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Safety of HPV vaccine

Helen Petousis-Harris, PhD

Department of General Practice and Primary Health Care

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MEDICAL AND HEALTH SCIENCES

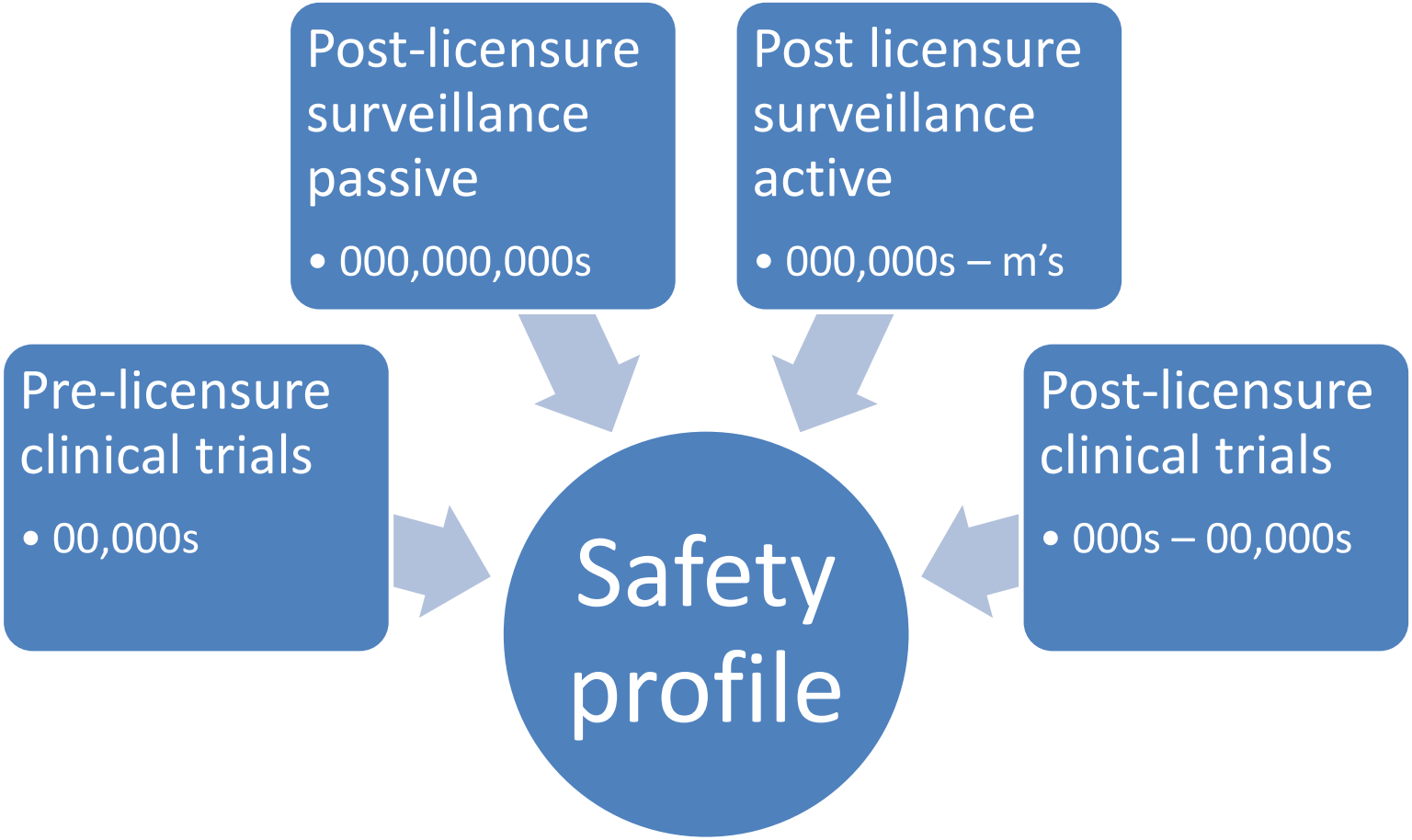
Objectives

- Current evidence on the safety of HPV vaccine
- What are people worried about?

