Vacinação contra o HPV: questões para o debate e insumos da literatura

Hillegonda Maria Dutilh Novaes

13 de março de 2014

Tendências da incidência do câncer de colo de útero: mudanças nos fatores de risco e impacto do rastreamento

European Journal of Cancer (2013) 49, 3262–3273

Available at www.sciencedirect.com

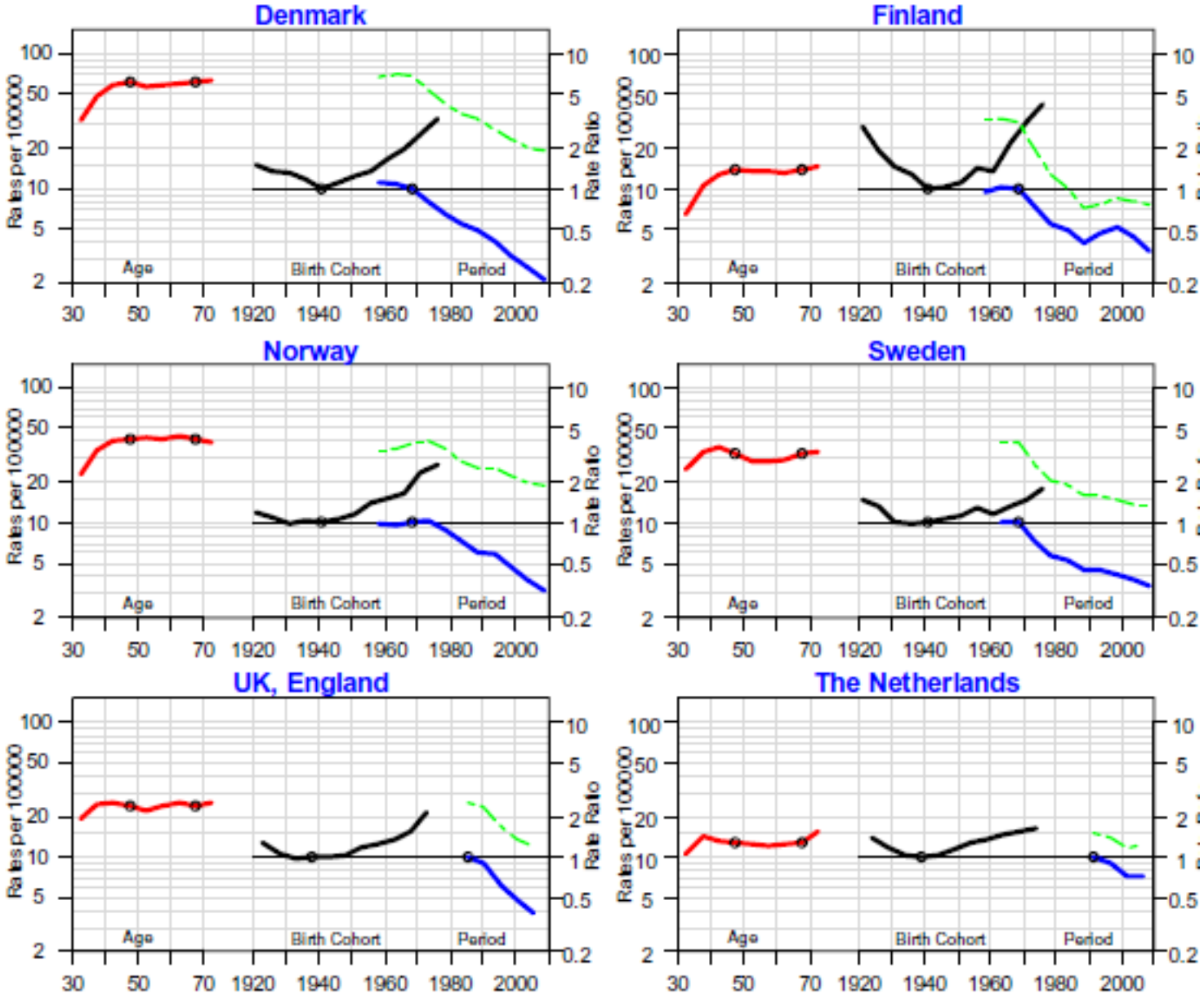
SciVerse ScienceDirect

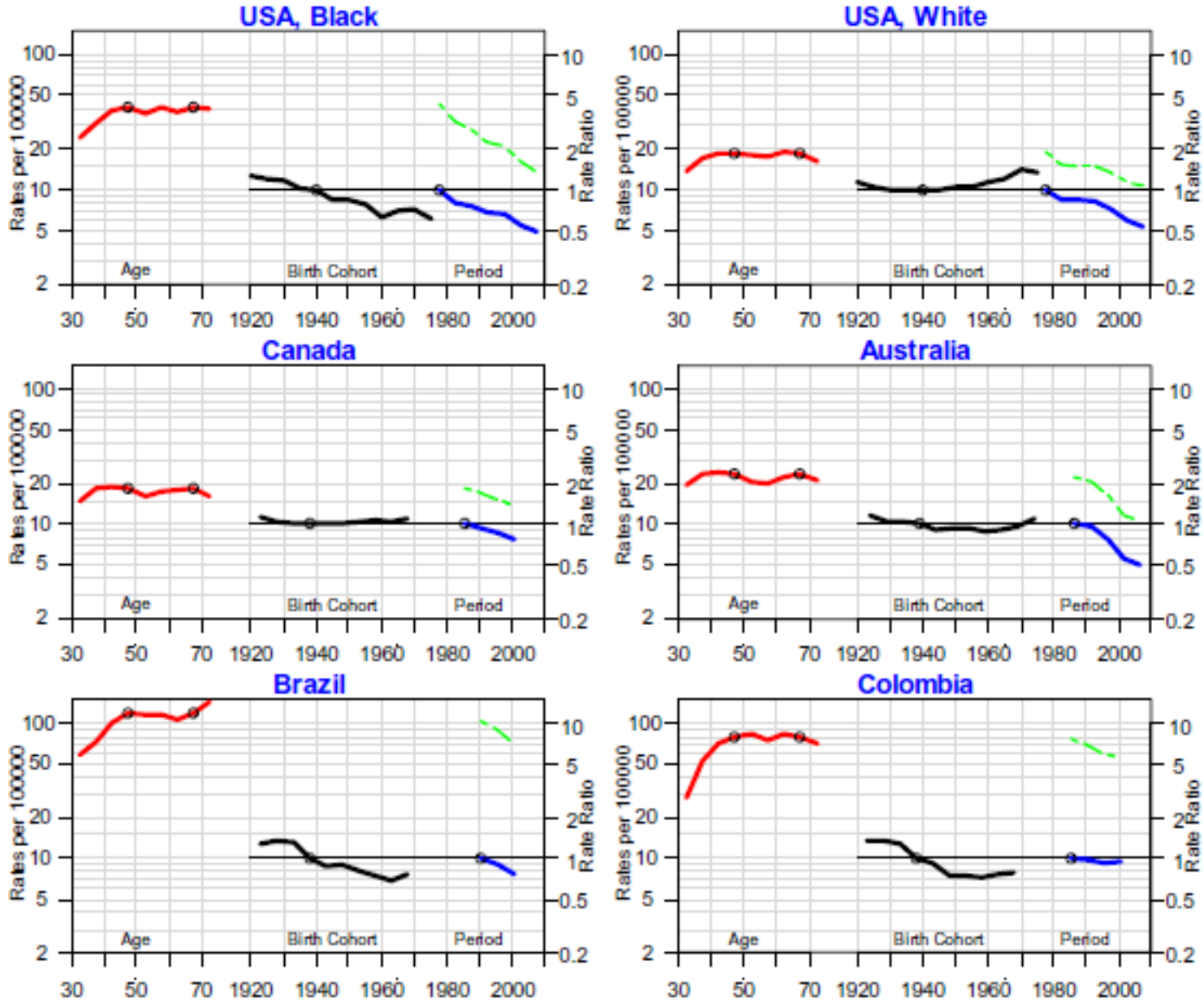
journal homepage: www.ejcancer.com

Worldwide trends in cervical cancer incidence: Impact of screening against changes in disease risk factors

