1]; for the FUTURE I Investigators

Table 4. Reappearance of cervical HPV-6,11, 16, 18, 31, 33, 35, 45, 52, 58, and 59 infections following a period nondetection

HPV type (n = 827)	Proportion of infections reappearing by 12 mo* (95% CI)	Proportion of infections reappearing by 24 mo* (95% CI)	Proportion of infections reappearing by 36 mo* (95% CI)
HPV-6 (n = 89)	0.0 (–)	1.7 (0.2-11.2)	16.1 (5.6-41.1)
HPV-11 (n = 11)	9.1 (1.3-49.2)	9.1 (1.3-49.2)	9.1 (1.3-49.2)
HPV-16 (n = 162)	6.6 (3.6-11.9)	7.5 (5.2-13.3)	11.0 (6.1-19.4)
HPV-18 (n = 70)	5.8 (2.2-14.8)	8.8 (3.5-20.8)	8.8 (3.5-20.8)
HPV-31 (n = 112)	6.8 (3.3-13.7)	6.8 (3.3-13.7)	6.8 (3.3-13.7)
HPV-33 (n = 33)	3.0 (0.4-19.6)	7.9 (1.9-29.0)	7.9 (1.9-29.0)
HPV-35 (n = 26)	0.0 (–)	0.0 (–)	0.0 (–)
HPV-45 (n = 53)	3.8 (1.0-14.3)	3.8 (1.0-14.3)	3.8 (1.0-14.3)
HPV-52 (n = 100)	6.4 (2.9-13.6)	6.4 (2.9-13.6)	6.4 (2.9-13.6)
HPV-58 (n = 55)	2.3 (0.3-15.4)	2.3 (0.3-15.4)	2.3 (0.3-15.4)
HPV-59 (n = 116)	5.4 (2.5-11.7)	7.5 (3.4-16.0)	7.5 (3.4-16.0)

*These monthly intervals refer to time from the date of the second negative cervical swab following the initial infection. The actual time from infection nondetection corresponding to these data is therefore ~8 mo longer (is 9-21, 21-33, and 33-45 mo following nondetection).

Is there value in immunizing people who have/had infections or lesions?

- Antibodies are
  - Type specific
  - Not present in the long term
  - Not protecting against reinfection or new infection
    - Even with the same HPV genotype
  - Decreasing in frequency
    - Females > heterosexual males > men having sex with men

Seroconversion at 36 months after natural infection in males (HPV DNA detection)

Percentage	HPV 6	HPV 11	HPV 16	HPV 18	Overall[a]
All sites	19.3	8.6	3.6	3.4	7.7
Genital	12.5	9.1	4.1	2.6	18.9
Anal	69.2	0	0	9.1	6.3
Oral	0	0	0	0	0

aHPV DNA-positive for HPV 6

- Seroconversion was highest for **HPV 6** (19.3%).
- Overall, seroconversion was highest following **anal HPV 6 infection** (69.2%).
- **HPV persistence** was the only factor found to influence seroconversion (for HPV 6 only).
- **Median time to seroconversion** following any HPV DNA detection at genitals was 257 days.
- Infection at Anogenital **mucosal epithelia** such as the cervix and anal canal (not oral)may induce stronger immune responses compared to infection at keratinized epithelia such as the genital skin

Giuliano A R et al. Seroconversion Following Anal and Genital HPV Infection in Men: The HIM Study. *Papillomavirus Res.* 2015 December 1; 1: 109–115

Men are different from women in their response to HPV

Cumulative probability[1] to acquire HPV, irrespective of age	High in younger ages	High for all ages
Prevalence of antibodies to HPV after natural infection[1,2]	Higher	Lower
Antibody titres in people with circulating HPV antibodies[1]	Higher	Lower
Reinfection or reactivation of infections	Low	High
Protection from future infections in seropositive subjects[6]	Shown	Not shown
Transmission to opposite sex[2,3]	Less easily	More easily
Probability of acquiring oncogenic and non oncogenic virus[3]	Onco> non onco	Similar
Homologous immunity[5]	Shown in women	Not shown
Fertility[3]	Pregnancy loss rate higher in females whose males partners were HPV +	HPV bind sperm and reduce motility.
Oral HPV infection prevalence[4]	high	3 times higher in men than in women. higher in Smokers.

1. Giuliano AR, et al. Incidence and clearance of genital human papillomavirus infection in men (HIM): a cohort study. The Lancet, 377 932–940, 2011
2. Giuliano AR, et al Epidemiology of Human Papillomavirus Infection in Men, in Cancers other than Cervical and in Benign Conditions. Vaccine. 2006 August 10; 26(0 10).
3. Cerqua P, et al. HPV-related diseases in males: a heavy vaccine-preventable burden. J prev med hyg 2013; 54: 61-70
4. Hinrichs JM et al. Strengthening the case for gender-neutral and the nonavalent HPV vaccine. European Archives of Oto-Rhino-Laryngology
5. Ranjeva SI et al. Recurring infection with ecologically distinct HPV types can explain high prevalence and diversity. PNAS 2017 December, 114 (51) 13573-13578
6. Lu B et al. Cancer Res. 2011;71:4778–4784

Objectives

- Recognize the burden of HPV-related diseases and cancers in Canada
- **Summarize the impact of public health vaccination programs in the reduction of HPV related diseases in Canada**
- Describe the Canadian efforts to further reduce the burden of HPV associated diseases and cancers
- Discuss the challenges of HPV vaccine public programs in the future in Canada
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Monitoring the impact of 4vHPV vaccination

Outcomes of interest

- Short-term (months)
  - Prevalence of infection with HPV 6/11/16/18
  - Incidence of genital warts
- Intermediate-term (years)
  - Reductions in incident precancerous or dysplastic cervical, vulvar, vaginal, or anal lesions
  - Reduction in incidence of Juvenile Onset Recurrent Respiratory Papillomatosis (JORRP)
- Long-term (decades)
  - Incidence of cervical, vulvar, vaginal, or anal cancers

REVIEW ARTICLE

A Review of the Impact and Effectiveness of the Quadrivalent Human Papillomavirus Vaccine: 10 Years of Clinical Experience in Canada

Steben M. et al., JOGC 2018

Impact and effectiveness of the qHPV vaccine: a systematic review of 10 years of real-world experience

- Systematic review on the impact of 4vHPV vaccination on:
  - HPV infection
  - anogenital warts
  - cervical cytological and histological abnormalities

- 1 January 2007- 29 February 2016: PubMed and Embase databases
  - 58 publications, 9 countries

- More than 205 million doses of 4vHPV vaccine had been distributed worldwide as of 31 December 2015.

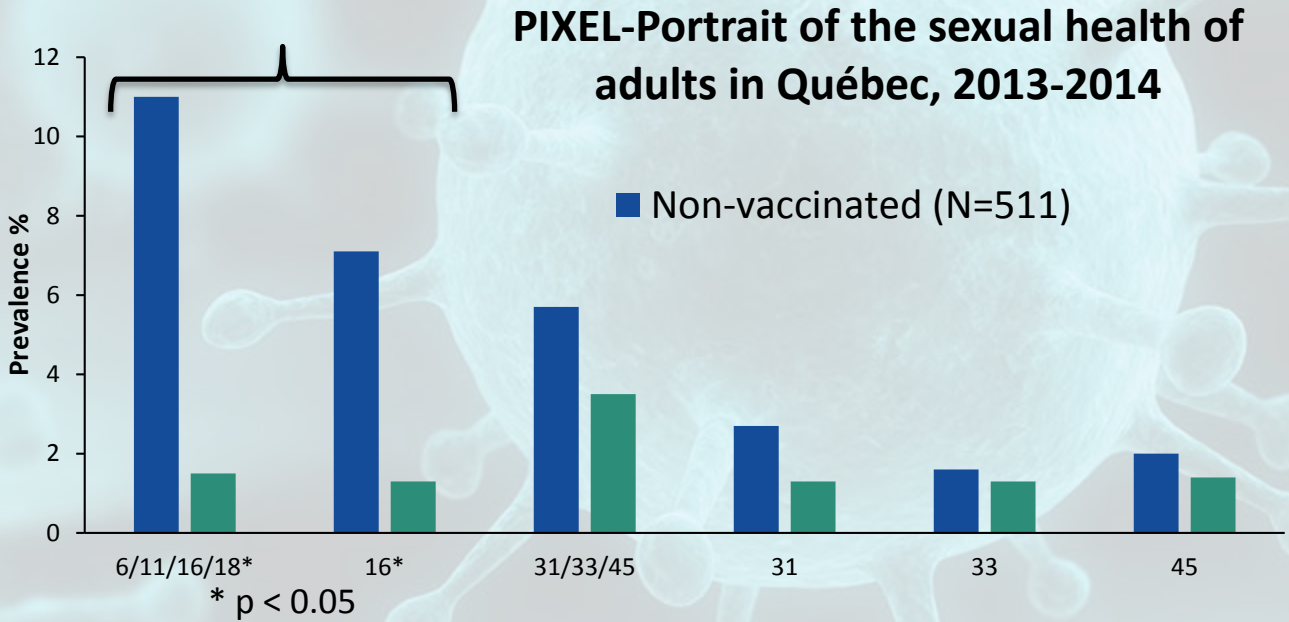
Table 1. Characteristics of records included in the review