Vaccine safety

- Vaccine safety is closely monitored
  - every country has surveillance, globally pooled
  - Modern approaches
- Safety issues have arisen in the past
  - Signals detected, verified, studied
- Concerns about vaccine safety, real or perceived, jeopardise immunisation programmes

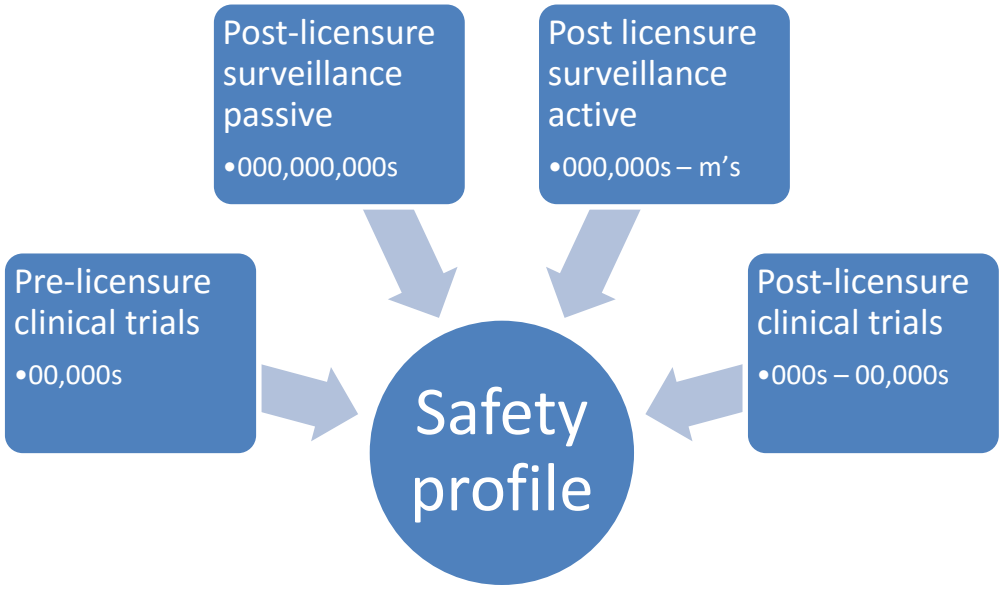
How is vaccine safety assessed



Generally by comparing vaccinated with unvaccinated

What happens when a safety question arises?

- Signals in passive surveillance systems?
- Case reports of adverse events following immunisation?



Scientific evidence on the safety of quadrivalent HPV vaccine

From pivotal trials and post-licensure surveillance 2002 - 2015

Pivotal trials to 2006

- Safety evaluated in placebo-controlled double blind trials in 22 countries
  - Placebo aluminium adjuvant OR saline
  - 11,778 vaccinated/9686 unvaccinated
- Local & systemic events
  - Detailed diary card 14 days
  - Long term follow up >800 days
- Safety during pregnancy

Local reactions among females aged 9-23 years 1-5 days after any vaccination with GARDASIL®

Local Reaction	GARDASIL® n=11778 (%)	Aluminium-containing placebo (%) n=9686	Saline placebo (%)
Pain	83.9	75.4	48.6
Mild/Mod	81.1	74.1	48.0
Severe	2.8	1.3	0.6
Swelling*	25.4	15.8	7.3
Mild/Mod	23.3	15.2	7.3
Severe	2.0	0.6	0
Erythema*	24.7	18.4	12.1
Mild/Mod	23.7	18.0	12.1
Severe	0.9	0.4	0

*measured in inches: mild 0 - ≤1; Mod >1 to ≤ 2; Severe >2

Food and Drug Administration, Clinical Review of Biologics License Application for Human Papillomavirus 6, 11, 16, 18 L1 Virus Like Particle Vaccine (S. cerevisiae) (STN 125126 GARDASIL), manufactured by Merck, Inc, D.o.V.a.R.P.A. Vaccines Clinical Trial Branch, Office of Vaccines Research and Review, Centre for Biologics Evaluation and Research, Editor. 2006, Food and Drug Administration.

