

## HPV Primary prevention

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## Disclosure

- Merck and company completed antibody assay testing for monitoring of the HPV vaccine

## Objectives

- Review incidence and prevalence of HPV infection in Canada
- Discuss current vaccination programs in Canada, indications and contraindications for vaccination
- Review vaccine uptake in the Canadian school-based programs
- Vaccine effectiveness in adolescents
- Effectiveness of HPV vaccination in adult women- is there a benefit?
- Safety of HPV vaccine
- **Barriers to uptake**

## Case 1

- Ms. P brings her 11 year old daughter to see you
- Received a letter regarding HPV vaccine to be given at school

'Does my daughter need this vaccine? She is only 11! She's not having sex anytime soon! I've never heard of this vaccine before- is it safe? Does it even work?'

- How do you counsel Mrs. P and her daughter about the indications and effectiveness of the HPV vaccine?

## HPV risk and prevalence

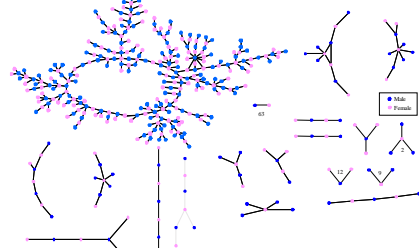
- HPV is the most common sexually transmitted infection
  - Lifetime risk approx. 75% for sexually active females
- Females: N= 4330 women 15-69
  - Overall prevalence 12.2%
  - By age group, the hrHPV positive was: 15–19, 25.7%; 20–24, 33.2%; 25–29, 21.9%; 30–34, 12.6%; 35–39, 9.5%; 40–44, 8.4%; ≥45, 3.4%
  - Highest prevalence in females <20 years old
- Males: limited data, mostly in high-risk populations
  - STI
- Transmission risk: discordant couples practicing vaginal intercourse without a condom x 6 months
  - HPV= 20% (Burchell et al. 2011)
  - HIV= 0.8% (Majugira et al. 2015)

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## HPV - What goes around... (Bearman et al. 2004)

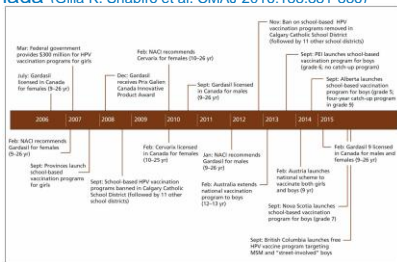


All reported skin to skin contacts ongoing in the last 18 months in a moderate sized high school (Romantic +/- intercourse, or nonromantic sexual relationship)



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## Timeline of HPV vaccine recommendations in Canada (Gilla K. Shabiro et al. CMAJ 2016;188:881-886)



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## HPV vaccines



Vaccine	HPV genotypes	Protection
HPV2	HPV-16, -18	70% of cervical cancers
HPV4	HPV-6, -11, -16, -18,	70% of cervical cancers 90% of AGWs
HPV9	HPV-6, -11, -16, -18, -31, -33, -45, -52, -58	90% of cervical cancers 90% of AGWs

- Prophylactic vaccine
  - Target population for primary immunoprevention is in youth, prior to initiation of sexual activity
  - Cannot cause HPV infection
  - Does not alter the course of an ongoing HPV infection



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## Indications for HPV vaccines (PHAC 2018)

Groups	Immunization Schedule	Vaccine(s)
Healthy [1] girls (9 to less than 15 years of age [2])	2 or 3 dose schedule	HPV2 or HPV4 or HPV9
Healthy [1] girls and women (15 years of age and older)	1 [1] dose schedule	HPV2 or HPV4 or HPV9
Healthy [1] boys (9 to less than 15 years of age [3])	2 or 3 dose schedule	HPV4 or HPV9
Healthy [1] boys and men (15 years of age and older)	1 [1] dose schedule	HPV4 or HPV9
Immunocompromised individuals and immunocompetent HIV-infected individuals	3 dose schedule	Females: HPV2 or HPV4 or HPV9 Males: HPV4 or HPV9

1 Immunocompetent, non-HIV infected.  
 2 A 2-dose schedule of HPV2 or HPV4 vaccine is sufficient for healthy girls and women 15 years of age and older in whom the first dose was administered between 9 and less than 15 years of age.  
 3 A 2-dose schedule of HPV4 vaccine is sufficient for healthy boys and men 15 years of age and older in whom the first dose was administered between 9 and less than 15 years of age.