Record	Publication	Level of evidence[a]	Outcome	Province or territory	Study design and data sources	Target population	Endpoint and measure of effect	Estimated qHPV vaccine coverage
1	Institut national de santé publique du Québec (INSPQ), 2016[25]	II-2	HPV infection	Québec	Prospective, population-based survey; questionnaire and vaginal self-samples	Girls and women aged 17–29; between March 2013 and July 2014	Prevalence of HPV infection by genotype and by vaccination status; proportion	62.3% overall 83.5%: aged 17–19 65.7%: aged 20–22 19.1%: aged 23–23
2	Steben et al. 2014[26]; Steben et al. 2018[27]	II-3	AGWs	Québec	Retrospective longitudinal study; administrative health database	Girls aged ≥9–14 Time periods: pre-vaccine program (2004–2007); post-vaccine program (2009–2012)	Pre- vs. post vaccine program incidence rates of AGWs; proportion	81% girls grade 4; 84% girls grade 9 (2012–2013)
3	Willows et al., 2016[30]	II-2	AGWs	Manitoba	Retrospective, historical matched cohort study; vaccine registry	Girls aged ≥9 vaccinated between September 2006 and March 2013; matched to three unvaccinated girls on the basis of age and area of residence	Development of AGWs by vaccination status; hazard ratio	65% in 2009 to 72% in 2012
4	Guerra et al., 2016[28]	II-3	AGWs	Ontario	Retrospective longitudinal study; administrative health database	Girls and women aged 15 older. Time periods: pre-vaccine program (2004–2007); post-vaccine program (2008–2014)	Pre- vs. post vaccine program incidence rates of AGWs; proportion	51% in 2007–2008 to 80% in 2012-2013[49]
5	Smith et al., 2015[29]	II-3	AGWs and cervical dysplasia	Ontario	Retrospective cohort study; administrative health database	Girls in grade 8 pre-vaccine program (2005–2006–2006–2007) and post-vaccine program (2007–2008–2008–2009)	Incidence rates of AGWs and cervical dysplasia in pre- vs. post vaccine program cohorts; RR	59 % for three doses with extended eligibility from grade 8 to grade 9 in 2008-2010[45]
6	Kim et al. 2016[31]	II-2	Cervical abnormalities	Alberta	Nested case-control study; provincial repositories of vaccination status and Pap test results	Women born between 1994 and 1997, who had at least one Pap test between 2012 and 2015	Incidence rates of cervical dysplasia by vaccination status; OR	44 % had at least one dose of the qHPV vaccine
7	Ogilvie et al., 2015[32]	II-3	CIN	British Colombia	Retrospective, population-based study; provincial cervical cancer program database	Girls and women aged 15–22 between 2004 and 2012. Time periods: pre-vaccine program (2004–2009); post-vaccine program (2010–2012)	Pre- vs. post-vaccine program incidence rates of CIN; IRR	58.1% and 61.7% per year from Sept 2009–2010 (grade 9)

[a]Rated using the ranking of the Canadian Task Force on Preventive Health Care[22]. II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group; II-3: evidence obtained from comparisons between times or places with or without the intervention.

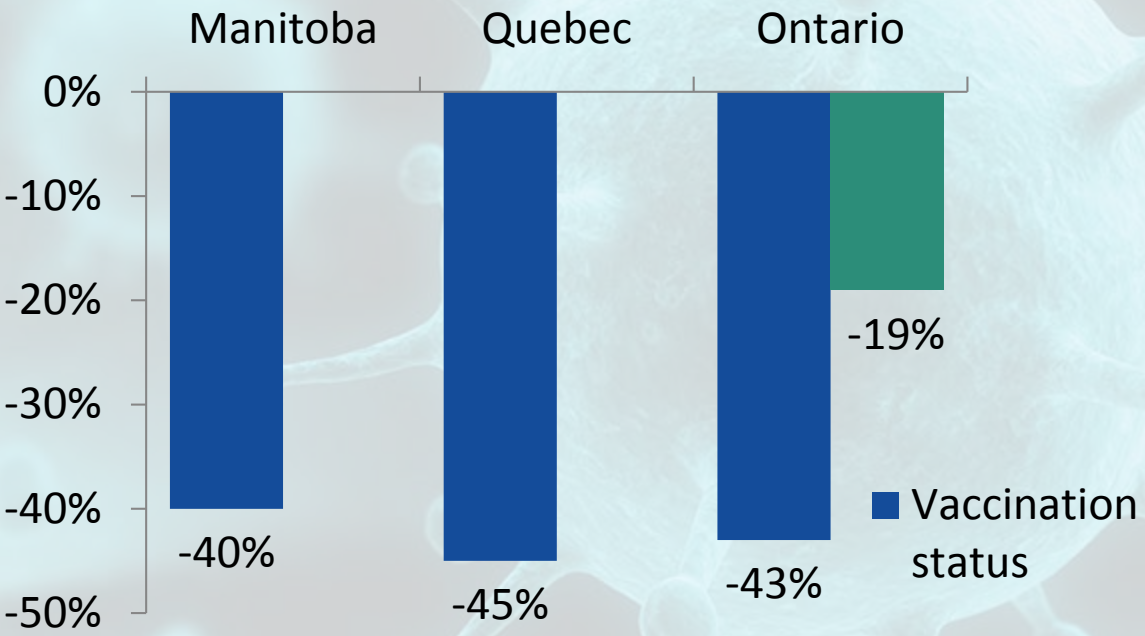
Adapted from Steben et al J Obstet Gynaecol Can 2018

HPV prevalence (%) in 17- to 29-year-old girls and women living in Québec.



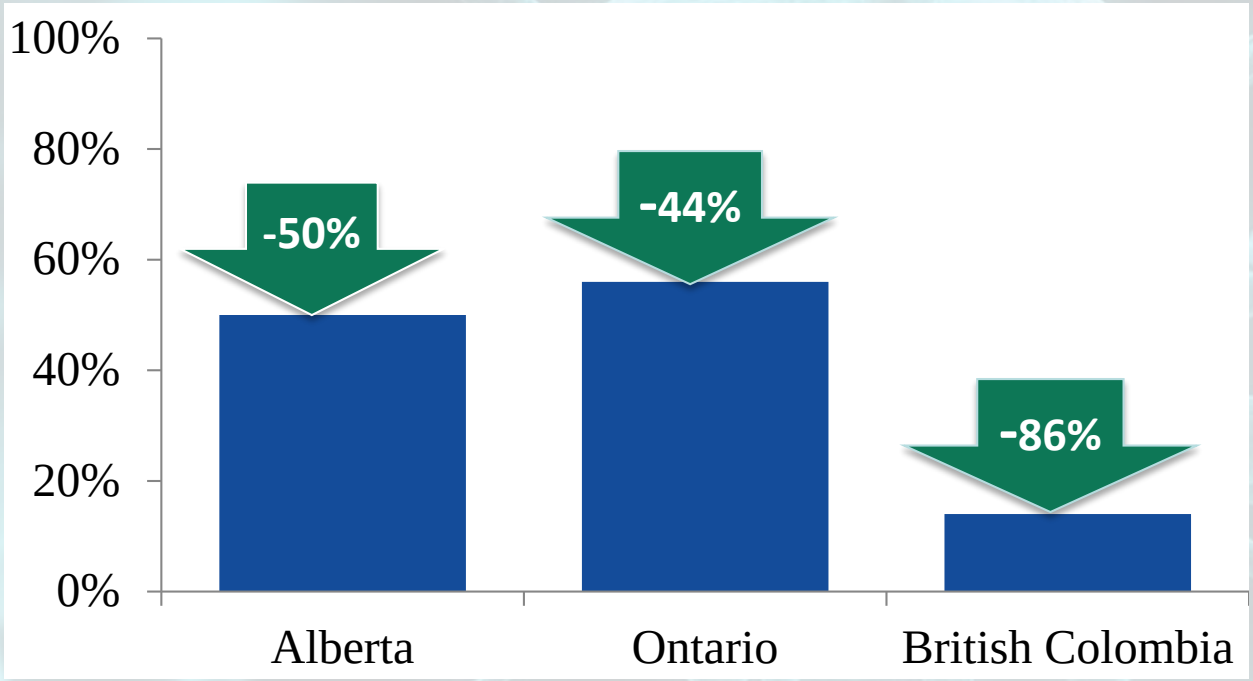
Adapted from Steben et al J Obstet Gynaecol Can 2018

Changes in anogenital warts (%) during the female-only vaccination era in Canada



Adapted from Steben et al J Obstet Gynaecol Can 2018

Changes in risk for cervical abnormalities during the female-only vaccination era



Adapted from Steben et al J Obstet Gynaecol Can 2018

RESEARCH

Quadrivalent human papillomavirus vaccination in girls and the risk of autoimmune disorders: the Ontario Grade 8 HPV Vaccine Cohort Study

Erin Y. Liu MSc, Leah M. Smith PhD, Anne K. Ellis MD MSc, Heather Whitaker PhD, Barbara Law MD, Jeffrey C. Kwong MD MSc, Paddy Farrington PhD, Linda E. Lévesque PhD

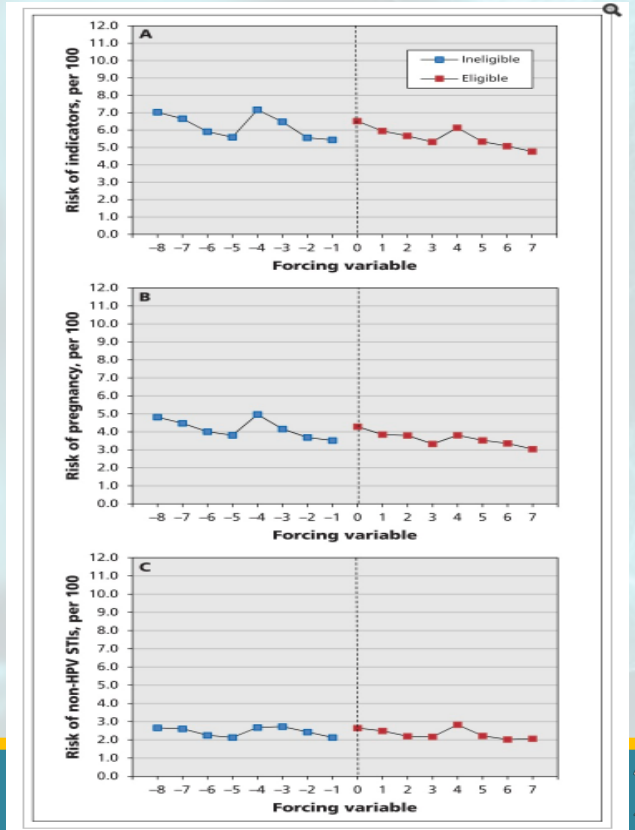
Cite as: *CMAJ* 2018 May 28;190:E648-55. doi: 10.1503/cmaj.170871

RESULTS: The study cohort consisted of 290 939 girls aged 12–17 years who were eligible for vaccination between 2007 and 2013. There was no significant risk for developing an autoimmune disorder following HPV4 vaccination (n = 681; rate ratio 1.12, 95% CI 0.85–1.47), and the association was unchanged by a history of immune-mediated disorders and time since vaccination.