Salvatore Vaccarella *, Joannie Lortet-Tieulent, Martyn Plummer, Silvia Franceschi, Freddie Bray

International Agency for Research on Cancer, 150 Cours Albert Thomas, 69372 Lyon Cedex 08, France


Denmark
Finland
Norway
Sweden
UK, England
The Netherlands
Rates per 100000
Rate Ratio
100
50
20
10
5
2
1
0.5
0.2
30
50
70
1920
1940
1960
1980
2000
Age
Birth Cohort
Period


USA, Black
USA, White
Canada
Australia
Brazil
Colombia
Rates per 100000
Rate Ratio
Age
Birth Cohort
Period
100
50
20
10
5
2
1
0.5
0.2
30
50
70
1920
1940
1960
1980
2000

Vacinas contra o HPV e resultados dos ensaios clínicos

Vaccine 30S (2012) F123–F138

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

A Review of Clinical Trials of Human Papillomavirus Prophylactic Vaccines

John T. Schiller[a,*], Xavier Castellsagué[b,c], Suzanne M. Garland[d,e,f,g]

[a] Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA
[b] Unit of Infections and Cancer (UNIC), Cancer Epidemiology Research Program (CERP), Institut Català d'Oncologia - Catalan Institute of Oncology (ICO), L'Hospitalet de Llobregat (Barcelona), Spain
[c] CIBER en Epidemiología y Salud Pública (CIBERESP), Spain
[d] Regional World Health Organization Human Papillomavirus Laboratory, Network, Department of Microbiology and Infectious Diseases, The Royal Women's Hospital
[e] Department of Obstetrics and Gynaecology, University of Melbourne
[f] Department of Microbiology, Royal Children's Hospital
[g] Murdoch Childrens Research Institute

Table 1
Characteristics of HPV VLP vaccines.

	Gardasil®	Cervarix®
Manufacturer	Merck	GlaxoSmithKline
VLP Types	6/11/16/18	16/18
Dose of L1 Protein	20/40/40/20 μg	20/20 μg
Producer Cells	*Saccharomyces cerevisiae* (baker's yeast) expressing L1	*Trichoplusia ni* (Hi 5) insect cell line infected with L1 recombinant baculovirus
Adjuvant	225 μg aluminum hydroxyphosphate sulfate	500 μg aluminum hydroxide, 50 μg 3-O-deacylated-4′-monophosphoryl lipid A
Injection Schedule	0, 2, 6 months	0, 1, 6 months

Gardasil® (Merck & Co., Whitehouse Station, NJ USA).
Cervarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium).
HPV: human papillomavirus; VLP: virus-like particle.
Data from [1].

Table 2
Characteristics of phase III efficacy studies in young women.

Characteristic	FUTURE I	FUTURE II	PATRICIA	CVT
Vaccine	Gardasil®	Gardasil®	Cervarix®	Cervarix®
Funding source	Merck & Co., Inc.	Merck & Co., Inc.	GlaxoSmithKline	National Cancer Inst.
No. study sites	62	90	135	7
Countries included	16	13	14	1
Length	4 years	4 years	4 years	4 years
Control	225 μg Aluminum hydroxyphosphate sulfate	225 μg Aluminum hydroxyphosphate sulfate	Hepatitis A Vaccine	Hepatitis A Vaccine
Age	16–24	15–26	15–25	18–25
Lifetime no. sexual partners	≤4	≤4	≤6[a]	No restriction
Exclusion criteria	Pregnancy, history of abnormal Pap smear or genital warts	Pregnancy, history of abnormal Pap smear	Pregnancy, breastfeeding, history of colposcopy, autoimmume disease or immunodeficiency	Pregnancy, breastfeeding, history of immunosuppression, hysterectomy, hepatitis A vaccination
Primary endpoints	Incident HPV6/11/16/18-associated genital warts, CIN1-3, VIN1-3, VaIN1-3, AIS and cervical, vaginal or vulvar cancer	Incident HPV16/18 –associated CIN2-3, AIS or cervical cancer	Incident HPV16/18 –associated CIN2+	Incident 12 mo. persistent HPV16/18 infection

[a] No limitation for Finnish subjects.
AIS: Adenocarcinoma in situ; CIN: Cervical intraepithelial neoplasia; CVT: Costa Rica HPV trial; HPV: Human papillomavirus; VIN/VaIN: Vulvar/vaginal intraepithelial neoplasia.
Data from [14–17].

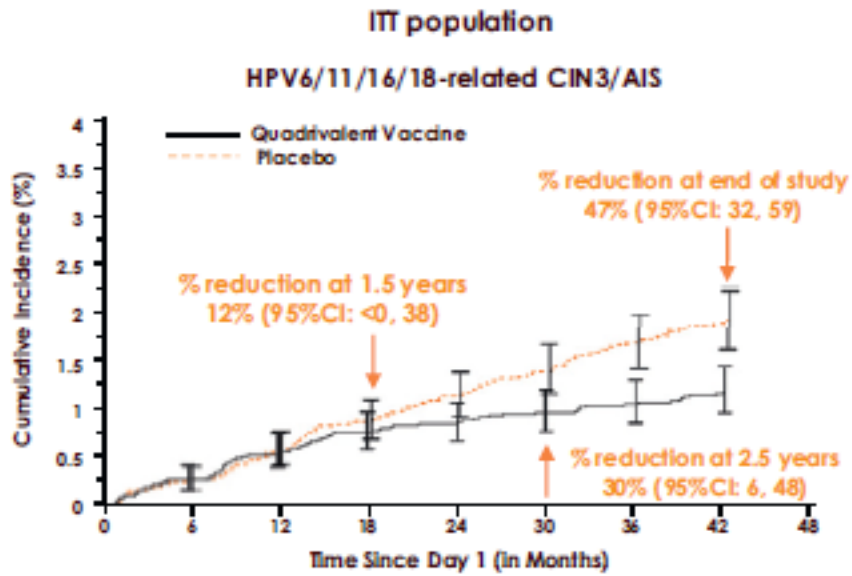


Figure 1. Rate reduction and vaccine efficacy are time dependent variables. Time-to-event curves for acquisition of HPV6/11/16/18-related CIN3/AIS in Gardasil® (Merck & Co., Whitehouse Station, NJ USA) and placebo recipients in the ITT cohort. AIS: Adenocarcinoma in situ; CI: Confidence interval; CIN3: Grade 3 cervical intraepithelial neoplasia; HPV: Human papillomavirus; ITT: Intention-to-treat. Taken with permission from [21].

Table 7
Cross-type protection against 6-month persistent infection.