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## Contraindications and special circumstances

- Contraindications
  - Anaphylaxis or hypersensitivity following previous HPV vaccine or to any components of the vaccine or its container
- Immunocompromised
  - 3-dose schedule, regardless of age
- MSM
  - Disproportionately high risk of HPV infection
  - Recommended for all MSM, limited data in males > age 27
- Pregnancy and breast feeding
  - Limited data, but HPV vaccine has not been causally associated with adverse outcomes of pregnancy or teratogenicity
  - Recommend delaying vaccination until completion of pregnancy
  - Report exposure during pregnancy:
    - HPV4 or HPV9- Merck Canada Inc. at 1-800-567-2594
    - HPV2- GlaxoSmithKline Inc. at 1-800-387-7374.



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## HPV immunization programs in Canada (CPAC 2018)

	Immunization Program for Girls		Immunization Program for Boys	
	Date of implementation	School grade when immunization is given	Date of implementation	School grade when immunization is given
<b>NU</b>	2013	Grade 6	2017	Grade 6
<b>NWT</b>	2009	Grade 4-6	2017	Grade 4-6
<b>YK</b>	2009	Grade 6	2017	Grade 6
<b>BC</b>	2008	Grade 6	2017	Grade 6
<b>AB</b>	2008	Grade 5	2014	Grade 5
<b>SK</b>	2008	Grade 6	2017	Grade 6
<b>MB</b>	2008	Grade 6	2016	Grade 6
<b>ON</b>	2007	Grade 8 (2007-2016) Grade 7 (2016-present)	2016	Grade 7
<b>QC</b>	2008	Grade 4	2016	Grade 4
<b>NB</b>	2008	Grade 7	2017	Grade 7
<b>NS</b>	2007	Grade 7	2015	Grade 7
<b>PEI</b>	2007	Grade 6	2013	Grade 6
<b>NL</b>	2007	Grade 6	2017	Grade 6

\* In the 2016-2017 school year, Ontario's program expanded to include boys in addition to girls and switched to delivering immunization in grade 7 instead of grade 8. Grade 8 females were also offered HPV vaccine in the 2016-2017 school year so that this cohort would not be missed in the transition from grade 8 to grade 7 delivery.



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	ATP cohort	ITT cohort
<b>HPV2</b>		
<b>Females age 15-25</b>		
Persistent (<12 month) infection	90.9 (82.0-95.9)	49.0 (38.1-58.1)
HPV 16/18	94.9 (87.7-98.4)	60.7 (49.6-69.5)
CIN2+	91.7 (66.6-99.1)	45.7 (22.9-62.2)
<b>HPV4</b>		
<b>Females age 15-26</b>		
Asymptomatic warts	-	79.5 (73.0-84.6)
CIN2	100 (94.7-100)	54.8 (40.8-66.7)
CIN3	96.8 (88.1-99.6)	45.1 (29.8-57.3)
AS	100 (80.9-100)	60.0 (0-87.3)
VIN 2/3 or VaIN 2/3+	100 (82.6-100)	78.5 (55.2-90.8)
<b>Males age 16-26</b>		
Persistent (<6 month) genital infections	85.6 (73.4-92.9)	27.1 (16.6-36.3)
Persistent (<6 month) anal infections	94.9 (80.4-99.4)	59.4 (43.0-71.4)
Asymptomatic warts	90.4 (69.2-98.1)	65.5 (45.8-78.6)
AIN (any grade)	77.5 (80.4-99.4)	59.4 (43.0-71.4)
<b>HPV9</b>		
<b>Females age 16-26</b>		
Any high grade lower genital tract disease (includes invasive disease)	96.7 (80.9-99.8)	42.5 (7.9-65.9)

## HPV vaccine effectiveness in HPV-naïve adolescents and young adults

- ATP cohort= 'best case scenario'
- ITT cohort= approximates effectiveness
- Data shown here includes only subjects with less than five lifetime sexual partners, or serologically HPV-naïve at onset of study