Exploratory analyses of individual autoimmune disorders found no significant risks, including for Bell palsy (n = 65; rate ratio 1.73,95% CI 0.77–3.89), optic neuritis (n = 67; rate ratio 1.57, 95% CI 0.74–3.33) and Graves disease (n = 47; rate ratio 1.55,95% CI 0.92–2.63).

We did not observe an increased risk of autoimmune disorders following HPV4 vaccination among teenaged girls. These findings should reassure parents and health care providers.

Effect HPV vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario grade 8 HPV vaccine cohort.



- «Strong evidence that HPV vaccination does not have any significant effect on clinical indicators of sexual behaviour among adolescent girls»

Absence of Herd protection in males in Canada: Data from two studies

Ontario study[1]

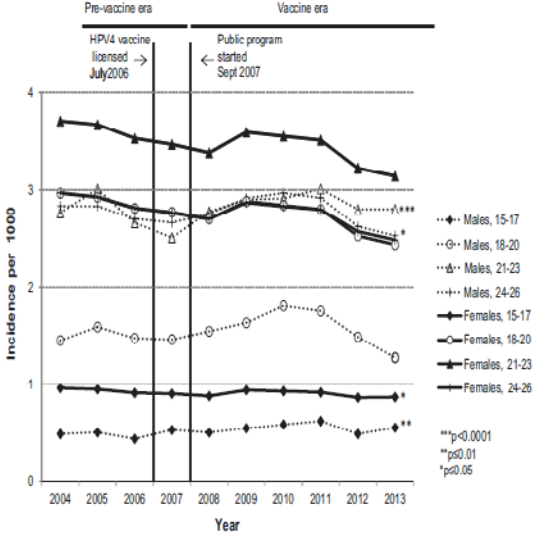


Fig. 2. Annual incident AGWs captured by physician office visits in 15–26 year olds, 2004–2013, for females (adjusted for Pap testing rate) and males (crude). Statistical significance reflects average annual changes in incidence relative to 2004.

Male AGW incidence rates increased an average of 4.1%, 2.8%, and 0.9% per year in 15–17, 21–23, and 24–26 year old males respectively

Quebec study[2]

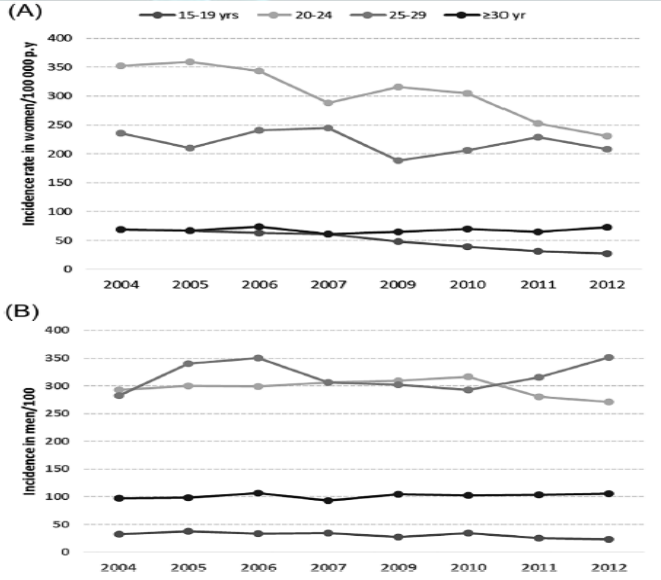


FIGURE 4 AGW Incidence rate by sex and age group, Québec, 2004-2012 (A) women (B) men

Females(20-24yrs) the peak incidence declined from 342.9/100 000 (2006) to 230.2/100 000(2012).

No change over time was observed in the peak incidence among males aged 25-29 years

1. Guerra FM et al. Early impact of Ontario's human papillomavirus (HPV) vaccination program on anogenital warts (AGWs): A population-based assessment. Vaccine 34 (2016) 4678–4683
2. Steben M et al. The early impact of human papillomavirus vaccination on anogenital warts in Québec, Canada. J Med Virol. 2018;90:592–598

Effectiveness of one dose qHPV vaccine against cervical dysplasia

Canada

Effectiveness of one-dose of qHPV vaccine against HSIL and CIN; a data-linkage study in BC

- Aim: to estimate effectiveness of one-dose of qHPV vaccine against HSIL* and CIN2+ in screened young women (YW).
- Data-linkage was performed between the population Cervical Cancer Screening Program (CCSP) and immunization registries in British Columbia, Canada
- Results: **significant protection among YW completely vaccinated** (n=12,910) adjusted RR for HSIL 0.62 (0.49-0.80), CIN2+ 0.50 (0.34-0.74) compared to unvaccinated (n=12,762).
- **No significant protection after one dose** (n=348) against HSIL and CIN2+ was observed

* HSIL: high-grade squamous intraepithelial lesion; CIN2+: cervical intraepithelial neoplasia grade 2 or higher

Donken R et al; Abstract presented at IPV Sydney 2018

Impact on cancers ?

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Letter to the Editor | Full Access

Vaccination protects against invasive HPV-associated cancers

Tapio Luostarinen, Dan Apter, Joakim Dillner, Tiina Eriksson, Katja Harjula, Kari Natunen, Jorma Paavonen, Eero Pukkala, Matti Lehtinen

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Cited by: 4

Impact on cancers

Malignancy	HPV vaccinated women Person yrs	n	Rate (95%CI)	Non-HPV vaccinated women Person yrs	n	Rate (95% CI)
Cervix cancer	65,656	0	-	124,245	8	6.4 (3.2, 13)
Vulva cancer	65,656	0	-	124,245	1	0.8 (0.1, 5.7)
Oropharyngeal cancer	65,656	0	-	124,245	1	0.8 (0.1, 5.7)
Other HPV cancers*	65,656	0	-	124,245	0	-
All HPV associated invasive cancers	65,656	0	-	124,245	10	8.0 (4.3, 15)
Breast cancer	65,656	2	3.0 (0.8,12)	124,245	10	8.0 (4.3, 15)
Thyroid cancer	65,656	1	1.5 (0.2,11)	124,245	9	7.2 (3.8, 14)
Melanoma	65,656	3	4.6 (1.5,14)	124,245	13	10.5 (6.1, 18)
Non-melanoma skin cancer	65,656	2	3.0 (0.8,12)	124,245	3	2.4 (0.8,7.5)

*vaginal carcinoma, anal carcinoma

- Finland populationnal register

Luostarinen, T International Journal of Cancer, 2018

Long term follow-up data for the 4vHPV and 9vHPV vaccine

Ongoing long term follow-up studies: immunogenicity and effectiveness

4vHPV vaccine: no breakthrough cases

- 10 years for boys and girls age 9-15 yo[1]
- 12 years for women age 16-23 yo[2]
- 10 years for men age 16-26 yo[3]
- 10 years for women 24-45 yo[4]

9vHPV vaccine

- 6 years for boys and girls 9-15 yo[5]

1.Ferris DG et al Pediatrics 2017; 2.Kjaer SK et al CID 2018; 3.Goldstone S et al Abstract presented at ASCO 2018; 4.Das R et al Abstract presented at Eurogin 2018; 5.Luxembourg A et al: Abstract presented at IPV 2018

We are only starting to understand the full value of HPV vaccine

PROPHYLACTIC

To prevent new infections and transmission

- Youths and adolescents before sexual debut
- Adult women
  - *To 26, 30,* 45+…
- Males
  - To 18, 50+…
- Infants (EPI)

From Xavier Bosch, ICO, Barcelona

Objectives

- Recognize the burden of HPV-related diseases and cancers in Canada
- Summarize the impact of public health vaccination programs in the reduction of HPV related diseases in Canada
- **Describe the Canadian efforts to further reduce the burden of HPV associated diseases and cancers**
- Discuss the challenges of HPV vaccine public programs in the future in Canada
- Recognize the importance of cohorts and high risk groups not protected by public health program to further reduce the HPV burden

Primary prevention technology

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Institut national

Recommendations for HPV Vaccination in Canada 2016

NACI: National Advisory Committee on Immunization

Females	**2v, 4v or 9v HPV vaccine is recommended for females:** • Immunocompetent **aged 9-14** according to either a 2-dose or 3-dose immunization schedule • Immunocompetent **aged ≥15** according to a 3-dose immunization schedule
Males	**4v or 9v HPV vaccines is recommend for males:** • Immunocompetent **aged 9-14** according to either a 2-dose or 3-dose immunization schedule • Immunocompetent **aged ≥15** according to a 3-dose immunization schedule
General	• HPV vaccines should be administered using a 3-dose schedule in **immunocompromised** populations according to **existing age guidelines** • There is **insufficient evidence** at this time to **recommend,** at a population level, **re-immunization with 9v HPV** vaccine in individuals who have completed an immunization series with another HPV vaccine.