	Efficacy (95% CI)		
Trial:	FUTURE I/II	PATRICIA	CVT
Vacccine:	Gardasil®	Cervarix®	Cervarix®
Cohort:	ITT-Naïve	TVC-Naïve	ATP
Mean Follow-up:	3.6 yrs	3.3 yrs	4 yrs
HPV31	46.2 (15.3-66.4)	77.1 (67.2-84.4)	64.7 (42.6-78.9)
HPV33	28.7 (−45.1-65.8)	43.1 (19.3-60.2)	32.1 (−41.1-68.2)
HPV35	17.8 (−77.1-62.5)	−21.8 (−102.5-26.2)	25.0 (−40.6-60.6)
HPV52	18.4 (−20.6-45.0)	18.9 (3.2-32.2)	19.6 (−8.1-40.4)
HPV58	5.5 (−54.3-42.2)	−6.2 (−44.0-21.6)	2.8 (−48.0-36.2)
Non-Vaccine A9	21.9 (0.6-38.8)	27.6 (17.6-36.5)	NR
HPV39	NR	20.9 (−2.3-39.9)	−30.8 (−109.2-17.6)
HPV45	7.8 (−67.0-49.3)	79.0 (61.3-89.4)	73.0 (45.3-87.8)
HPV59	18.7 (−22.8-46.4)	−3.9 (−61.7-33.1)	−30.3 (−130.3-25.6)
HPV68	NR	8.9 (−18.8-30.1)	NR
Non-vaccine A7	14.8 (−19.9-39.6)[a]	22.3 (8.4-34.2)	NR
HPV51	NR	25.5 (12.0-37.0)	−56.1 (−114.3-−14.2)
HPV56	NR	1.4 (−24.8-22.0)	25.8 (−12.7-51.4)
HPV66	NR	−1.5 (−29.3-20.3)	1.6 (−41.0-31.3)

[a] HPV45 and 59 only.

ATP: According to protocol; CVT: Costa Rica HPV Trial; CI: Confidence interval; HPV: Human papillomavirus; ITT: Intention-to-treat; NR: Not reported; TVC: Total vaccine cohort.

Data from [26,29,30].

Table 8
Assessment of serious adverse events.

Outcome	Study	Vaccine	% Vaccine	% Control	Relative risk (95% CI)
SAE					
	FUTURE I	Gardasil®	1.8	1.7	1.07 (0.71-1.60)
	FUTURE II	Gardasil®	0.7	0.9	0.83 (0.56-1.24)
	PATRICIA	Cervarix®	7.5	7.5	1.00 (0.91-1.11)
Injection-related SAE					
	FUTURE I	Gardasil®	0.03	0.00	3.00 (0.12-73.58)
	FUTURE II	Gardasil®	0.05	0.03	1.50 (0.25-8.99)
	PATRICA	Cervarix®	0.12	0.06	1.83 (0.68-4.96)

CI: Confidence interval; SAE: serious adverse event.
Data from [38].

Table 5
Protection of young women against incident cervical disease by Cervarix® in the PATRICIA trial.

A. HPV16 or HPV18-related endpoints

	% Efficacy (95% CI)	Rate reduction[a]
ATP-E		
CIN2+	94.9 (87.7-98.4)	0.38
CIN3+	91.7 (66.6-99.1)	0.09
AIS	100 (-8.6-100)	0.02
TVC-naïve		
CIN2+	99.0 (94.2-100)	0.47
CIN3+	100 (85.5-100)	0.13
AIS	100 (15.5-100)	0.03
TVC		
CIN2+	60.7 (49.6-69.5)	0.43
CIN3+	45.7 (22.9-62.2)	0.13
AIS	70.0 (-16.6-94.7)	0.02

B. Endpoints irrespective of HPV DNA

	% Efficacy (95% CI)	Rate reduction[a]
TVC-naïve		
CIN2+	64.9 (52.7-74.2)	0.54
CIN3+	93.2 (78.9-98.7)	0.20
AIS	100 (31.0-100)	0.03
TVC		
CIN2+	33.1 (22.2-42.6)	0.44
CIN3+	45.6 (28.8-58.7)	0.22
AIS	76.9 (16.0-95.8)	0.03

[a] per 100 women years.
AIS: Adenocarcinoma in situ; ATP-E: According to protocol for efficacy; CI: Confidence interval; CIN: Cervical intraepithelial neoplasia; HPV: Human papillomavirus; TVC: Total vaccine cohort.
Data from [23].

Monitoramento pós-introdução da vacina contra o HPV

Vaccine 30S (2012) F139–F148

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Human Papillomavirus Vaccine Introduction – The First Five Years

Lauri E. Markowitz[a,*], Vivien Tsu[b], Shelley L. Deeks[c], Heather Cubie[d], Susan A. Wang[e], Andrea S. Vicari[f], Julia M.L. Brotherton[g]

[a] Centers for Disease Control and Prevention, 1600 Clifton Rd, Atlanta, Georgia, 30333, US
[b] PATH, P.O. Box 900922, Seattle, Washington, 98109, US
[c] Public Health Ontario, 480 University Ave, Suite 300, Toronto, Ontario M5G1V2, Canada
[d] National HPV Reference Laboratory, Royal Infirmary of Edinburgh, 51 Little France Cres, Edinburgh EH16 4SA, Scotland
[e] Expanded Programme on Immunization, Department of Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland
[f] Comprehensive Family Immunization Project, Pan American Health Organization, Apartado 3745, San Jose, Costa Rica
[g] Victorian Cytology Service Registries, PO Box 310, East Melbourne, Victoria 8002, Australia

Table 1
Countries that have included HPV vaccine in their national immunization programs, date, target age groups and coverage, 2006–2011[a].

Region/Country	Year introduced	Target age group or grade for females[b]	Catch-up age group	Delivery for primary target group	Estimated 3-dose coverage[c] % (calendar year)
Europe					
Austria[d]	2006	Females/males		-	
Belgium[e]	2007	12–18	13–18	Varies by region	82% (2010) [91]
Denmark	2009	12	13–15	PC/Health centers	79%(2009) [15]
France	2007	14	15–23	PC/Health centers	24% (2008) [13]
Germany	2007	12–17		PC/Health centers	
Greece	2008	12–15		PC/health centers	
Greenland	2008	12	13–15	Mixed	
Ireland	2010	12–13		PC/Health centers	
Italy	2007–2008	11	Varies by region [14]	PC/Health centers	56% (2009) [13]
Latvia	2010	12		Mixed	
Luxemburg	2008	12	13–18	PC/Health centers	17% (2009) [13]
FYR Macedonia	2010	12	13–26	Schools	67% (2011) [92]
Netherlands	2010	12	13–16	Mixed	
Norway	2009	11–12		Schools	63% (2011) [15]
Portugal	2009	13	17	PC/health centers	81% (2009) [13]
Romania	2009	9–12		Mixed	
San Marino	2009	NA			
Slovenia	2009	11–12		Schools	55% (2010) [92]
Spain	2008	11–14		Varies by region	77% (2008) [23]
Sweden	2012	11–12	13-18	Schools	
Switzerland	2008	10–14	through age 19	Mixed	
United Kingdom	2008	12–13	13–17	Schools	84-92% (2009) [16,17]
Americas					
Argentina	2011	11		Mixed	
Canada[f]	2007–2009	Varies by province	Varies by province	Schools	Varies by province
Mexico[f]	2008	9–12		Mixed	67%[g] (2010) [35]
Panama	2008	10		Mixed	67% (2010) [35]
Peru	2011	10		Schools	
United States[h]	2006	11–12	13–26	PC/Health centers	32% (2010) [4]
South East Asia					
Bhutan	2010	12	13–18	Mixed	
Eastern Mediterranean					
Abu Dhabi, UAE	2008	15–17	18–26	Schools	59% (2011) [72]
Western Pacific					
Australia	2007	12–13	13–26	Schools	71% (2009) [11]
Cook Islands	2011	9–13			
Fiji[i]	2008	NA			
Kiribati	2011	NA			
Malaysia	2010	PG 7 (age 13)	13–18	Schools	
FS Micronesia[j]	2009	11-12		PC/Health centers	
Marshall Islands[j]	2008	11-12		PC/Health centers	
New Zealand	2008	PG 8 (age 12)	13–18	Mixed[k]	40% (2010) [93]