## HPV vaccine effectiveness in 9-14 year olds-based on immunogenicity

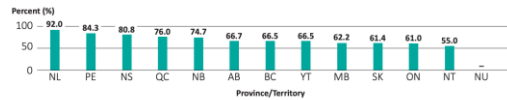
- Extrapolated from immunogenicity non-inferiority trials:
  - 2-dose schedule in 9-14 year olds is equally immunogenic as a 3-dose schedule in 15-24 year olds
- Too early to show effectiveness, low event rates
- Based on follow-up immunogenicity studies to date, protection lasts at least 10 years



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## HPV Vaccine uptake among school-based programs in Canada (CPAC 2018)

Percentage of girls who received a full course\* of human papillomavirus (HPV) vaccination from school-based HPV immunization programs, by jurisdiction — most recent reported year<sup>†</sup>

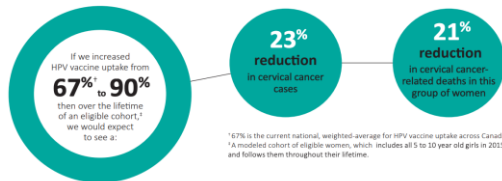


\*As of the 2015/16 school year, the full course of vaccination for school-based HPV vaccination programs is three doses in AB, SK, NT and NU, and two doses in all other provinces and territories. <sup>†</sup>2015/16: MB, ON, NS, PE, NL, NT, 2016: SK, 2016/17: BC, AB, QC, NB, YT. — Data not available. Data source: Provincial and territorial immunization programs.



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## 90% target vaccination rates for Canadian adolescents (CPAC 2018)



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## Case 1 cont'd...

- 5 years later...
- Ms. P brings her (now) 16 year old daughter back to see you.

' My daughter had the HPV vaccine in school, like you recommended. I hear there is now a better vaccine that covers more types of HPV. I think the one she had only covers 4 types. Should she have a 'booster'?"

- How do you counsel Ms. P and her daughter now?



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## Re- vaccination with HPV9? (Garland et al. 2015)

- Females age 12-26 who had previously received HPV4 were randomized to 3 doses of HPV9 v. placebo, 1-3 years after initial immunization
  - Re-vaccinated females had significantly lower anti-HPV31/33/45/52/58 titers compared to females who received HPV9 de novo
  - Unknown whether these lower titers would provide type- specific protection
- Not cost-effective
- Not eligible for publicly funded re-vaccination
- **ACS-NACI statement 2016: 'There is insufficient evidence at this time to recommend, at a population level, re-immunization with HPV9 vaccine in individuals who have completed an immunization series with another HPV vaccine.'**

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## HPV Vaccines Effectiveness in Adult Women: is there a benefit?

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Gynecologist  
Centre Médical Santé Femme



[www.g-o-c.org](http://www.g-o-c.org)

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## Case 2

- 40 years old woman, G2 P2, University Professor at law school
- Married for 15 years, recently divorced
- 3 lifetime partners
- Normal biennial Pap smears
- No significant past medical history; tubal ligation
- Looking forward to a new relationship
- She seeks counseling about prevention of STD's

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## Discussion

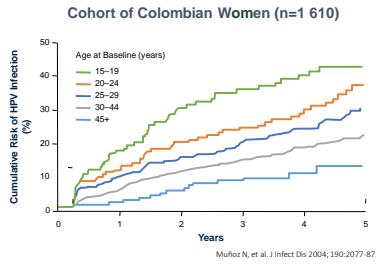
- After discussion on Chlamydia, gonorrhea, syphilis, you open the door to HPV infections.
- Do you discuss the risk of HPV transmission with your older patients?