Note the NACI recommendations do not have an upper age limit for vaccination for men or women

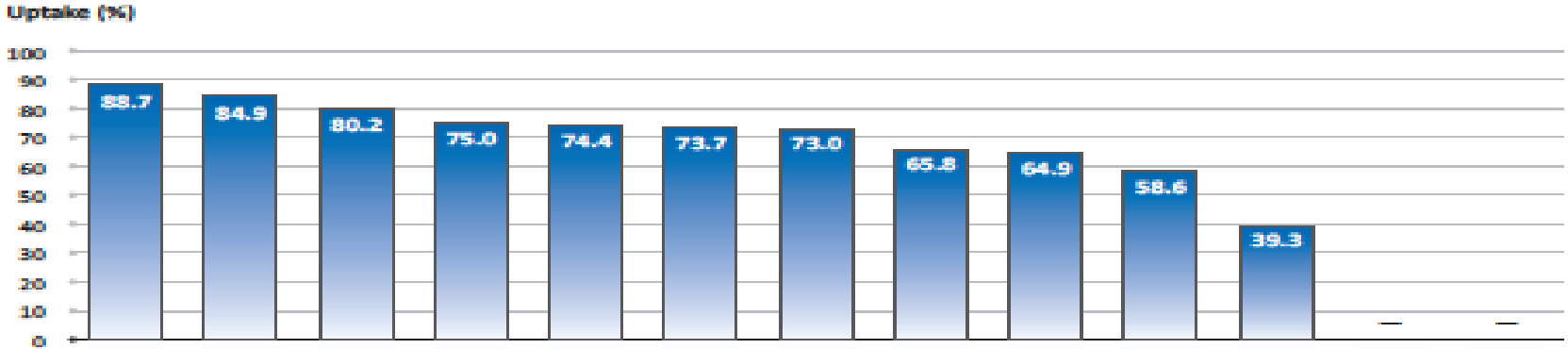
1. Public Health Agency of Canada. An advisory committee statement (ACS) National Advisory Committee on Immunization. Updated Recommendations on Human Papillomavirus (HPV) Vaccines: 9-valent HPV vaccine 2-dose immunization schedule and the use of HPV vaccines in immunocompromised populations. Dec 2016.

Publically Funded HPV Immunization Programs Canada *(as of May 16, 2017)*

Province/Territory	Programs & Eligibility	Uptake Rate
British Columbia ∇	• Males (Sept'15)[23]/Females: Gr. 6 (2 dose)[1] [9v][19] • HR males 9-26yo (Sept'15)[8] [4v], HIV+ females 9-26yo (Sept'16) [9v] • Catch up: females born 1994-2004 (up to 26yo) [4v]	64.8%[15]
Alberta	• Males (Sept'14)/Females: Gr. 5; catch up Gr. 9 (ends '18)[1] [9v – all][20]	64.9%(M);66.3%(F)[22]
Saskatchewan	• Males (Sept'17)[25]/Females: Gr. 6 (2 dose)[1] • HIV+ males 9-17yo (Feb'16)[12]	73.7%[14]
Manitoba	• Males (Sept'16)/Females: Gr. 6 (2 dose)[1]; catch up Gr. 9 boys (2016-19)[2]	58.6%[14]
Ontario	• Males (Sept'16)/Females: Gr. 7 (2 dose)[1]; catch up until Gr. 12[5] • MSM: up to 26yo[18] • Females: Gr. 8 (2016-17)[5]	80.2%[14]
Quebec ++	• Males (Sept'16)/Females: Gr. 4 (2 dose)[1] [9v][21] ; catch up <18yo[3] [4v] • MSM: 9-26yo (Jan'16)[9] [4v] • Males (9-26yo)/Females (18-26yo):Immunosuppressed/HIV+ (Apr'14)[4] [4v]	73%[17]
New Brunswick	• Males (Sept'17)[24]/Females: Gr. 7 (2 dose)[1] [9v][26]	73.0%[14]
Nova Scotia	• Males (Sept'15)/Females: Gr. 7 (2 dose)[1]	75.0%[14]
Prince Edward Island *	• Males (Apr'13)/Females: Gr. 6 (2 dose)[10] • HR males (18-26yo), MSM (all ages), HR females (18-45yo) (Apr'16)[11]	84.9%[14]
NFL & Labrador	• Males Gr 6 (Sept'17)[27]/Females: Gr. 6 (2 dose)[1]	88.7%[14]
NWT	• Females: Gr. 4-6 (2 dose)[1]; catch up to 26yo (3 dose)[6]	39.3%[14]
Yukon	• Males Gr 6 (Sept'17)[28]/Females: Gr. 6, free for 13-18 yo[7] (2 dose)[1]HR males	67% (1st)[16]
Nunavut	• Females: Gr. 6[13]	-

FIGURE 1.3

Percentage of girls in immunizing grade who completed human papillomavirus vaccine series based on provincially/territorially recommended vaccination schedules,† by province/territory — most recent vaccination year



	NL	PE	ON	NS	QC	SK	NB	BC	AB	MB	NT	YT	NU
School year	2013/14	2013/14	2012/13	2013/14	2014/15	2012/13	2014/15	2013/14	2013/14	2014/15	2013/14	—	—
Grade	8	8	Age 13	7	4	Age 13	7	8	5	6	7	—	—
First dose uptake (%)	92.8	90.6	—	88.8	78.2	80.3	>73.0	—	74.2	70.1	46.7	—	—
Second dose uptake (%)	93.7	88.7	—	84.5	74.4	78.4	>73.0	65.8	—	65.8	44.2	—	—

Province/Territory

Table 1. NNV Estimates by case of diseases prevented by the nonavalent vaccine in Canada

Diseases prevented	Nb of cases annually	HPV Prevalence (%)	Proportion Attributed to HPV-9 vaccine types (%)	Nonavalent Vaccine Efficacy (%)	NNV
Women					
Cervical cancer	1,295[1]	100[1]	89.3[4]	96.7[10]	165
Anal cancer	338[1]	92[5]	97.3[8]	74.9[12]	816
Vulvar Cancer	410[1]	25[5]	85.0[7]	96.7[10]	2194
Vaginal Cancer	80[1]	74[5]	80.0[7]	96.7[10]	4036
Any HPV cancers	**2123**				**117**
CIN 2/3	52,000[2]	96.3[4]	85.0[6]	96.7[10]	4
Genital warts	22,755[3]	100[14]	90.0[3]	99.0[11]	9
Any HPV disease	**76,878**				**3**
Men					
Anal Cancer	150[1]	92[5]	97.3[8]	74.9[12]	1937
Genital warts	28,040[3]	100[14]	90.0[3]	89.4[13]	9
Any HPV disease	**28,190**				**9**

International Papillomavirus conference Oct 2-6 2018

- Vaccination of a cohort of 12 years old girls and boy
- Lifetime vaccine protection for the HPV type contained in the vaccine (no cross protection considered)
- Current vaccine recommendations and approved indications in Canada
- Epidemiology of HPV related disease and current screening management remain stable over time

Secondary prevention technology

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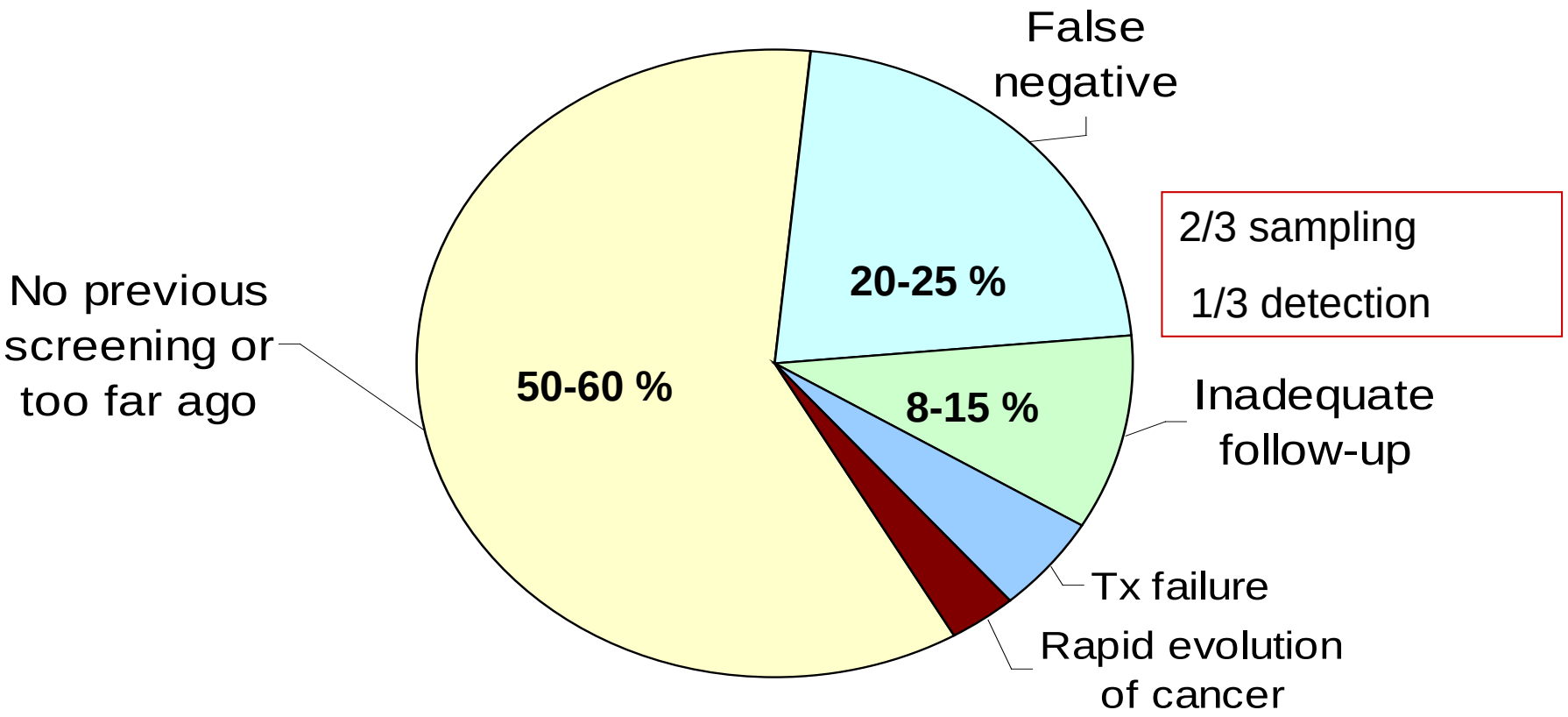
Institut national