4. Post-licensure evaluation: safety, impact and acceptability

4.1. Safety

Post-licensure safety studies are important because, while large phase III trials were conducted for both vaccines, rare adverse events may not have been detected. Furthermore, monitoring and communication about vaccine safety is critical, as events temporally associated with vaccination can be falsely attributed to vaccination. Safety monitoring is part of routine activities post-introduction in many countries (Table 3) [39]. These passive monitoring systems have limitations, including reporting of events that may have occurred coincidentally following vaccination as well as incomplete reporting. A formal evaluation of the passive surveillance system in the US, the Vaccine Adverse Event Reporting System (VAERS), was conducted after over 23 million doses of quadrivalent HPV vaccine were distributed (June 2006 through December 2008) [40,41]. In Australia, a review of data after 6 million doses of quadrivalent vaccine were distributed did not reveal unusual patterns of reports [42]. Similarly, in the UK, no pattern of adverse events or reason for concern was found after 4.5 million doses of bivalent vaccine had been administered [43]. Many other countries have safety monitoring systems as well. Registries for women inadvertently vaccinated during pregnancy have been

Continuando...

established or expanded, including those by both manufacturers; data to date do not raise any concerns [44,45].

In the US, evaluation of specific events that might be associated with vaccination is done through the Vaccine Safety Datalink (VSD), a system which evaluates adverse events in those vaccinated compared to a control group [46]. Data were analyzed in VSD after more than 600,000 doses of quadrivalent HPV vaccine had been administered to females and raised no concerns. Post-licensure studies by the manufacturers comparing rates of adverse events in vaccinated with unvaccinated groups are ongoing or have been completed [47].

WHO's Global Advisory Committee on Vaccine Safety has reviewed data on HPV vaccine three times, most recently after >60 million doses of the quadrivalent or bivalent HPV vaccine had been distributed worldwide [48]. The Institute of Medicine also reviewed data on quadrivalent HPV vaccine safety in 2011 [49]. All reviews show that the accumulating evidence on the safety of HPV vaccines is reassuring.

Specific events that have occurred temporally related to administration of HPV vaccine have impeded vaccine acceptance in several countries, or resulted in disruption of immunization programs [50–52]. For example, two cases of status epilepticus temporally related to receipt of quadrivalent vaccine resulted in suspension of Spain's vaccination program for over 2 months and deaths temporally associated with vaccine receipt in Germany and Austria caused concern across Europe [52]. When possible, determination of the cause of death can allay concerns that these are vaccine-related [53]. Official national investigation and response to these reports has been important for the vaccination programs [54].

4.2. Impact and effectiveness

A variety of efforts are ongoing to monitor impact of HPV vaccine post-licensure. Because cancer endpoints take longer to observe, efforts are ongoing to determine more proximal measures. Both manufacturers have post-licensure commitments to monitor duration of protection against precancerous lesions by following women who had been enrolled in the phase III trials in the Nordic countries where registries allow follow-up and determination of cervical screening and biopsy results, as well as access to specimens [55,56]. For the quadrivalent HPV vaccine, women will be followed for a total of 14 years (10 years after termination of the phase III trial) in Denmark, Sweden, Norway and Iceland. The first results from the quadrivalent HPV vaccine follow-up found no cases of HPV-associated disease among vaccinees through 6 years post-vaccination. For the bivalent vaccine, follow-up data will be available from Finland in 2012.

Biologic outcomes ranging from HPV prevalence to cancer are being monitored by public health efforts in some developed countries [55,57–59]. Countries with cancer registries will be able to monitor the incidence of cervical and other HPV-associated cancers. Several more proximal outcomes are being monitored, including HPV prevalence, genital warts and cervical precancerous lesions. In Australia, where high coverage with the quadrivalent vaccine was achieved soon after introduction, impact on genital warts has been observed in the age group of women targeted for vaccination, as well as in males [58]. The proportion of women 12–26 years of age diagnosed with genital warts decreased by 73% within 3 years of vaccine introduction [60]. There was also a decrease observed for heterosexual men (25%), but none in men who have sex with men. As men were not included in the vaccination program, this suggests impact from herd immunity. Decreases in cervical precancerous lesions may also have been observed [59].

While monitoring vaccine impact is of interest for many countries, it is difficult and can be expensive. WHO guidance states that monitoring HPV-associated disease or infection is not a prerequisite to vaccination initiation [61].

Table 3
Post-licensure HPV vaccine safety evaluations or reviews.

Organization	System or review	Country data reviewed	Description	Reference or website
Therapeutic Goods Administration, Australia	Routine passive surveillance	Australia	National passive reporting system that accepts reports from the providers, public, and vaccine manufacturers on adverse events associated with vaccines licensed in Australia.	http://www.tga.gov.au/safety/alerts-medicine-gardasil-070624.htm
Public Health Agency of Canada	Canadian Adverse Events Following Immunization Surveillance System (CAEFISS)	Canada	National passive reporting system that accepts reports from the providers, public and vaccine manufacturers on adverse events associated with vaccines licensed in the Canada.	http://www.phac-aspc.gc.ca/im/vs-sv/caefiss-eng.php
Public Health Agency of Canada	Canadian Immunization Program Active (IMPACT)	Canada	Hospital-based national active surveillance network: reports the more serious hospitalized cases and selected outpatient visits for adverse events and vaccine-preventable diseases.	http://www.cps.ca/English/surveillance/IMPACT/IMPACT.htm
Ministry of Health, Netherlands	Active follow-up study	Netherlands	Investigation of adverse events within 7 days after vaccination with the bivalent HPV vaccine. One week after each of the three doses, the participants received by e-mail a Web-based questionnaire focused on local reactions and systemic events.	Klooster TM *et al.* [94]
Medicines and Healthcare products Regulatory Agency, UK	Yellow Card Scheme	United Kingdom	National passive reporting system that accepts reports from the providers and the public on adverse events associated with vaccines licensed in the UK.	http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON096806
Centers for Disease Control and Prevention, US	Vaccine Adverse Event Reporting System (VAERS)	US	National passive reporting system that accepts reports from providers, the public and vaccine manufacturers on adverse events associated with vaccines licensed in the United States.	Slade B *et al.* [40] http://www.cdc.gov/vaccinesafety/vaccines/hpv/gardasil.html
Centers for Disease Control and Prevention, US	Vaccine Safety Datalink (VSD)	US	Large linked database that uses administrative data sources from participating managed care organizations. Rates of adverse events in people who have received a particular vaccine are compared to rates among those not vaccinated.	Gee J *et al.* [46] http://www.cdc.gov/vaccinesafety/Activities/vsd.html
GlaxoSmithKline	Vaccine in Pregnancy Registry	US and European Union	Registry of women who inadvertently receive vaccine in pregnancy. Around the patient's estimated date of delivery, a short follow-up form is sent to the registering healthcare provider to report on the pregnancy course and outcome.	http://pregnancyregistry.gsk.com/Cervarix.html
Merck and Company, Inc.	Vaccine in Pregnancy Registry	US, France, Canada	Registry of women who inadvertently receive vaccine in pregnancy. Around the patient's estimated date of delivery, a short follow-up form is sent to the registering healthcare provider to report on the pregnancy course and outcome.	Dana A *et al.* [45] http://www.merckpregnancyregistries.com/gardasil.html
Merck and Company, Inc.	Post marketing commitment (to US FDA)	US	Retrospective cohort study with follow-up through electronic medical records, supplemented with medical record review conducted at two large managed care organizations.	Chao C *et al.* [47]
Global Advisory Committee on Vaccine Safety, WHO	Review	Worldwide	Review of existing or published data on vaccine safety.	Velicer C. (presentation) [95] http://www.who.int/vaccine_safety/Jun_2009/en/
Institute of Medicine, US	Adverse Effects of Vaccines: Evidence and Causality	Worldwide	Review of evidence to determine if adverse events following vaccination are causally linked to a specific vaccine.	http://www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx

FDA: Food and Drug Administration; WHO: World Health Organization.