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## Women Remain at Risk for Acquiring HPV Infection Throughout Their Lifetime



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## Number of Partners & Marital Status Affect Risk of HPV Infection Among Women Aged 24–45 Years

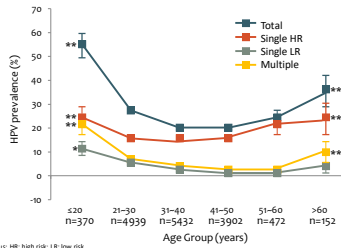
Baseline characteristic	Number	Incident infection HPV 6, 11, 16 and/or 18 (n % (N = 147))	Age-adjusted HR for incident infection (95% CI)
<b>Lifetime number of sex partners</b>			
1	683	38 (5)	1.0
2-3	517	46 (8)	1.5 (1.0, 2.3)
≥ 4	476	63 (12)	1.9 (1.3, 2.9)
<b>Number of sex partners (last 6 months)</b>			
0	1,539	121 (7)	1.0
1	322	19 (14)	1.5 (0.9, 2.4)
2-3	13	7 (35)	5.2 (2.4, 11.1)
≥ 4	1	0 (0)	0.0 (0.0, 1.0)
<b>Marital status</b>			
Married, first marriage	727	33 (4)	1.0
Single, never married	265	51 (16)	2.8 (1.8, 4.4)
Remarried	106	6 (5)	1.3 (0.6, 3.2)
Divorced/separated/widowed	121	18 (13)	3.8 (2.2, 6.6)
Living with partner	461	39 (8)	1.5 (0.9, 2.4)

Velicer C et al. Sex Transmitt Dis 2009.



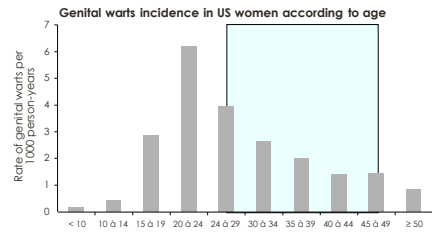
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## HPV Infection Has a Bimodal Distribution



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## Adult Women Are at Risk of Contracting HPV Infection or Disease



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## Social Behavior is a Risk Factor for HPV Infection

- Changes in social behavior have occurred during the last 30 years
  - Older age at first marriage with more partners before marriage
    - Young males: 62.4% contaminated in a 2 year follow up <sup>1</sup>
    - Viral type concordance in infected couples <sup>2</sup>
  - Increase in divorce in many societies
- These changes have led to new partnering and acquisition of new sexual partners during middle age
- Literature suggests that in the U.S., nearly 40% of men and women have married and divorced by age 55, and that over 25% of these people have remarried at least once <sup>3</sup>

1. Partridge JM et al. J Infect Dis 2007;196:1128
2. Burchell AN et al. Epidemiol 2010
3. Velicer C et al. Sex Transmitt Dis 2009.



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## Discussion

- What about use of condoms for prevention of HPV infections?



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## Condom Use and HPV prevention

- Condom use may reduce the risk for HPV-associated diseases (e.g., genital warts and cervical cancer) and may mitigate the other adverse consequences of infection with HPV
- Condom use has been associated with higher rates of regression of cervical intraepithelial neoplasia (CIN) and clearance of HPV infection in women, and with regression of HPV-associated penile lesions in men.
- A limited number of prospective studies have demonstrated a protective effect of condoms on the acquisition of genital HPV.
- While condom use has been associated with a lower risk of cervical cancer, the use of condoms should not be a substitute for routine screening with Pap smears to detect and prevent cervical cancer, nor should it be a substitute for HPV vaccination among those eligible for the vaccine.

<https://www.cdc.gov/condomeffectiveness/latex.html>



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## Discussion

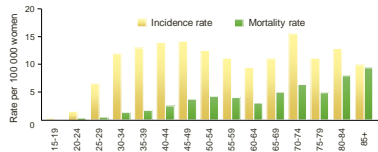
- Do you discuss cervical cancer prevention?



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## Cervical Cancer

- Second female cancer in incidence worldwide
- In 2005, around 1 million women affected with cervical cancer and 250,000 died of the disease
- In Canada
  - Highest incidence in women over 40 years of age, with another peak in women  $\geq 70$  years of age
  - 1356 new cases per year



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## What are the Key Risk Factors for HPV Infection?



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## Persistence of HPV Infection in Women $\geq 25$ Years of Age

- 90% of HPV infections spontaneously clear within 2 years
- Older age is associated with persistence and progression of HPV infection<sup>1</sup>
- Women  $\geq 25$  years of age are more likely to have persistent HPV infection<sup>1-3</sup>
- HSIL occurring in increasing age carries a higher risk of progressing to carcinoma<sup>1</sup>

1. Moscicki AB, et al. Vaccine 2006; 24 (Suppl 3):S42-S51. 2. Hildesheim A, et al. J Infect Dis 1994; 169:235-40. 3. Castle PE, et al. J Infect Dis 2006; 191:1808-16.