Limits of screening with cytology



We will cause more harm than benefit if we dot not change our screening paradigm!

REVIEW ARTICLE

The Expected Impact of HPV Vaccination on the Accuracy of Cervical Cancer Screening: The Need for a Paradigm Change

Eduardo L. Franco,[a,b] Salaheddin M. Mahmud,[a,c,h] Joseph Tota,[a,b] Alex Ferenczy,[d,e,f] and François Coutlée[a,g]

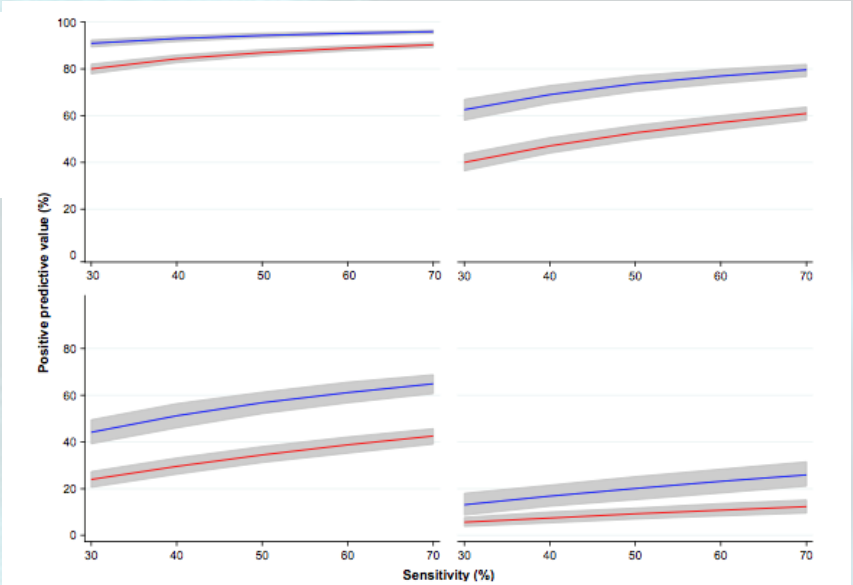


Figure 2. Joint effects of changes in sensitivity, specificity, and cervical lesion prevalence on the positive predictive value of cytology as a primary screening test. The two curves in each graph represent different specificity values of 98% (blue line) and 95% (red line). Each graph represents a different prevalence rate as follows: upper left: 40%, upper right: 10%, lower left: 5%, and lower right: 1%. The gray bands represent 95% credibility intervals (see text and legend for Figure 1 for details). Three of the prevalence scenarios are intended to illustrate situations found in Pap cytology screening in different settings as well as the ones anticipated post-vaccination. A 40% prevalence is shown to represent the situation found in triage following an initially positive referral HPV test.

Accuracy of HPV screening vs. cytology

Screening test	N	Sensitivity (95% CI)	Specificity (95% CI)
Detection of CIN2+			
Cytology (ASC-US+)	25	70.0% (62.5–77.6%)	91.9% (90.3–93.6%)
HC2	31	**90.4% (88.0–92.8%)**	**88.5% (87.0–90.0%)**
Co-testing*	13	94.2% (90.8–97.6%)	87.7% (85.0–90.3%)
Detection of CIN3+			
Cytology (ASC-US+)	21	74.6% (65.6–83.6%)	91.8% (90.0–93.7%)
HC2	**22**	**95.3% (93.3–97.3%)**	**89.0% (87.2–90.8%)**
Co-testing*	12	96.7% (93.7–99.7%)	82.9% (77.1–88.6%)

*Cytology (ASC-US+) and HC2

Updated meta-analysis data from Arbyn et al.[21,22]
In Bosch FX et al. Nature reviews Clinical oncology 2015

Comparison of Prevention Interventions

- Compared to secondary prevention, primary prevention is always:
  - Cheaper
  - More equitable
  - More efficient
  - More accessible

Examples:

Primary prevention	Secondary prevention
Seat belts, alcohol laws and driving laws	Emergency rooms
Condoms	Antiretroviral drugs

QUESTION

Are there any conditions for which we prefer to limit the impact rather than prevent the disease?

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- Describe the Canadian efforts to further reduce the burden of HPV associated diseases and cancers
- **Discuss the challenges of HPV vaccine public programs in the future in Canada**
- Recognize the importance of cohorts and high risk groups not protected by public health program to further reduce the HPV burden

Laziness!

Laziness!

- We had sufficient success to rest on our laurels!
- There are gaps in our successes
- There are unreached populations
- There are threats around the programs

Not changing our screening programs

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But to optimize the value of the vaccine program we need new screening guidelines

- Vaccinated women should start screening at age 30, instead of 25, with HPV test.
- Furthermore, there is a strong rationale for applying longer intervals for re-screening HPV negative women than the currently recommended 5 years.
- For non-vaccinated women and for women vaccinated in their fifteenth year or later, the current protocol should be kept

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com

ELSEVIER

Cervical cancer screening in women vaccinated against human papillomavirus infection: Recommendations from a consensus conference

Paolo Giorgi Rossi[a, b], Francesca Carozzi[c, *], Antonio Federici[d], Guglielmo Ronco[e], Marco Zappa[f], Silvia Franceschi[g]

The Italian Screening in HPV vaccinated girls Consensus Conference group[1]

http://dx.doi.org/10.1016/j.ypmed.2016.11.020

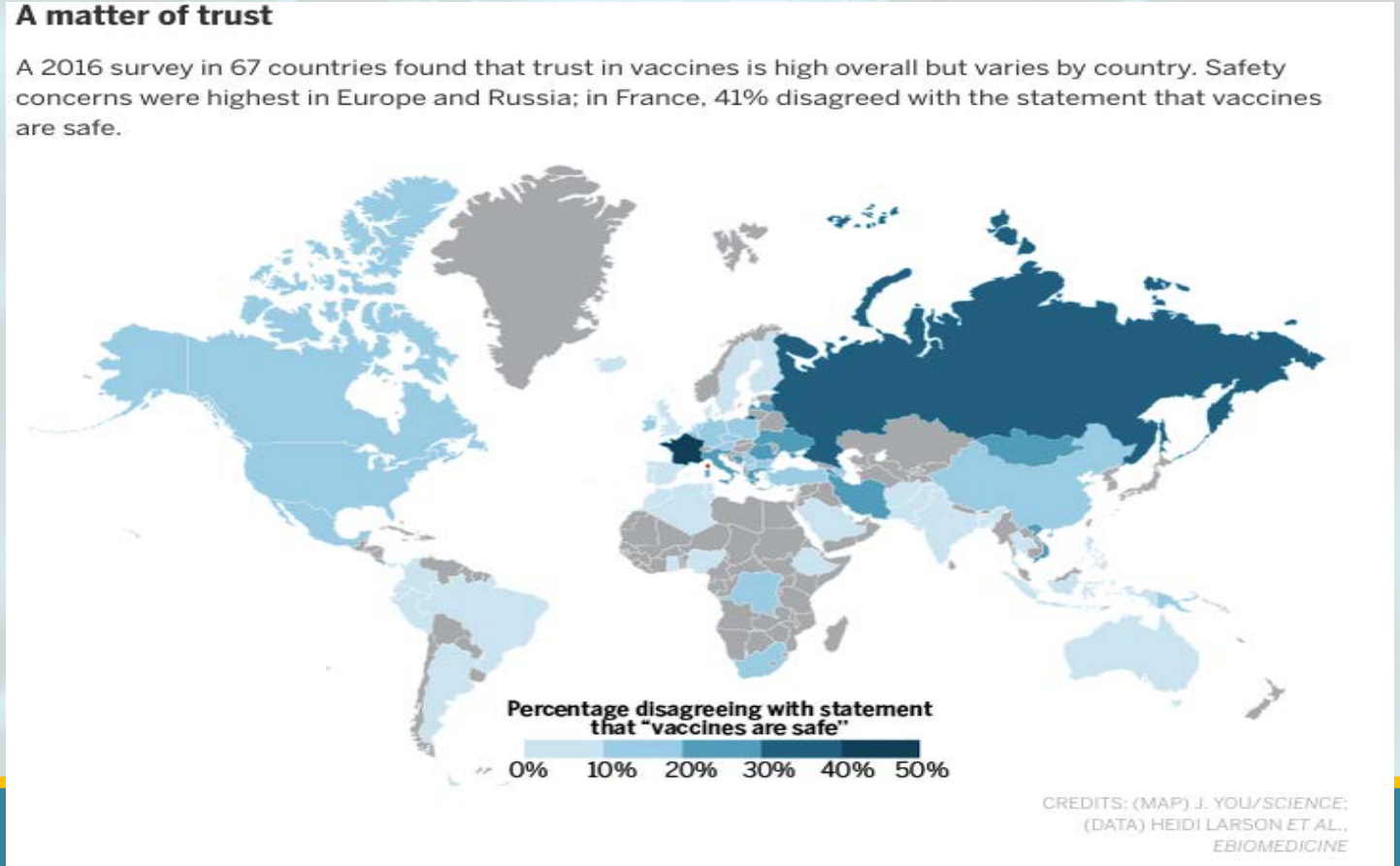
Not gearing up our communication efforts