4.3. Vaccine acceptability

Studies conducted post-licensure have determined predictors of vaccination, reasons for non-vaccination and intent to receive vaccine among those unvaccinated. While vaccine acceptability has generally been high, some studies in high-income countries have found that a sizable minority of parents of unvaccinated daughters reported that they did not intend to have their daughter vaccinated in the near future. In British Columbia, even with public financing for vaccine and school-based vaccination, 35% of parents decided not to have their daughter vaccinated [62]. Reported major reasons were concerns about vaccine safety (30%), wanting to wait until their daughter is older (16%), and not having enough information about the vaccine (13%). In the US, a national survey found that 33% of parents of unvaccinated girls did not intend to have their daughter vaccinated in the next year. The most commonly reported reasons included: lack of knowledge about the vaccine (19%), belief that the vaccine is not needed (19%), belief that their daughter is not sexually active (18%), lack of a provider recommendation (13%), and concerns about vaccine safety (7%) [63]. Smaller, qualitative studies also found that the recommended age for receipt of vaccine in early adolescence is a concern [64–66]. Consistent with studies of other vaccines, a strong provider recommendation has been found to be important for vaccine initiation [63,67–69]. With regard to concerns that vaccination might promote early sexual debut or risky behavior, studies have not identified this as a major reason for vaccine refusal [68]; however, concern about adverse behavioral consequences has been identified in some studies and has been associated with lower vaccine acceptance [65,70].

Concerns raised about vaccine safety and information spread by some anti-vaccination groups have impacted acceptability in some countries. Intention to vaccinate in Greece was found to decrease significantly between 2006 and 2010 [71]. Reasons for refusal changed during this time period, with safety concerns becoming the most common reason for rejecting vaccination in 2010. Safety concerns have resulted in decreased vaccine uptake in other countries as well (Jumaan A *et al.*, Vaccine, this issue [72]).

In the four countries where PATH demonstration projects were conducted, vaccine acceptance was high [30]. Factors inhibiting vaccine acceptance varied by country but included fears about pos-

5. HPV vaccine debate and anti-immunization efforts

HPV vaccine introduction has generated considerable debate in many countries [15,73]. Issues include concerns about cost and affordability, benefits of vaccination, which of the two vaccines to introduce, extent of catch-up vaccination, and the role of manufacturers and special interest groups in promotion. In Germany, publication of a 'Manifest' in 2008 that criticized the recommendation for HPV vaccination and implementation in the national vaccination schedule, led to widespread public debate. Written by a group of 13 prominent public health professionals and physicians, this document stated that the effectiveness of vaccination had not been sufficiently studied and the efficacy for prevention of precancer and cancer had not been adequately communicated [74]. This publication and the ensuing debate likely resulted in decreased vaccine promotion by the medical community and increased skepticism by the public. Similar debate occurred in some Nordic countries [15]. Concerns have also been expressed by religious communities in several countries. A public letter released from the Catholic Bishops of Ontario stating concern about vaccine

introduction without further study of the program effects might have contributed to low uptake in some provinces [75].

Manufacturer efforts to promote HPV vaccination requirements for school attendance soon after vaccine introduction in the US resulted in widespread debate [76]. The backlash against these requirements included many groups, including not only those opposed to vaccination but also those opposed to government interference with parental autonomy and those concerned that HPV vaccine would promote risky sexual behavior [6]. While the manufacturer abandoned these lobbying efforts, consequences of these efforts were still evident in 2011 [77].

Several countries have active anti-vaccine movements, which have capitalized on the HPV vaccine debate. Some anti-vaccination groups are well established and organized to oppose HPV vaccine soon after introduction [78,79]. Many of these groups focus on concerns about safety and use reports of adverse events temporally related to vaccination to promote opposition to vaccination programs; groups in the US regularly post anti-vaccine messages to their website or issue press releases [80,81]. An article which misused post-licensure safety data was published in a medical journal in 2011 [82]. While these groups are mainly in high-income countries, access to the internet has facilitated spread of anti-vaccination information around the globe.

Revisão impacto populacional

Journal of Adolescent Health 53 (2013) 679–682

ELSEVIER

JOURNAL OF ADOLESCENT HEALTH

www.jahonline.org

Commentary

Population Impact of HPV Vaccines: Summary of Early Evidence

Susan Hariri, Ph.D. [a,*], Lauri E. Markowitz, M.D. [a], Eileen F. Dunne, M.D., M.P.H. [a], and Elizabeth R. Unger, M.D., Ph.D. [b]

[a] *Division of STD Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia*
[b] *Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia*

Keywords: HPV vaccine; Cervical cancer; Prevention

A B S T R A C T

Human papillomavirus (HPV) vaccines are available in the United States and around the world to prevent HPV-associated diseases including cervical cancer and genital warts. HPV vaccination is currently recommended for adolescents: target ages for routine and catch-up vaccinations vary by country. Because the time from vaccination to cancer development can be several decades, many studies are evaluating more immediate outcomes. In the 4 years since the vaccine was introduced, reductions in HPV vaccine type prevalence and genital warts have been reported in young females in the United States and other countries. Many questions remain about the long-term impact, but the initial studies show promising results for the relatively new HPV vaccine.