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## Discussion

- Do you recommend HPV vaccination in older women?
- Do you provide information on vaccine efficacy?



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## Is there a Benefit in Vaccinating Older Women

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## The Adult Women Efficacy Study (FUTURE III): Description

- International, multicentre, randomized, placebo-controlled trial
- Women 24 to 45 years of age (n = 3,819\*)
- Inclusion criteria
  - Not pregnant
  - No history of hysterectomy
  - No current or past cervical disease (CIN or cancer)
  - No history of genital warts
  - No history of cervical definitive therapy
  - No cervical biopsy within past 5 years
  - No history of HIV or immune compromise
  - Lifetime number of sexual partners not grounds for exclusion
- Pap testing, cervicovaginal sampling and external genital inspections at ~6-month intervals for a total of 48 months



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## Reduction in Incidence of HPV 6/11/16/18-related Pap Diagnoses

Per-protocol Efficacy Population, Mean Follow-up: 3.8 Years

	Quadrivalent HPV Vaccine (n = 1,576)	Placebo (n = 1,563)	% Reduction	95% CI
ASC-US (HR+) or worse	1	38	97%	84.5, 99.9
ASC-US HR(+)	1	13	92%	48.8, 99.8
LSIL	0	25	100%	84.1, 100
ASC-H	0	1	100%	< 0, 100
HSIL	0	0	–	–

n = number of subjects who have at least 1 follow-up visit after month 7.  
Caulinque X, et al. Br J Cancer 2011;105(1):28-37.



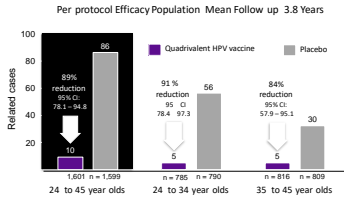
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What is the impact of immunization on the incidence of HPV infection?



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## Combined Incidence of HPV 6/11/16/18-related Persistent Infection, CIN (Any Grade), and EGLs

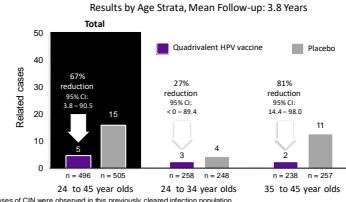


Castellgual X, et al. Br J Cancer 2011; 105(1):28-37.  
Forns D, et al. Presented at EUROGIN 2010 Congress, February 17-20, 2010, Monte Carlo, Abstract 55-3-3.



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## Quadrivalent HPV Vaccine is Efficacious in Subjects With Previously Cleared Vaccine HPV Type Infection (Seropositive/DNA Negative)



Castellgual X, et al. Br J Cancer 2011; 105(1):28-37.



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## Summary: HPV Vaccination for Older Women – When?

### When:

- Administer to older women (aged > 26 years) when risk factors are present:
  - past history of HPV, unstable relationship, or new relationship

Adapted from: Kahn JA. N Engl J Med 2009; 361:271-8.



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## Summary: HPV Vaccination for Older Women – Why?

### Why:

- They remain at risk for infection with oncogenic and non-oncogenic HPV types throughout their lives
- Sexually active women in this age group are unlikely to have been unknowingly infected with all HPV types included in current vaccines
- Take opportunity to reinforce the importance of practicing safe sexual behaviors to prevent sexually transmitted infections, and of returning for future screening

Adapted from: Kahn JA. N Engl J Med 2009; 361:271-8.



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## Summary: HPV Vaccination for Older Women – How?

### How:

- “Same Day” vaccination, as patient may not come back
- Counsel about vaccine per recommended scheduled (refer to product monograph)
- Document information given and patient’s responses
- Take opportunity to reinforce the importance of practicing safe sexual behaviors to prevent sexually transmitted infections, and of returning for future screening

Adapted from: Kahn JA. N Engl J Med 2009; 361:271-8.