Systemic reactions among females aged 9-23 years 1-15 days after any vaccination with GARDASIL® vaccine

Adverse Event (1-15 days PV)	GARDASIL® (n=5088)	Placebo (n=3790)
Pyrexia*	13.0%	11.2%
Nausea	6.7%	6.6%
Nasopharyngitis	6.4%	6.4%
Dizziness	4.0%	3.7%
Diarrhoea	3.6%	3.5%
Vomiting	2.4%	1.9%
Myalgia	2.0%	2.0%
Cough	2.0%	1.5%
Toothache	1.5%	1.4%
URTI	1.5%	1.5%
Malaise	1.4%	1.2%
Arthralgia	1.2%	0.9%
Insomnia	1.2%	0.9%
Nasal Congestion	1.1%	0.9%

* 4.0% to 4.4% receiving vaccine reported fever over 38ºC after any dose. Slightly more than placebo (3.1% to 3.8%)

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Serious adverse events – all safety studies

- Vaccine related serious events occurred in <0.1% (1/1000) of persons.
- **Proportion similar in vaccine and placebo groups**
- 7 persons had events possibly, probably or definitely related to vaccine or placebo
  - 5 among the GARDASIL® recipients (bronchospasm, gastroenteritis, headache, vaginal haemorrhage, severe site reaction)
  - 2 among the placebo group
- Death
  - 10/11778 (0.08%) GARDASIL® group (none vaccine-related)
  - 7/9686 (0.07%) Placebo group
  - Non prescription drug overdose, MVA, suicide, DVT, sepsis, cancer, arrhythmia, asphyxia

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Summary of deaths in trial participants

	GARDASIL ® n=11778	Days post last dose	Placebo n=9680	Days post last dose
Trauma	4	373, 8, 90, 800	3	2, 342, 798
DVT/PE	1	19	1	202
Sepsis, DIC	1	359		
Pneumonia, sepsis	1	625		
Pancreatic Cancer	1	578		
Arythmia	1	27		
Convulsion, drug use	1	4		
Suicide			2	200, 517
Asphyxiation			1	256
TOTAL (%)	**10 (0.08%)**		**7 (0.07%)**	

Note: no causal link has been shown between GARDASIL® vaccination and any cause of death

What may be mistaken for an AEFI following HPV vaccine?

- **PRIOR** to licensure global experts conducted studies – what events might be mistaken for adverse reactions
- Cohort study of 436,368 female adolescents and young adults 2007
  - Emergency consultations, hospitalisations, outpatient consultations

Siegrist C-A, Lewis EM, Eskola J, Evans SJW, Black SB. Human Papilloma Virus Immunization in Adolescent and Young Adults: A Cohort Study to Illustrate What Events Might be Mistaken for Adverse Reactions. The Pediatric Infectious Disease Journal. 2007;26(11):979-84.

TABLE 3. Coincident Temporal Associations With Putative Placebo Injections Administered at 0–1–6 Months to All Adolescent and Young Women

Age Group	Condition	Rate per 100,000 by Temporal Association Windows		
		1 d	1 wk	6 wk
Adolescent	ER consultation/asthma	2.7	18.8	81.3
	ER consultation/allergy	1.5	10.6	45.8
	ER consultation/diabetes	0.4	2.9	12.8
	Hospitalization/inflammatory bowel disease	0.2	1.0	4.5
	Hospitalization/thyroid disease	0.1	0.9	4.0
	Hospitalization/SLE	0.1	0.5	2.0
	Hospitalization/MS or optic neuritis	0.0	0.2	1.0
Adults	ER consultation/asthma	3.0	21.2	91.5
	ER consultation/allergy	2.5	17.4	75.3
	ER consultation/diabetes	0.6	3.9	17.0
	Hospitalization/thyroid disease	2.4	16.6	71.8
	Hospitalization/inflammatory bowel disease	0.3	2.0	8.8
	Hospitalization/SLE	0.3	1.8	7.8
	Hospitalization/MS or optic neuritis	0.1	0.7	3.0

MS indicates multiple sclerosis; SLE, systemic lupus erythematosus.