The effects of pseudoscience

- What will it take to stop the pseudoscience to influence parents/patients mind?
- This is not only for HPV vaccine!
- HPV is seen as the test before more STI vaccines such as HIV, HSV, CT and GC become available
- Cancer is not enough to have some people immunized!

http://scienceblogs.com/insolence/2016/11/18/torturing-more-mice-in-the-name-of-antivaccine-pseudoscience/

Most people trust vaccines in Canada!



Predisposition of the patient to be vaccinated

If a vaccinator meets 4 patients (Quebec example):

are favorable to vaccination

is reluctant or concerned about real or presumed risks

The perception of risk varies from one person to the next

Publications du ministère de la Santé et des Services sociaux, 2013.
Available at: www.publications.msss.gouv.qc.ca/msss/document-000105/.

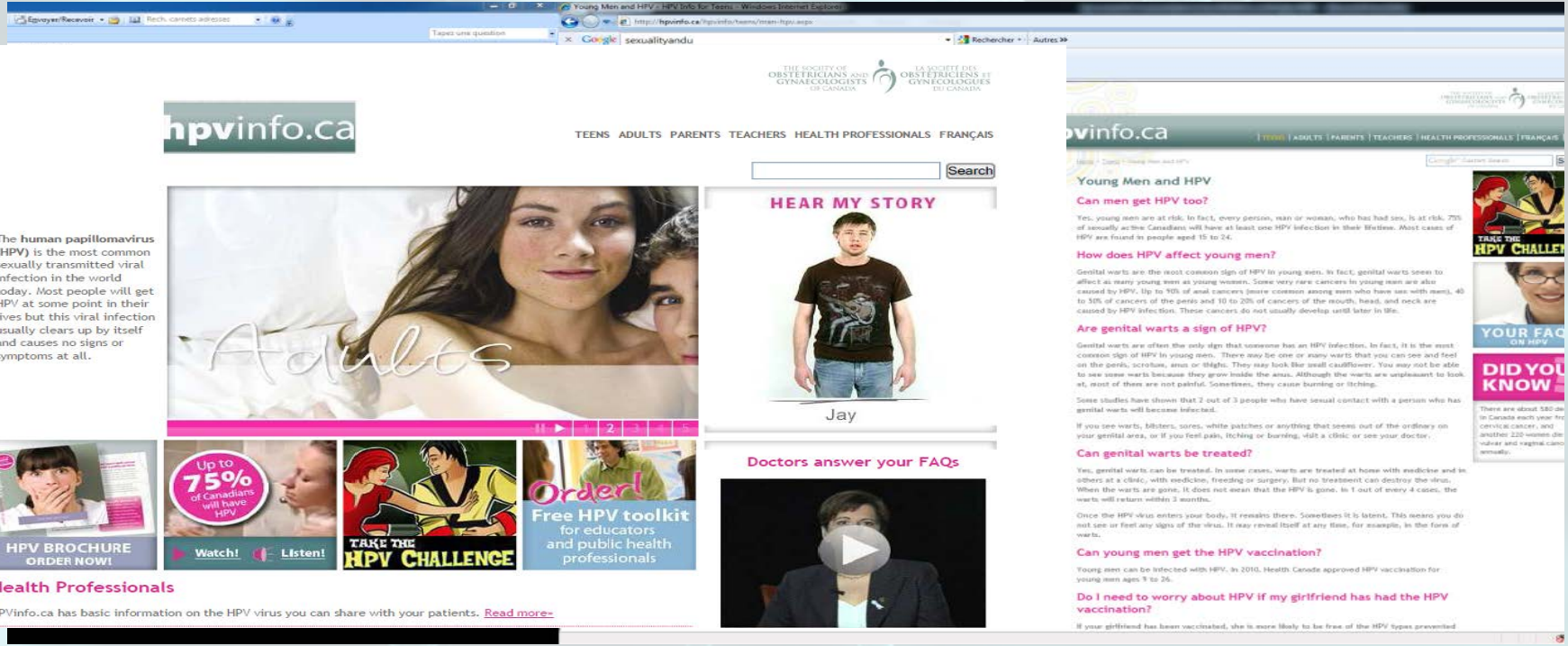
Will we flatly accept that we are loosing the communication war?

-

"I'm sorry, Jeannie, your answer was correct, but Kevin shouted his incorrect answer over yours, so he gets the points."

Wrong articles attract more attention than true articles!

hpvinfo.ca or sexualityandu.ca



HPV Vaccine Counselling

Keep the message simple:

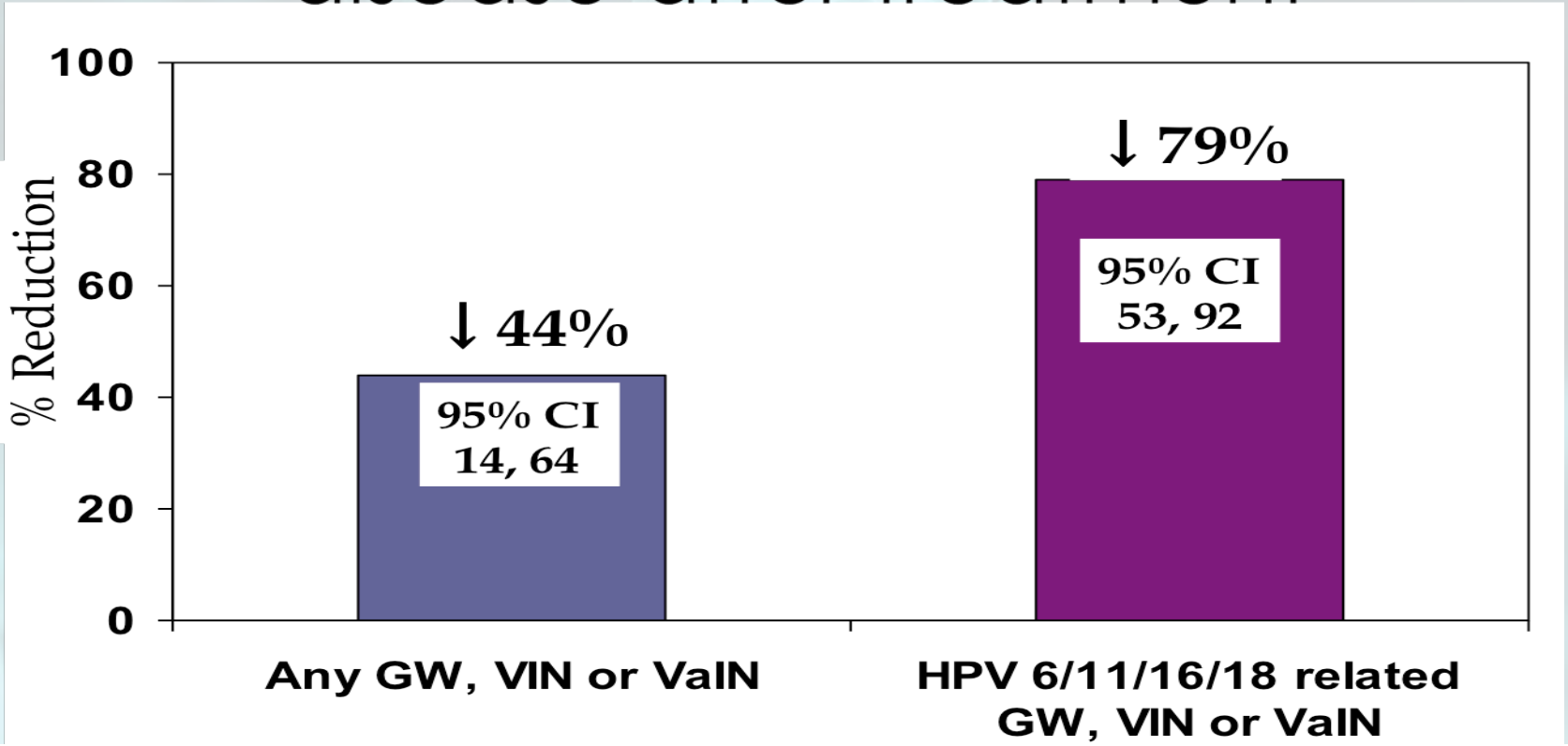
1. effective
2. safe
3. recommended

- Recognize the burden of HPV-related diseases and cancers in Canada
- Summarize the impact of public health vaccination programs in the reduction of HPV related diseases in Canada
- Describe the Canadian efforts to further reduce the burden of HPV associated diseases and cancers
- Discuss the challenges of HPV vaccine public programs in the future in Canada
- **Recognize the importance of cohorts and high risk groups not protected by public health program to further reduce the HPV burden**

Vulvectomy for GW!