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## GOC POSITION

- PAP-negative women 25-45 are the highest priority as the greatest evidence of benefit exists for this group.
- Women who have already undergone treatment for related cervical cancer lesions represent a further high-risk group, having a 2-to-6-fold risk of subsequent cervical cancer compared to women with normal cytology.
- Other higher-risk populations include:
  - pre-transplant patients
  - men who have sex with men (MSM),
  - immunocompromised individuals and
  - patients in whom immunosuppressive medications are being considered.

<https://a-s-c.org/publications/goc-position-statements/>



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## Conclusion

- Burden of HPV disease is mostly on mid-adult women and infection may have been acquired tardily
- Costs involved for screening and treatment are huge for this non-vaccinated group
- Natural infection does not protect from acquiring new infection
- Vaccination of this cohort may prevent future HPV related disease linked to change in sexual habit in mid-adult women



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## Case 3

- Your longtime patient, Mrs A, is in consultation for her periodic exam. As the consultation ends, Mrs A seeks your advice on the HPV vaccine. She has received documentation from her daughter’s school regarding the planned vaccination session, which will include HPV vaccination. She has heard that maybe the vaccine is not safe and wants your opinion on the matter.



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### What are the important points to address ?

- Obtain information as detailed as possible on what “she has heard” to address her concerns specifically
- The difference between bothersome side effects and serious adverse reactions
- Review the type and frequency of side effects
- Explain, in lay terms, the results of independent research into serious adverse reactions, including the lack of risk of :
  - Auto-immune diseases (neurological, endocrine, rheumatoid)
  - Adverse effects of fertility
  - Complex diseases



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### Bothersome side effects

- Frequent
- Appear during or shortly after vaccination
- Self-limited
  - Pain at the site of injection (up to 90%)
  - Redness/swelling at the site of injection (up to 50%)
  - Headache (up to 15%)
  - Fever, chills, aching muscles in the days following vaccination (up to 5%)
- Note: anaphylaxis is a rare serious immediate adverse event(1-2/1 000 000)

[https://www.who.int/vaccine\\_safety/initiative/foods/HPV\\_vaccine\\_rates\\_information\\_sheet\\_1217.pdf?ua=1](https://www.who.int/vaccine_safety/initiative/foods/HPV_vaccine_rates_information_sheet_1217.pdf?ua=1); Gardasil-9 monography  
[https://pdf.hres.ca/dpd\\_pm/00037506.PDF](https://pdf.hres.ca/dpd_pm/00037506.PDF)



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### Serious, delayed adverse effects

- Rare and remote from vaccination time point
- Usually cannot be studied in RCTs, which are too small and too short in duration
- May seem like a moving target: as one “fear” is laid to rest, others will emerge



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### What are the main concerns that have been raised?

- Auto-immune diseases (neurological, endocrine, rheumatoid, etc)
- Other “Complex diseases”
- Impact on sexual behaviors



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### Vaccine adverse effects reporting databases

- Exist in most jurisdictions (Quebec, Canada, USA, Europe, Australia, Asia)
- Based on voluntary reporting
- Reports registered without verification of causality
- Aim: identify "signals" that can then be investigated with proper methodology
- Pubmed lists several updates of analysis from those databases from around the world: no signal has ever been consistently identified
- Number of reports can increase following media coverage of HPV vaccination

Ward D, Ego Sunmaji. 2019, May;24(19). Bonaldo G, Br J Clin Pharmacol. 2019; Scypion C, Expert Opin Drug Saf. 2019; Mahajan D, Commun Dis Intell Q Rep. 2015; [https://www.who.int/vaccine\\_safety/initiative/tools/HPV\\_vaccine\\_rates\\_information\\_sheet\\_1217.pdf?ua=1](https://www.who.int/vaccine_safety/initiative/tools/HPV_vaccine_rates_information_sheet_1217.pdf?ua=1)



### Population based studies: what to look for

- Studies more credible if conducted by investigators independent from vaccine manufacturers
- Control group of unexposed is paramount:
  - A report of a new diagnosis following vaccination does not mean vaccination caused it
  - Rare things happened in the past and will continue happening
  - Valid and consistent diagnosis criteria
  - Importance of documenting "background" frequency of outcomes that existed before the implementation of HPV vaccination



### Rates of ER consultations/hospitalizations for auto-immune diseases, that can be expected post HPV vaccination, based on rates observed in 2005