TABLE 3. Coincident Temporal Associations With Putative Placebo Injections Administered at 0-1-6 Months to All Adolescent and Young Women

Human Papilloma Virus Immunization in Adolescent and Young Adults: A Cohort Study to Illustrate What Events Might be Mistaken for Adverse Reactions.
Siegrist, Claire-Anne; Lewis, Edwin; Eskola, Juhani; Evans, Stephen; Black, Steven

Pediatric Infectious Disease Journal. 26(11):979-984, November 2007.
DOI: 10.1097/INF.0b013e318149dfea

Observational studies

Passive and active surveillance

Examples – most compare outcomes in vaccinated with unvaccinated

Table 1. Post-licensure published quadrivalent human papillomavirus vaccine (4vHPV) safety studies.

System or review (country)	Year of Publication	Number of doses evaluated	Type of concern addressed	Description	Methods	Findings
VAERS (US)[a]	2009	N/A	General safety	Summary of 12,424 VAERS reports following 4vHPV between 2006–2008	Spontaneous reporting; data mining for disproportional reporting	Disproportional reporting of syncope and VTE
Vaccine Safety Datalink (US)[b]	2011	600,558	General safety	Large database used for active surveillance and research; safety assessment of 9 pre-specified health outcomes among females vaccine recipients aged 9–26 years	Cohort design with weekly sequential analyses of electronic medical data	No statistically significant increase in risk for the outcomes monitored; non-significant elevated risk detected for VTE
Institute of Medicine review (US)[c]	2011	N/A	Review of safety data	Review of available 4vHPV safety data	Review of published studies, case reports, and surveillance systems	No evidence to support association among 12 outcomes; anaphylaxis causally associated with 4vHPV; syncope associated with all injectables
Post-marketing commitment to FDA (US)[d]	2012	346,972	General safety, VTE, neurologic, death	General assessment of safety following routine administration of 4vHPV at two large managed care organizations	Self-controlled risk interval design supplemented with medical record review	4vHPV associated with syncope on the day of vaccination and skin infections in the two weeks after vaccination; no other vaccine safety signals detected
Post-marketing commitment to FDA (US)[e]	2012	346,972	Autoimmune	Assessment of 16 pre-specified autoimmune conditions following routine use of 4vHPV at two large managed care organizations	Retrospective cohort using electronic medical data, supplemented with medical record review	No confirmed safety signals for monitored conditions
VAERS (US)[f]	2013	N/A	General safety	Review of 21,194 VAERS reports following 4vHPV between 2006–2013	Spontaneous reporting; data mining for disproportional reporting	No disproportional reporting observed; no new concerns
Register-based cohort study (Denmark and Sweden)[g]	2013	696,420	Autoimmune, Neurologic, VTE	Assessment of 23 different autoimmune, 5 neurologic conditions, and VTE following 4vHPV among females aged 10–17 years	Retrospective cohort using national patient registers	No consistent evidence of causal association between 4vHPV and the events monitored
VAERS (US)[h]	2014	N/A	General safety	Review of 25,176 VAERS reports following 4vHPV between 2006–2014	Spontaneous reporting; data mining for disproportional reporting	No disproportional reporting observed; no new concerns
Pharmacoepidemiologic General Research Extension (France)[i]	2014	N/A	Autoimmune	Assessment of 6 different autoimmune outcomes following 4vHPV among 211 cases and 875 controls aged 14–26 years	Case-control study with recruitment of cases and controls through registries	No increased risk for combined endpoint of six autoimmune disorders
Register-based cohort study (Denmark)[j]	2014	500,345	VTE	Assessment of VTE following 4vHPV among women aged 10–44 years	Self-controlled case series using national patient registers	No increased risk for VTE