- Blocking vagina
  - For sex
  - For her period …
- Blocking urine that had to seep out from folds of the skin
- Vulvectomy was proposed and succeeded

Impact of the vaccine on "new" vulvar disease after treatment*



*Case counting begins post-treatment.

qHPV Vaccine Efficacy in ♀Exposed to Vaccine-related HPV Type Whose Infection has Cleared

(Seropositive, DNA Negative)

Combined Results from 3 Phase III Trials END OF STUDY
MITT-2 Population* ~4 year Follow-up in Women 16-26 years

Endpoint	Quadrivalent Vaccine		Placebo		Efficacy (%)	95% CI
	n	Cases	n	Cases*		
CIN (any grade)	1,243	0	1,283	7	**100**	(29, 100)
External genital lesions	1,268	0	1,301	8	**100**	(40, 100)

*The 15 placebo cases were due to re-infection or re-activation of a latent infection

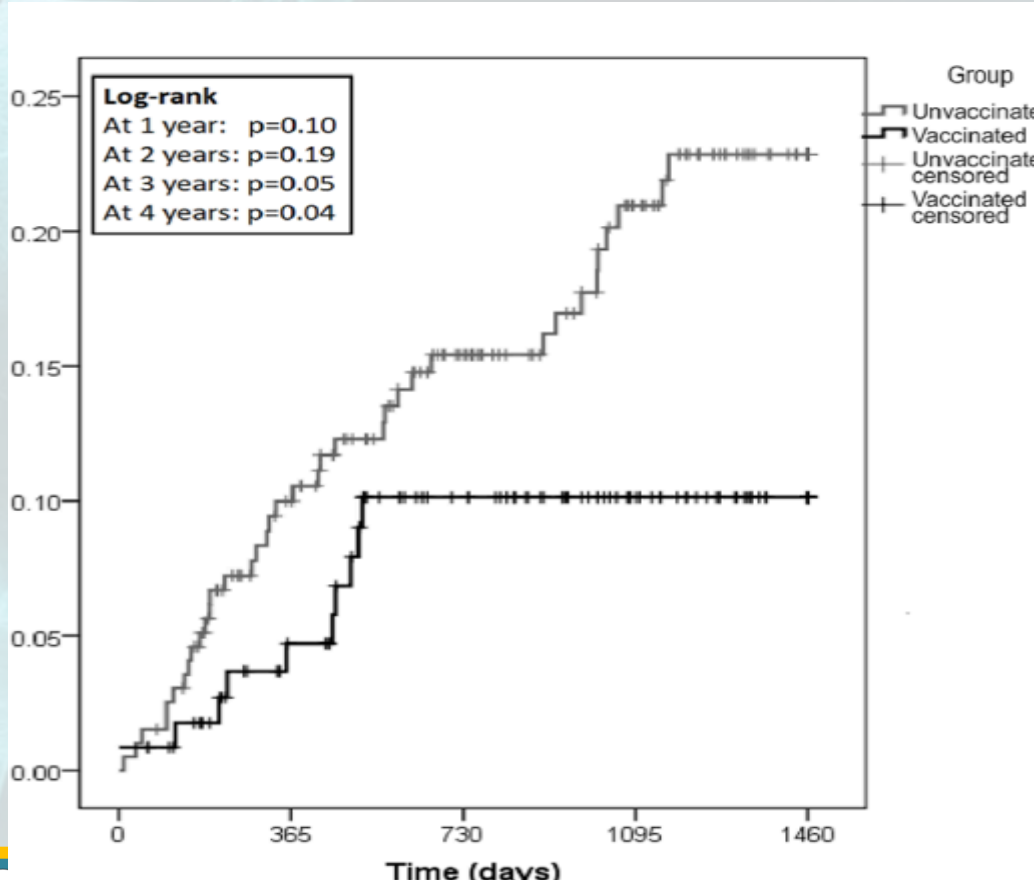
This suggests efficacy against recurrence of disease
with same vaccine HPV types (re-activation/re-infection)

MITT-2 analysis (Protocols 007, 013 and 015), HPV specific naive population; received at least one dose, case counting starts 30 days after dose 1.

Olsson SE, et al. Hum Vaccin 2009; 5(10):696-704.

Prevention of new anal warts

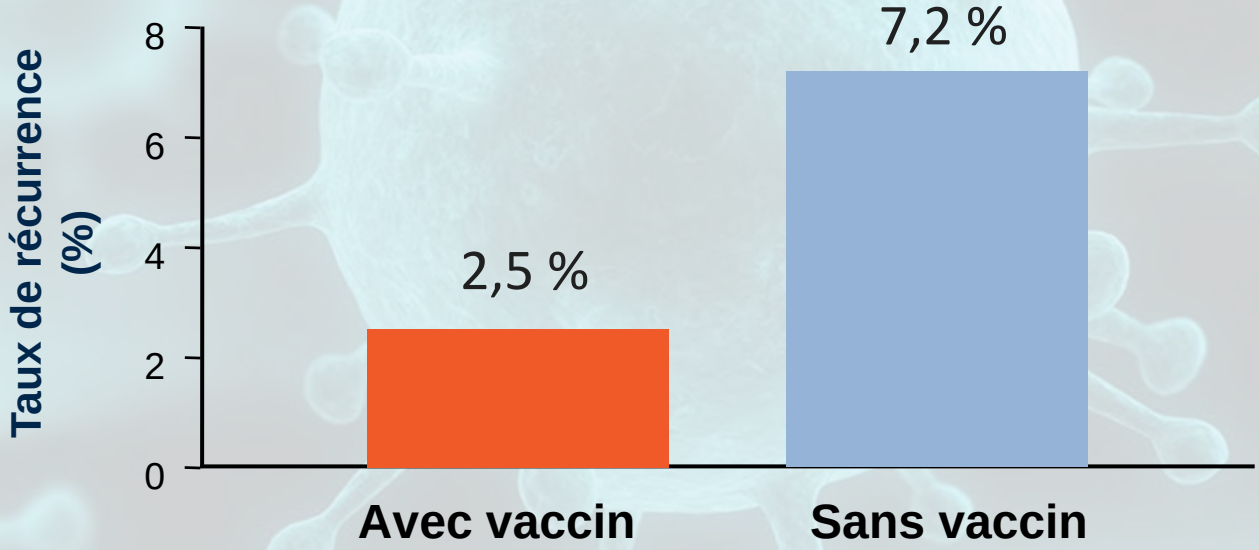
- MSM
- 26 and + years
- Offered vaccine
- Mean age = 42



Citation: Swedish KA, Goldstone SE (2014) Prevention of Anal Condyloma with Quadrivalent Human Papillomavirus Vaccination of Older Men Who Have Sex with Men. PLoS ONE 9(4): e93393. doi:10.1371/journal.pone.0093393

La vaccination après un traitement par LEEP prévient-elle les récurrences chez les patientes porteuses de lésions CIN 2/3?

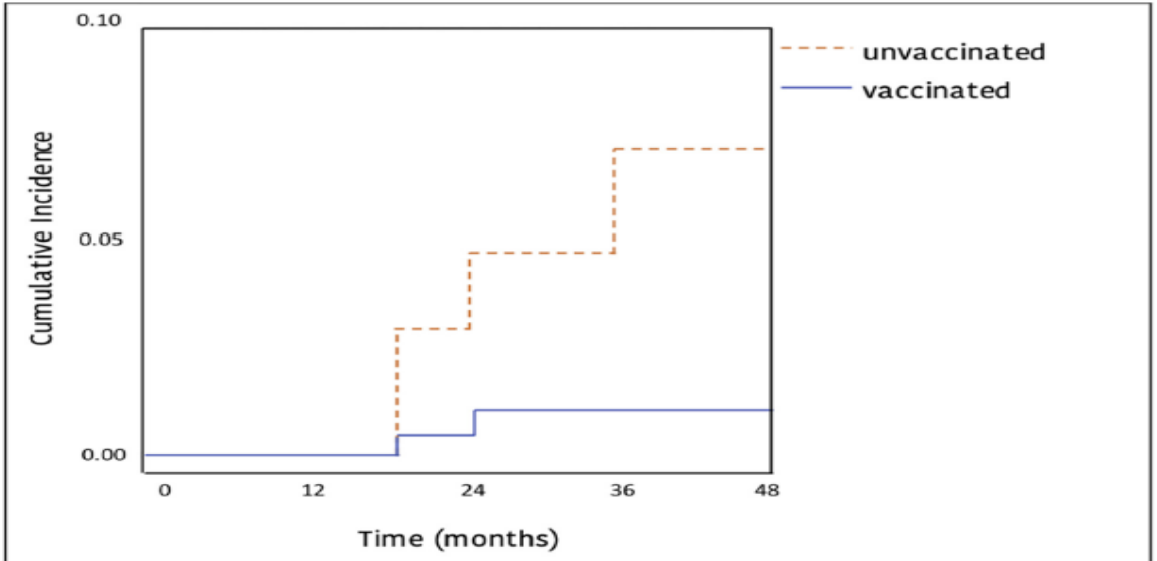
L'ABSENCE de vaccination après un traitement par LEEP était un facteur de risque indépendant de récurrence des lésions CIN 2/3; RR = 2,840 ($p < 0,01$)



LEEP = technique d'excision électrochirurgicale à l'anse; RR = risque relatif

Kang WD, *et al. Gynecol Oncol* 2013;130:264.