**TABLE 3. Coincident Temporal Associations With Paired HPV Vaccination Injections Administered at 0–1–6 Months to All Adolescent and Young Women**

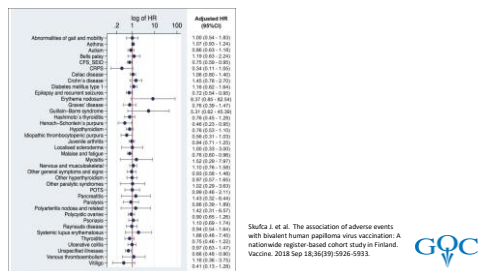
Age Group	Condition	Rate per 100,000 by Temporal Association Window		
		1 d	1 wk	6 wk
Adolescent	ER consultation/hospitalization	2.7	18.6	81.3
	ER consultation/hospitalization	1.6	10.6	65.8
	ER consultation/hospitalization	0.4	2.9	12.8
	Hepatitis/autoimmune disease	0.2	1.0	4.5
	Autoimmune disease	0.1	0.9	4.0
Adult	ER consultation/hospitalization	0.3	0.3	2.0
	Hepatitis/autoimmune disease or autoimmune disease	0.0	0.2	1.0
	ER consultation/hospitalization	0.0	0.2	1.0
	ER consultation/hospitalization	0.0	0.2	1.0
	ER consultation/hospitalization	0.0	0.2	1.0
Adult	ER consultation/hospitalization	0.0	0.2	1.0
	ER consultation/hospitalization	0.0	0.2	1.0
	ER consultation/hospitalization	0.0	0.2	1.0
	ER consultation/hospitalization	0.0	0.2	1.0
	ER consultation/hospitalization	0.0	0.2	1.0
Autoimmune disease	ER consultation/hospitalization	0.0	0.2	1.0
	ER consultation/hospitalization	0.0	0.2	1.0
	ER consultation/hospitalization	0.0	0.2	1.0
	ER consultation/hospitalization	0.0	0.2	1.0
	ER consultation/hospitalization	0.0	0.2	1.0

Slagter, CA et al. Human Papilloma Virus Immunization in Adolescent and Young Adults: A Cohort Study to Illustrate What Events Might be Mistaken for Adverse Reactions. PEDI Journal 29(11):979-984, November 2007.



Results on risk of auto-immune diseases following HPV vaccination from key population-based studies

No significant increase found in 38 outcomes following bivalent HPV vaccination in Finland

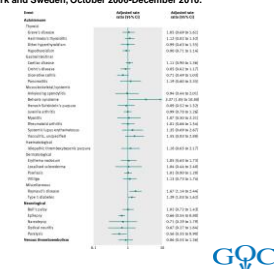


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Association between exposure to quadrivalent human papillomavirus (qHPV) vaccine and adverse events in adolescent girls in Denmark and Sweden, October 2006-December 2010.

No association was found between HPV vaccination and 26 outcomes.

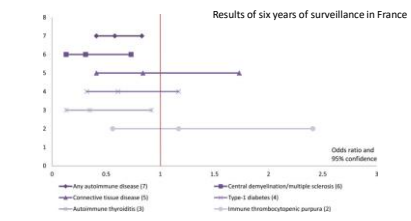
Additional analysis of the association between Behçet's, Raynaud's disease, and type 1 diabetes, revealed no temporal trend in relation to vaccination.



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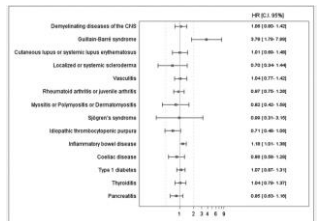
### Risk of auto-immune diseases and HPV vaccination



Lamiae Grimaldi-Bastoux, Michel Hacquard, Isabelle Khad-Paak, et al. Risk of autoimmune diseases and human papilloma virus (HPV) vaccine: Six years of case-report surveillance. Journal of Autoimmunity, Volume 79, 2017, 84-90

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Conclusion: Among 2.2 million girls, overall auto-immune diseases incidence was not increased after vaccination.