System or review (country)	Year of Publication	Number of doses evaluated	Type of concern addressed	Description	Methods	Findings
Register-based cohort study (Denmark and Sweden)[k]	2015	1,927,581	Autoimmune	Assessment of multiple sclerosis and other demyelinating diseases of the central nervous system among females aged 10–44 years	Cohort design using data linked to national registers	No association with the development of multiple sclerosis and other demyelinating diseases
Vaccine Safety Datalink (US)[l]	2015	1, 240, 000	VTE	Assessment of VTE among adolescents and young adults aged 9–26 years	Self-controlled case series; cases confirmed by medical record review	No increase risk for VTE
Sentinel System (US)[m]	2015	1,423,399	VTE	Assessment of VTE among females aged 9–26 years	Self-controlled risk interval design; cases confirmed by medical record review	No increased risk for VTE
VAERS (US)[n]	2015	N/A	Neurologic	Review of 21 CRPS-related VAERS reports following 4vHPV between 2006 and 2015	Spontaneous reporting; clinical review of CRPS cases	Lack of evidence to suggest an association; data suggest CRPS following HPV vaccine is rare
Post-marketing commitment to FDA (US)[o]	2015	N/A	Pregnancy	Review of 4,919 reports of pregnancy following 4vHPV between 2006–2012	Voluntary reporting to pregnancy registry	Data were reassuring with no elevated reporting of adverse pregnancy outcomes
VAERS (US)[p]	2015	N/A	Pregnancy	Review of 147 VAERS pregnancy reports following 4vHPV between 2006 and 2013	Spontaneous reporting; data mining for disproportional reporting	No unexpected patterns fetal adverse events after 4vHPV
Vaccine Safety Datalink (US)[q]	2016	1,355,535	Death	Evaluation of deaths among individuals aged 9–26 years	Case-centered method; medical record review	Rate of death was lower than the national expected rate of death in this population

Abbreviations

CRPS- Chronic Regional Pain Syndrome, FDA- Food and Drug Administration, HIV- Human immunodeficiency virus, 4vHPV- Quadrivalent Human Papillomavirus vaccine, VAERS- Vaccine Adverse Event Reporting System, VTE- Venous thromboembolism

Sources

[a]Slade, B.A., et al., Post-licensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA, 2009. 302(7): p. 750–757.
[b]Gee, J., et al., Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine, 2011. 29(46): p. 8279–8284.
[c]Institute of Medicine. Adverse Effects of Vaccines: Evidence and Causality. 2011.
[d]Klein, N.P., et al., Safety of quadrivalent human papillomavirus vaccine administered routinely to females. Arch Pediatr Adolesc Med, 2012. 166(12): p. 1140–8.
[e]Chao, C., et al., Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. J Intern Med, 2012. 271(2): p. 193–203.
[f]Stokley S, et al., Human Papillomavirus Vaccination Coverage Among Adolescent Girls, 2007–2012, and Postlicensure Vaccine Safety Monitoring, 2006–2013 — United States. MMWR Recomm Rep, 2013. 62(29); p. 591–595
[g]Arnheim-Dahlstrom, L., et al., Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ, 2013. 347: p. f5906.
[h]Stokley S, et al., Human papillomavirus vaccination coverage among adolescent girls, 2007–2012, and post-licensure vaccine safety monitoring, 2006–2013 — United States. MMWR Recomm Rep. 2014. 63(29); p. 620–4.
[i]Grimaldi-Bensouda, L., et al., Autoimmune disorders and quadrivalent human papisslomavirus vaccination of young female subjects. J Intern Med, 2014. 275(4): p. 398–408.
[j]Scheller, N.M., et al., Quadrivalent human papillomavirus vaccine and the risk of venous thromboembolism. JAMA, 2014. 312(2): p. 187–8.
[k]Scheller, N.M., et al., Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system. JAMA, 2015. 313(1): p. 54–61.
[l]Naleway, A.L., et al., Absence of venous thromboembolism risk following quadrivalent human papillomavirus vaccination, Vaccine Safety Datalink, 2008–2011. Vaccine, 2016; 34(1): p. 167–71.
[m]Yih, W.K., et al., Evaluation of the risk of venous thromboembolism after quadrivalent human papillomavirus vaccination among US females. Vaccine, 2016; 34(1): p. 172–8.
[n]Weinbaum C, et al.. HPV Vaccination and Complex Regional Pain Syndrome: Lack of Evidence. EBioMed, 2015. 2(9): p. 1014–1015.
[o]Goss, M.A., et al., Final report on exposure during pregnancy from a pregnancy registry for quadrivalent human papillomavirus vaccine. Vaccine, 2015. 33(29): p. 3422–8.
[p]Moro, P.L., et al., Safety of quadrivalent human papillomavirus vaccine (Gardasil) in pregnancy: adverse events among non-manufacturer reports in the Vaccine Adverse Event Reporting System, 2006–2013. Vaccine, 2015. 33(4): p. 519–22.
[q]McCarthy, N.L., et al. Lack of association between vaccination and death in individuals 9–26 years of age. Pediatrics, 2016; 137(3): p. 1–8.