Impact of vaccination on disease relapse after cervical conization



CDR irrespective of causal HPV type (CIN2+)			
	V-group	NV-group	% risk reduction in rate with vaccine
No. of evaluable women	172	172	**81,2%** [95% CI: 34,3-95,7]
No. of women with CDR	2	11	
recurrence rate (%)	1.2	6.4	

Legend: CDR: clinical disease relapse; V-group: vaccinated patients; NV-group: unvaccinated patients. Impact of quadrivalent HPV vaccine on incidence of subsequent disease relapse among women who had undergone cervical conization; 95% CI: confidence interval of the estimates.

Clinical disease recurrence (CDR):

- NV-group: 11 cases
- V-group: 2 cases
- Vaccination was associated with significant reduced risk of subsequent HPV-related high-grade CIN after cervical surgery by **81,2%** (95%CI 34,3-95,7)

This does not imply a therapeutic effect of the vaccines but underlines its role as an adjuvant to surgical treatment

We are only starting to understand the full value of HPV vaccine

PROPHYLACTIC

To prevent new infections and transmission

- Youths and adolescents before sexual debut
- Adult women
  - *To 26, 30,* 45+…
- Males
  - To 18, 50+…
- Infants (EPI)

AS PART OF THERAPY

To interrupt reinfections and transmission

- HPV + women in screening
- Post treatments in CIN lesions
- RRP
- GW
- HPV cancer survivors
- Therapeutic / mixed vaccines

Are we delivering to those that need it the most?

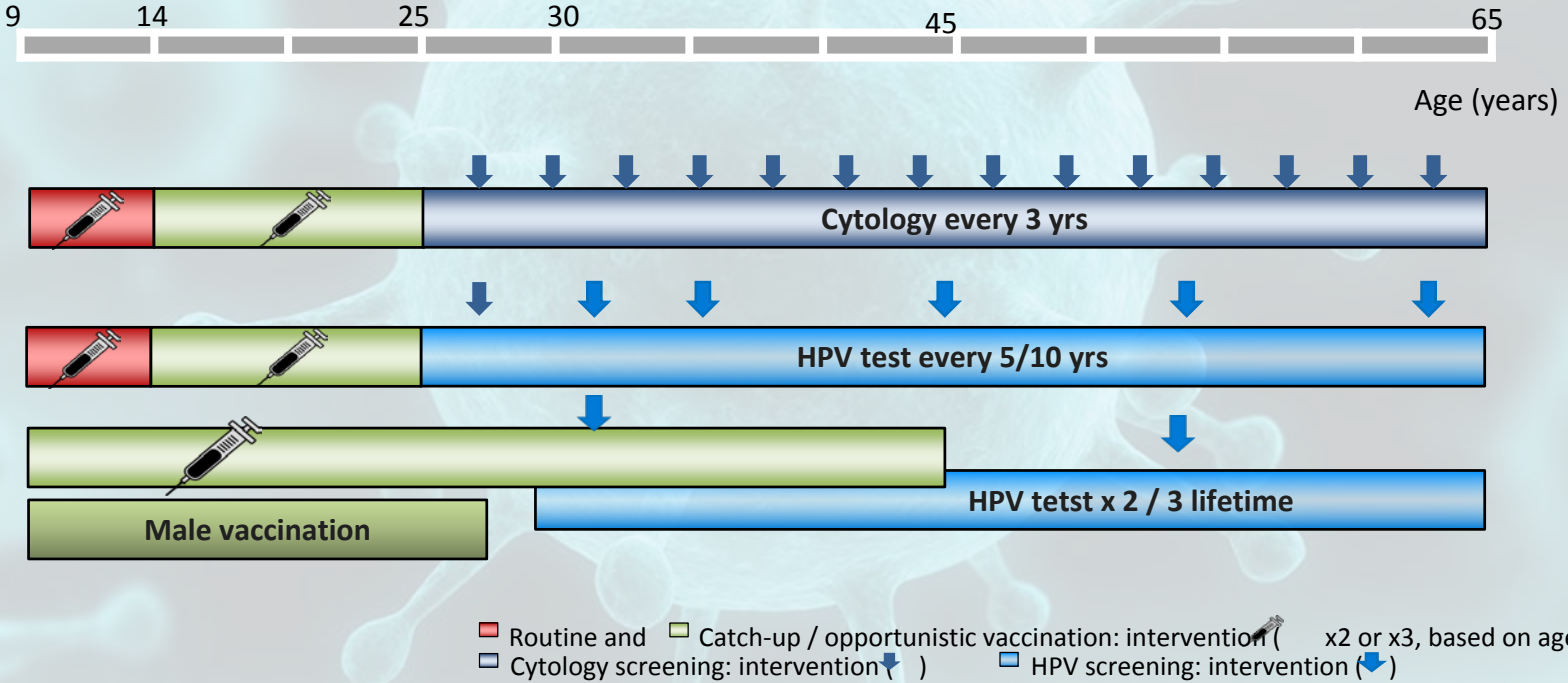
- Are worried well shadowing the situation for most at risk population
  - Vulnerable women: aboriginals, street-involved, IDU, refugees and immigrants, immunocompromised and HIV+
  - Vulnerable men: MSM HIV- as well as HIV+ and other immunocompromised men…

HPV vaccine efficacy in mid-adult

Outcome	4vHPV (to age 45)	2vHPV (to age 55)
'per-protocol'/'according-to-protocol' (HPV negative)		
6M Persistent infection	**VE: 89.6% (95%CI 79.3–95.4)**	**VE: 82.9% (95%CI 53.8–95.1)**
CIN2+	VE: 83.3% (95%CI −37.6–99.6)	VE: 100% (95%CI −100.7–100.0)
External genital lesions	**VE: 100% (95%CI 30.8–100.0)**	NR
'intention-to-treat'/'total-vaccinated-cohort' (irrespective of HPV)		
6M Persistent infection	**VE: 49.0% (95%CI 35.5–59.9)**	**VE: 47.0% (95% CI 25.4-62.7)‡**
CIN2+	VE: 22.4% (95% CI −42.5–58.3)	VE: 29.1% (95% CI −22.5–59.6)‡
External genital lesions	VE: 8.5% (95% CI −126.6–63.4)	NR
Baseline seropositive but HPV-DNA-negative (previous infection)		
6M persistent infection (≥ 1 dose)	**VE: 66.8% (95% CI 3.8-90.5)**	NR
6M Persistent infection or + (3 doses)	NR	**VE: 86.4% (30.1–99.0)**

Bold blue: statistically significant under trial conditions

Current HPV vaccination and cervical cancer screening strategy in developed countries *and proposed FASTER initiative*



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- Therapeutic / mixed vaccines

HIGH RISK GROUPS

To prevent infections, reinfections and transmission

- HIV cohorts
- MSM
- Transplants & immunosuppressed
- Autoimmune patients
- STI clinics
- Partners of HPV+
- Migrants / marginal
- Abused children

From Xavier Bosch, ICO, Barcelona

ENDING THE CERVICAL CANCER EPIDEMIC

Montréal's objectives for 2030

- Achieving 90-90-90 WHO Targets on HPV prevention
- 90% HPV vaccination rate
- 90% HPV testing rate
- 90% HPV+ women will receive recommended treatments and follow-up

The projected timeframe until cervical cancer elimination in Australia: a modelling study

Michaela T Hall, Kate T Simms, Jie-Bin Lew, Megan A Smith, Julia ML Brotherton, Marion Saville, Ian H Frazer, Karen Canfell

Summary

Background In 2007, Australia was one of the first countries to introduce a national human papillomavirus (HPV) vaccination programme, and it has since achieved high vaccination coverage across both sexes. In December, 2017, organised cervical screening in Australia transitioned from cytology-based screening every 2 years for women aged from 18–20 years to 69 years, to primary HPV testing every 5 years for women aged 25–69 years and exit testing for women aged 70–74 years. We aimed to identify the earliest years in which the annual age-standardised incidence of cervical cancer in Australia (which is currently seven cases per 100 000 women) could decrease below two annual thresholds that could be considered to be potential elimination thresholds: a rare cancer threshold (six new cases per 100 000 women) or a lower threshold (four new cases per 100 000 women), since Australia is likely to be one of the first countries to reach these benchmarks.

Lancet Public Health 2018
Published Online
October 2, 2018
http://dx.doi.org/10.1016/S2468-2667(18)30183-X
See Online/Comment
http://dx.doi.org/10.1016/S2468-2667(18)30189-0

Cancer Research Division, Cancer Council NSW, Sydney, NSW, Australia

If high-coverage vaccination and screening is maintained, at an elimination 4 new cases per 100 000 women annually, cervical cancer could be considered to be eliminated as a public health problem in Australia within the next 20 years.

HPV prevention key messages!

- Evidence shows that cervical cancer screening reduces morbidity and mortality only from cervical cancer.
- HPV vaccine is effective for reducing morbidity from cervical cancer but is insufficient to eliminate cervical cancer screening.
- The HPV vaccine is safe, efficient and recommended

Conclusion

- The greatest impact has been seen where the vaccine is routinely administered before HPV exposure.
- Most at risk populations may well be the most under-immunized people in Canada
- With all we have learned in the last 10 years, we can safely upgrade our efforts
- Remembering that the HPV vaccine was develop because someone was struck by the high burden of HPV disease in specific populations… not just the general population!
- **But HPV prevention starts with a clear and strong recommendation from the healthcare provider!**


Merci!