Table 1
Summary of published studies of HPV vaccine impact on biologic endpoints

Country (year vaccine introduced)	Data source and/or location	First author, publication year, [reference no.]	Population	Study design	Results[b]
HPV infection[a]					
Australia (2007)	Family planning clinics in Victoria	Tabrizi, 2012 [10]	Females 18–24 years	Ecologic, compared pre- to postvaccine periods	VT prevalence decreased from 28.7% (2005–2007) to 5.0% (vaccinated, 2010–2011) and 15.8% (unvaccinated, 2010–2011)
USA (2006)	Adolescent/ community health clinics in Ohio	Kahn, 2012 [9]	Females 13–26 years	Compared pre- to postvaccine periods by vaccination status	VT prevalence decreased from 31.8% (2006–2007) to 9.9% (vaccinated, 2009–2010) and 15.4% (unvaccinated, 2009–2010)
	Urban STD/ community health clinics in Indiana	Cummings, 2012 [8]	Females 14–17 years	Ecologic, compared pre- to postvaccine periods	VT prevalence decreased from 24% (1999–2005) to 5.3% (2010)
	Nationally representative survey	Markowitz, 2013 [7]	Females 14–59 years	Ecologic, compared pre- to postvaccine periods	VT prevalence decreased in 14–19 year olds from 11.5% (2003–2006) to 5.1% (2007–2010). No decrease in older age groups
Genital warts					
Australia (2007)	Sexual health clinic in Melbourne	Fairley, 2009 [11]	Females and males, all ages	Ecologic, trend analysis	New GW diagnoses decreased from 12.7% (2004–2007) to 6.6% (2008) in females <28 years and from 14.3% (2004/7) to 11.8% (2008) in heterosexual males. No decrease in females ≥28 years or homosexual males
		Read, 2011 [15]	Females and males, all ages	Ecologic, trend analysis	New GW diagnoses decreased from 18.6% (2007–2008) to 1.9% (2010–2011) in females <21 years and from 22.9% (2007–2008) to 2.9% (2010–2011) in heterosexual males <21 years. No decrease in females, heterosexual males ≥30 years or homosexual males
	Sexual health clinics throughout country	Donovan, 2011 [12]	Females and males, all ages	Ecologic, trend analysis	New GW diagnoses decreased from 11–12% (2004–2007) to 4.8% (2010–2011) in female residents aged 12–26 years and from 13–14% (2004–2007) to 8.9% (2010–2011) in heterosexual males. No decrease in females >26 years or homosexual males
		Ali, 2013 [13]	Females and males, 3 age groups (<21, 21–30, >30 years)	Ecologic, compared pre- to postvaccine periods	New GW diagnoses decreased from 11.5% (2007) to 8.5% (2011, unvaccinated) and 0 (2011, vaccinated) in females <21 years, from 11.3% (2007) to 3.1% (2011) in females 21–30 years, and from 18.2% (2007) to 8.9% (2011) in heterosexual males
	Medicare registry	Ali, 2013 [14]	Females and males, 15–44 years, 10-year age groups	Ecologic, trend analysis	In-patient vulvar/vaginal and penile GW treatments decreased 85% (from 285 [2007] to 42 [2011]), in females 15–24 years, 24% (from 202 [2007] to 153 [2011]), in females 25–34, 71% (from 51 [2007] to 15 [2011]) in males 15–24 years, and 59% (from 39 [2007] to 16 [2011]) in males 25–34 years. No decrease in males or females 35–44 years
New Zealand (2008)	Sexual health clinic in Auckland	Oliphant, 2011 [20]	Females and males, two age groups (<20, ≥20 years)	Ecologic, trend analysis	GW diagnoses decreased from 13.7% (2007) to 5.9% (2010) in females <20 years and from 11.5% (2007) to 6.9% (2010) in males <20 years. No decrease in older males or females
Denmark (2009)	National patient registry	Baandrup, 2013 [21]	Females and males, all ages	Ecologic, trend analysis	GW incidence per 100,000 person-years decreased from 381.5 (2008) to 39.8 (2011) in females 16–17 years. Smaller decrease in females 18–19, 20–21, 22–25, and 26–29. Nonsignificant decrease in males 22–25 and 26–29 years
		Blomberg, 2013 [16]	Females, birth cohorts eligible for vaccination (1989–99)	Retrospective cohort	Decrease in risk of GW among vaccinated (≥1 dose) girls compared with unvaccinated girls. Significant trend in relative risk from oldest to youngest cohort: .62, .25, .22, .12. No GW in vaccinated girls in youngest age cohort
Germany (2007)	Research database	Mikolajczyk, 2013 [19]	Females and males, 10–79 years	Ecologic, trend analysis	New GW diagnoses per 100,000 person-years decreased from 316 (2005) to 242 (2008) in females 15–19 years
Sweden (2007)	National patient registry	Leval, 2012 [17]	Females, 10–44 years	Ecologic, trend analysis	GW incidence per 100,000 person-years decreased from 617 (2006) to 523 (2010) in females 15–19 years, from 1,018 (2006) to 885 (2010) in females 20–24 years, from 584 (2006) to 500 (2010) in females 25–29 years, and from 1,070 (2006) to 1,028 (2010) in males 20–24 years. Nonsignificant increase in older males and females

Monitoramento eventos adversos

Vaccine 32 (2014) 1061–1066

Contents lists available at ScienceDirect

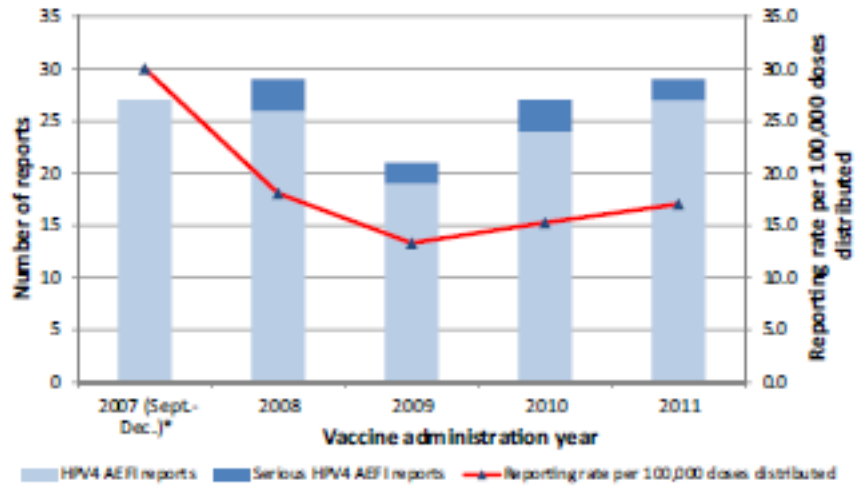
Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Adverse events following immunization in Ontario's female school-based HPV program

Tara Harris[a,*], Dawn M. Williams[a], Jill Fediurek[a], Tsui Scott[c], Shelley L. Deeks[a,b]

[a] Public Health Ontario, Toronto, ON, Canada
[b] Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada
[c] Immunization Policy and Programs, Ontario Ministry of Health and Long-Term Care, Toronto, ON, Canada



*HPV4 AEFI count for 2007 encompasses data from Sept.-Dec. only. The rate for 2007 is using HPV4 doses distributed during this same time period (Sept.-Dec. 2007)

Table 1
Confirmed adverse events following administration of quadrivalent human papillomavirus vaccine among females 12–15 years of age in Ontario, September 1, 2007 to December 31, 2011 (n= 133).

Adverse event[*]	Number of events[†]	Percent of reports (%) [**]	Rate (per 100,000 doses distributed)
Other severe/unusual events	34	26	5.1
Allergic reaction—dermatologic/mucosa	33[‡]	25	4.8
Rash	29	22	4.2
Local/injection site reaction	26	20	3.8
Allergic reaction—respiratory[§§]	6	5	0.9
Allergic reaction–gastrointestinal[§§]	5	4	0.7
Arthritis	4	3	0.6
Oculorespiratory syndrome (ORS)	3	2	0.4
Anaphylaxis	2	1	0.3
Severe vomiting and/or diarrhea[††]	2	1	0.3
Allergic reaction—not specified	2	1	0.3
Seizure	2	1	0.3
Thrombocytopenia	1	1	0.1
Fever of 38 °C or higher	1	1	0.1
Death[‡‡]	1	1	0.1
Total	152[§]		

[*] Case definitions corresponding to adverse events are available from: <http://www.health.gov.on.ca/english/providers/program/pubhealth/oph_standards/ophs/progstds/idprotocol/appendixb/aefi_cd.pdf>.

[†] Includes only those events categories where the number was ≥1.

[‡] Includes three reports where epinephrine was administered however the event was classified as 'Allergic reaction—dermatologic/mucosa' (not 'anaphylaxis').

[**] Adverse event categories are not mutually exclusive. Each report may include 1 or more events. Percentages will not sum to 100%. Denominator is 133 (total number of 'confirmed' HPV4 AEFI reports).