Reviews on safety

Examples

- Macartney KK, Chiu C, Georgousakis M, Brotherton JM. Safety of Human Papillomavirus Vaccines: A Review. *Drug Saf* 2013; PMID:23637071 AUSTRALIA
- Vichnin M, Bonanni P, Klein NP, Garland SM, Block SL, Kjaer SK, Sings HL, Perez G, Haupt RM, Saah AJ, et al. An Overview of Quadrivalent Human Papillomavirus Vaccine Safety: 2006 to 2015. *Pediatr Infect Dis J* 2015; 34:983-91; MULTI COUNTRY INDUSTRY AND ACADEMIA
- Stillo M, Carrillo Santisteve P, Lopalco PL. Safety of human papillomavirus vaccines: a review. *Expert Opin Drug Saf*. 2015;14(5):697-712. SWEDEN
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- Nakalembe M, Mirembe FM, Banura C. Vaccines against human papillomavirus in low and middle income countries: A review of safety, immunogenicity and efficacy. *Infectious Agents and Cancer*. 2015;10(1). UGANDA
- Coelho PLS, Da Silva Calestini GL, Alvo FS, De Moura Freitas JM, Castro PMV, Konstantyner T. Safety of human papillomavirus 6, 11, 16 and 18 (recombinant): Systematic review and meta-analysis. *Revista Paulista de Pediatria.* 2015;33(4):474-82. BRAZIL

No increased risk for serious events in vaccination people

What about those stories on the internet about….

Complex Regional Pain Syndrome (CRPS)

Postural Orthostatic Tachycardia Syndrome (POTS)

Safety Profile of the 9-Valent HPV Vaccine: A Combined Analysis of 7 Phase III Clinical Trials

Edson D. Moreira Jr, MD, PhD,[a] Stan L. Block, MD,[b] Daron Ferris, MD,[c] Anna R. Giuliano, PhD,[d] Ole-Erik Iversen, MD,[e] Elmar A. Joura, MD,[f] Pope Kosalaraksa, MD,[g] Andrea Schilling, MD,[h] Pierre Van Damme, MD, PhD,[i] Jacob Bornstein, MD, MPA,[j] F. Xavier Bosch, MD,[k] Sophie Pils, MD,[f] Jack Cuzick, PhD,[l] Suzanne M. Garland, MD,[m] Warner Huh, MD,[n] Susanne K. Kjaer, MD,[o] Hong Qi, MD, MPH,[p] Donna Hyatt, BA,[p] Jason Martin, MS,[p] Erin Moeller, MPH,[p] Michael Ritter, BA,[p] Martine Baudin, MD,[q] Alain Luxembourg, MD, PhD[p]

- >15,000 received ≥1-dose HPV9
- Pregnancies were followed to outcome (n=2950)
- Safety outcomes followed for 7 – 72 months
- New medical conditions collected at each visit
  - 2 developed CRPS, both related to a previous injury
  - 2 developed POTS, one case >3 years after vaccination

Moreira ED, Jr., Block SL, Ferris D, Giuliano AR, Iversen OE, Joura EA, et al. Safety Profile of the 9-Valent HPV Vaccine: A Combined Analysis of 7 Phase III Clinical Trials. Pediatrics. 2016:e20154387.

INTERNAL MEDICINE JOURNAL

Adverse event monitoring of the human papillomavirus vaccines in Scotland

R. L. Cameron, S. Ahmed and K. G. J. Pollock

Vaccine Preventable Diseases, Health Protection Scotland, Glasgow, UK

- Scottish hospital admissions
  - Sixty diagnosis 2004 – 2014 including POTS
  - 246,954, three doses of vaccine 2008 – 2014
  - 12 admissions
  - No increase over expected levels in any years

Cameron RL, Ahmed S, Pollock KG. Adverse event monitoring of the human papillomavirus vaccines in Scotland. Internal medicine journal. 2016;46(4):452-7.

Key points

- Significant clinical and observational data support the positive safety profile of HPV vaccines
- No increased risk for serious events
  - Exception syncope (fainting) at time of injection
- HOWEVER – positive impact on disease seen in countries using vaccine including NZ!

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