Identified signal (based on few cases) of GBS was further investigated

Miranda S et al. Human papillomavirus vaccination and risk of autoimmune diseases: A large cohort study of over 2 million young girls in France Vaccine Volume 35, Issue 16, 24 August 2017, Pages 4761-4768

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## Guillain-Barré

- Large UK study, focused on all girls eligible for vaccination, 2007-2019: “We can exclude a risk of about 1 per million doses.”

human  
Vaccine, 2017 Mar

Andrews N, Stowe J, Miller E. No increased risk of Guillain-Barré syndrome after papilloma virus vaccine: A self-controlled case-series study in England. *Vaccine*. 2017;35(13):1729-1732.

- Quebec study including 13 73161 p-y of follow-up-up, found no increase in rates of GBS in groups targeted for HPV vaccination

hospitalizations

Decourcinck G et al. Absence of association between Guillain-Barré syndrome and HPV vaccine. *Expert Rev Vaccines*. 2018;Jan17(1):99-102.



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## “Complex” diseases

- Their diagnostic criteria (if not their existence) is debated in the scientific literature
- Large database studies may be difficult because of lack of accepted diagnosis criteria
- Reports to vaccine registries typically increase after reports in the media
- Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME)
  - Persistent severe/disabling unexplained fatigue
  - No validated biomarkers/lab test for diagnosis
- Postural orthostatic tachycardia syndrome (POTS)
  - Increased heart rate and lightheadedness, palpitations, fatigue that occur with standing
  - Absence of orthostatic hypotension
- Chronic regional pain syndrome (CRPS)
  - Severe chronic pain in a limb, usually after an injury
  - Other, such as vasomotor changes, swelling, motor dysfunction



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## No association between complex diseases and HPV vaccination

- Public knowledge and diagnostic criteria fairly recent
- Increases in diagnostic predate HPV vaccine

Skufca J et al. *Papillomavirus Research* 2017

- Independent, controlled studies have not found a link with HPV vaccination
  - Cohort study in the Netherlands, including 69429 12–16-year-old girls: Fatigue is frequent in adolescent girls, rarely meeting diagnosis criteria for chronic fatigue syndrome and no significant difference in risk of diagnosis pre-post vaccination.

Schunke-Van't Klooster TM, et al., No evidence found for an increased risk of long-term fatigue following human papillomavirus vaccination of adolescent girls. *Vaccine*. 2019 Oct 29;38(45):8796-8802.



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## Impact of HPV vaccination on sexual behavior

- Some parents have expressed fear that children vaccinated against one STI (HPV) would conclude that there are no (less) risk to unprotected sex and thus engage in more risky sexual behavior
- Several studies have debunked this myth and found
  - No increase in pregnancies or STIs
  - No decrease in age at first intercourse
  - No increase in number of sexual partners

Smith LM, CMAJ 2005; Madhivanan P Am J prev Med 2016; Brouwer AF, BMC Public Health 2019



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## Conclusion

- Studies independent from the HPV vaccine manufacturers have consistently shown HPV vaccines to be safe
- Regional/national monitoring registries are in place internationally, and scrutinized periodically by public health authorities for signals of adverse events
- Signals that have been identified through such registries, or through lay media reporting, have been meticulously researched and no concern has been identified



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## Back to Mrs A.

- Your patient was worried over negative reports in the media generally
- Your discussion would need to address the potential benefits of vaccinating her daughter (see other presentations)
- While stressing:
  - The very large number of doses dispensed worldwide
  - Independent researchers continuously conducting research in different countries, using different methods, all concluding that HPV vaccines are extremely safe



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## Summary: HPV Primary prevention

- HPV is the most common STI, and is highly transmissible.
- As of 2017, all provinces and territories have school-based publicly-funded HPV immunization programs for both girls and boys.
- HPV vaccines have been shown to be efficacious in preventing clinically significant HPV-related disease in 15-26 year olds
- Licensing and recommendations in 9-14 year olds (the target group for primary prevention) is based on immunogenicity data
- The school-based immunization programs in Canada are falling below the 90% target rates for uptake
- Re-vaccination with HPV9 after receiving another HPV vaccine is not indicated at this time.
- Adult women with ongoing risk factors for HPV infection should be offered HPV vaccine.
- HPV vaccines are safe with no higher risk of adverse events compared to the non-vaccinated population.



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