[§§] Presence of minor Brighton anaphylaxis criteria in the absence of suspected anaphylaxis (25).

[††] This adverse event option was no longer available in iPHIS as of December, 2007. After this date events involving either vomiting or diarrhea may have been reported under "Other severe/unusual events" or "Allergic reaction—gastrointestinal".

[‡‡] Attributed to a pre-existing cardiac condition.

[§] 152 adverse events are based on 133 HPV4 AEFI reports from September 1, 2007 to December 31, 2011.

Jornais, internet, contexto e posições políticas e sua relação com os programas de vacinação contra o HPV

Journal of Adolescent Health 54 (2014) 289–295

ELSEVIER

JOURNAL OF
ADOLESCENT
HEALTH
www.jahonline.org

Original article

The Role of Media and the Internet on Vaccine Adverse Event Reporting: A Case Study of Human Papillomavirus Vaccination

Jan M. Eberth, M.S.P.H., Ph.D. [a,b,c,*], Kimberly N. Kline, Ph.D. [b,c], David A. Moskowitz, Ph.D. [d], Jane R. Montealegre, Ph.D. [e,f], and Michael E. Scheurer, Ph.D. [f,g]

[a] South Carolina Cancer Prevention and Control Program, University of South Carolina, Columbia, South Carolina
[b] Department of Epidemiology and Biostatistics, University of South Carolina, Columbia, South Carolina
[c] Department of Communication, University of Texas at San Antonio, San Antonio, Texas
[d] Department of Epidemiology and Community Health, New York Medical College, NY, New York
[e] Department of Epidemiology, Human Genetics and Environmental Sciences, University of Texas School of Public Health, Houston, Texas
[f] Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, Texas
[g] Department of Pediatrics, Baylor College of Medicine, Houston, Texas

Article history: Received April 16, 2013; Accepted September 11, 2013
Keywords: Vaccine Adverse Event Reporting System (VAERS); Papillomavirus vaccines; Meningococcal vaccines; Mass media; Newspapers; Internet

A B S T R A C T

Purpose: This study aimed to determine the temporal association of print media coverage and Internet search activity with adverse events reports associated with the human papillomavirus vaccine Gardasil (HPV4) and the meningitis vaccine Menactra (MNQ) among United States adolescents.

Methods: We used moderated linear regression to test the relationships between print media reports in top circulating newspapers, Internet search activity, and reports to the Vaccine Adverse Event Reporting System (VAERS) for HPV4 and MNQ during the first 2.5 years after Food and Drug Administration approval.

Results: Compared with MNQ, HPV4 had more coverage in the print media and Internet search activity, which corresponded with the frequency of VAERS reports. In February 2007, we observed a spike in print media for HPV4. Although media coverage waned, Internet search activity remained stable and predicted the rise in HPV4-associated VAERS reports.

Conclusions: We demonstrate that media coverage and Internet search activity, in particular, may promote increased adverse event reporting. Public health officials who have long recognized the importance of proactive engagement with news media must now consider strategies for meaningful participation in Internet discussions.

Women's Health Issues 23-3 (2013) e143–e151

WOMEN
HEALTH ISSU
www.whijournal.

Policy matters

Political and News Media Factors Shaping Public Awareness of the HPV Vacci

Sarah E. Gollust, PhD [a,*], Laura Attanasio, BA [a], Amanda Dempsey, MD, PhD, MPH [b], Allison M. Benson, BA [c], Erika Franklin Fowler, PhD [c]

[a] *Division of Health Policy and Management, University of Minnesota School of Public Health, Minneapolis, Minnesota*
[b] *Children's Outcomes Research Program, University of Colorado School of Medicine, Aurora, Colorado*
[c] *Department of Government, Wesleyan University, 238 Church Street, Middletown, Connecticut*

Article history: Received 20 June 2012; Received in revised form 4 February 2013; Accepted 7 February 2013

A B S T R A C T

Background: In 2006, the U.S. Food and Drug Administration licensed a vaccine for the human papillomavirus (HPV) that prevents the strains of HPV that cause 70% of cervical cancers. Within months, many states introduced legislation requiring the vaccine for girls, prompting controversy and heightened political and media attention to the issue. Previous research has shown differences in HPV vaccine awareness by individual-level characteristics such as race/ethnicity, income, and education levels. We examined how individual political orientation and exposure to media coverage can also shape awareness of the vaccine.

Methods: Using data from a 2009 Internet survey of 1,216 nationally representative adult respondents linked to data on state-specific news coverage, we assessed how political orientation, media exposure, and state political context predicted HPV vaccine awareness.

Results: Younger people, women, and those with more education were significantly more likely to be aware of the vaccine. Even after controlling for these characteristics, we found that exposure to news media was associated with higher HPV vaccine awareness. Whereas liberals and conservatives were both more aware of the vaccine compared with moderates, the data are suggestive that liberals were more sensitive to news coverage.

Conclusion: These findings suggest that individual-level political identities and their interaction with the informational environment may be important factors to consider in evaluating the determinants of individuals' attitudes and

Muita coisa ainda não se sabe sobre a vacina contra o HPV

Vaccine 30S (2012) F175–F182

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Human Papillomavirus and Cancer Prevention: Gaps in Knowledge and Prospects for Research, Policy, and Advocacy

Eduardo L. Franco[a,*], Silvia de Sanjosé[b,c], Thomas R. Broker[d], Margaret A. Stanley[e], Myriam Chevarie-Davis[a], Sandra D. Isidean[a], Mark Schiffman[f]

[a] Division of Cancer Epidemiology, McGill University, Montreal, Canada
[b] Unit of Infections and Cancer (UNIC), Cancer Epidemiology Research Program (CERP), Institut Català d'Oncologia - Catalan Institute of Oncology (ICO), L'Hospitalet de Llobregat (Barcelona), Spain
[c] CIBER en Epidemiología y Salud Pública (CIBERESP), Spain
[d] Department of Biochemistry and Molecular Genetics, University of Alabama, Birmingham, AL, USA
[e] Department of Pathology, University of Cambridge, Cambridge, United Kingdom
[f] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, USA

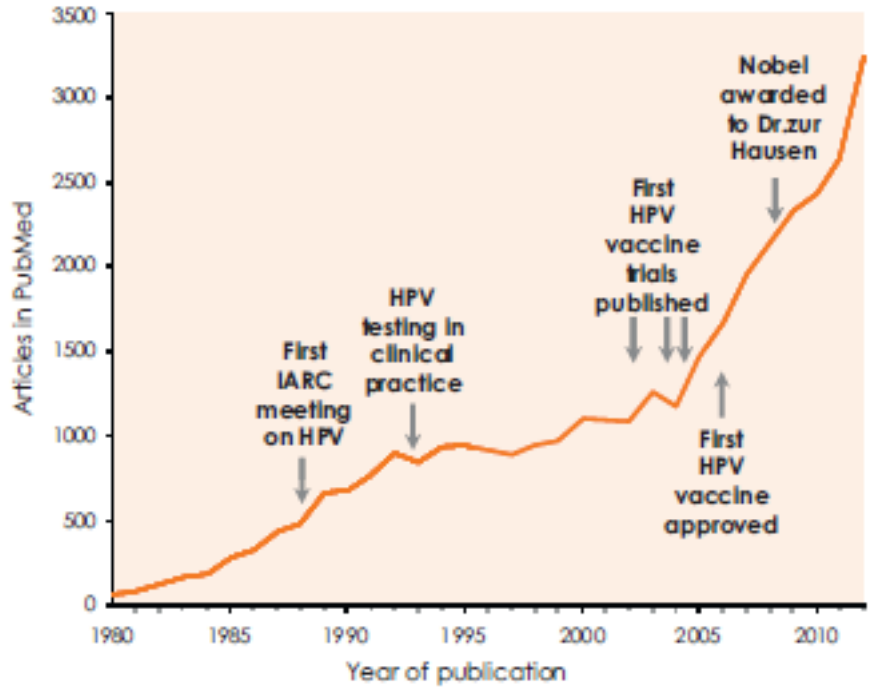


Figure 1. Number of research articles on papillomavirus in Medline's PubMed database by year of publication. Data for 2012 is a projection for a whole year based on article counts until the end of April. IARC: International Agency for Research on Cancer.

Table 3
Gaps in knowledge and pertinent research issues and hypotheses regarding the role of HPV vaccination as a primary prevention strategy.

Key questions	Research issues and ancillary hypotheses
What is the extent of cross-type protection by the existing L1 VLP-based vaccines: are benefits to be expected at the population level?	Cross-protection for types that are phylogenetically close to the vaccine types seems real but limited in efficacy and duration of protection. Differences between the vaccines, if real, could suggest adjuvant effects or be a result of how VLPs are produced.
Can correlates of immune protection be identified?	Serologic antibody titers post-vaccination or other immune markers do not predict protection at an individual level. Long-term follow-up of vaccinated populations may shed light on determinants of protection. Research is needed on different definitions of viral or lesion outcomes.
How many vaccine doses are needed? Could fewer doses provide protection? Could different injection intervals achieve equal protection?	Regulatory RCTs were designed to address the efficacy of three-dose regimens. Simplified regimens with fewer doses or different scheduling could enhance coverage and decrease costs of deploying vaccination. Can fewer doses elicit long-lasting protection?
Anamnestic response by sexual exposure post-HPV vaccination: is it expected?	Natural boosting of the immune response post-vaccination via sexual exposure to HPV infection could be examined in surveillance studies augmented by behavioral questionnaires. Is antigenic exposure high enough to heighten serological titers? Would response times be sufficient to prevent infection?
Is protection expected to be pan-mucosal?	Plausibly, vaccination exerts a prophylactic effect in all mucosal sites that serve as port of entry for HPV infections. However, there is scant data to document protection against new infections or lesions in non-cervical sites.

Does vaccination prevent recurrent infection in the same, adjacent, or distant mucosal sites?	Vaccination will not clear existing infections but may have a protective effect in adjacent areas, thus potentially having a benefit in preventing multi-focal infections and recurrent lesions in the cervix, vagina, and oral sites. More research is needed on mucosal immunity.
Is type replacement to be expected post-vaccination? Can vaccination be detrimental for the natural history of non-vaccine-target HPV types? What are the methodologic caveats in investigating this possibility?	HPVs are highly stable DNA viruses; thus, selective pressures from vaccination may not elicit the emergence of new types but may vacate existing ecological niches currently taken by HPVs16/18. Long-term follow-up of vaccinated populations will provide answers but analyses of existing cohorts can provide valuable insights as to whether or not some types are presently out-competed by HPVs 16 and 18 and could thus increase in prevalence later.
Should boys be vaccinated?	As one of the currently most pressing questions, it remains one of affordability for most countries. The benefits are the protection against HPV-associated diseases in men and the enhanced herd immunity with consequent reduction in HPV transmission in populations (ultimately benefiting both genders). Can countries attain sufficiently high male vaccination coverage rates?

RCTs: Randomized, controlled trials; VLP: Virus-like particle.

Table 4
Gaps in knowledge and pertinent research issues and hypotheses regarding the role of screening technologies in secondary cervical cancer prevention.

Key questions	Research and implementation issues
What answers are still needed from the studies of HPV testing in screening?	Is there sufficient buy-in for wide-scale implementation in high-resource settings? Can HPV DNA or RNA testing be implemented cost-effectively in middle- and low-resource settings?
Cotesting versus serial testing: what is the best option for high-resource settings?	Few countries have formally included cotesting (parallel use of HPV plus Pap cytology) in practice guidelines. Can serial testing (HPV followed by Pap triage of HPV positives) attain the same level of safety for guidelines?
If HPV testing is adopted for women ages 30 and older, what screening options should be recommended for younger women?	The technology "neglected" age range of 21–29 years continues to rely on cytology. What types of evidence will be required for increasing the age of screening initiation? Could a compromise solution exist via a single policy of serial testing (HPV followed by Pap triage) beginning at age 25?
Is VIA a solution for low-resource settings, either alone or as triage for low-cost HPV primary screening?	VIA is not as accurate as HPV testing but is easier to deploy. Is it a method that should only be combined with screen-and-treat strategies? What is the value of VIA for the triage of HPV-positive women to improve the effectiveness of screen-and-treat strategies?
Is self-sampling a solution to expand the coverage and bring equity to screening?	HPV testing of self-collected samples could permit reaching remote areas, urban women who are missed by invitations to screen, and women who refuse provider-assisted sampling. Is the balance between lower accuracy and higher coverage acceptable?
Algorithm management versus risk stratification: what is most suitable for guidelines?	Can healthcare providers learn and apply risk stratification via multiple biomarker testing as part of practice guidelines? Does it confer a more personalized level for screening and management? Is it cost-effective?
What is the role of HPV viral load as a clinical tool?	Should HPV testing be based on higher thresholds of viral load for improved specificity? Is the greater complexity of quantitative HPV assays worth the extra cost to be borne in screening?
Is there a role for genotyping in screening or triage?	Genotyping for HPVs 16, 18, and other priority hrHPVs improves the positive predictive value of screening and permits more rational colposcopy referral. Can genotyping become affordable in the near future to be implemented in screening, triage,

Table 5
Key public health and policy questions and related research issues in implementing cancer control mechanisms based on HPV prevention.

Question	Public health and policy issues and research directions
Are cost-effectiveness models coherent? Are they being used for policy decisions?	HPV vaccination and cervical cancer screening are not intended to be competing approaches to disease prevention but may be perceived as such in some settings. Decisions are highly complex and are influenced by commercial interests.
What is the role of WHO and NGOs in financing interventions?	WHO and NGOs provide guidance and assist with planning and implementation research, whereas financing of large-scale deployment must be borne by the countries (some of which will receive assistance from GAVI). Centralized procurement of vaccines and HPV tests by WHO may lower costs and enhance coverage.
How to address cross-cultural characteristics in delivering HPV-based interventions?	A one-size-fits-all approach to deploying HPV vaccination and new screen-and-treat strategies will not work well in low-resource settings. Culturally sensitive programs must take into account deeply seated beliefs stemming from religion, culture, and tradition.
How can preventive strategies be coordinated?	Integrating reproductive health programs (e.g., maternal & child health, family planning) with screening and vaccination activities may help to save resources. However, sound policies must establish priorities so as not to overload existing systems.
What does success look like?	What are the benchmarks for successful primary and secondary preventive interventions? Should they be different between high- and low-resource settings? What are the realistic goals in assessing disease prevention?
How to deal with the issue of privacy?	Proper surveillance and control require measures such as partner notification, specimen storage, linkage between vaccination records and screening, and referrals across different healthcare providers. More research is needed on the allowable ethical boundaries in the delivery of effective control programs.
How can advocacy deal with anti-vaccine activism?	Fear of undue influence by pharmaceutical companies, myths and misperceptions about the value and safety of HPV vaccination are amplified in the internet and in social media. Simple scientific reasoning is not sufficient to counter anti-vaccine activism. More research is needed on