HPV Vaccines: Efficacy Vs. Effectiveness, Next Generation Vaccines, and Controversies

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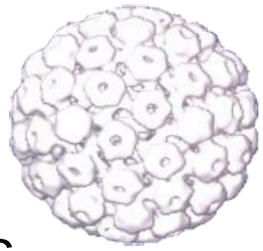
HPV-Related Diseases in the US

HPV- Related Disease	Estimated Number of Cases	Estimated Number (%) Related to HPV-6, -11, -16, or -18
Cervical cancer	11,100	7,800 (~70%)
Anal cancer	4,650	3,260 (~70%)
Vulvar, vaginal, and penile cancers	6,900	2,070 (~30%)
Head and neck cancers	34,000	5,100 (~15%)
Recurrent respiratory papillomatosis	1,000	900 (~90%)
Precancerous cervical lesions (CIN2+)	500,000	200,000 (~40%)
Genital warts	500,000	425,000 (~85%)

*ACS 2007, Chesson HW, *Persp Repro Health* 2004, Saslow D, *CA Cancer* 2007

Prophylactic HPV Vaccines

- Two vaccines based on L1 capsid (shell) protein of HPVs
- Bivalent HPV16/18, HPV2
  - Cervarix® GlaxoSmithKline
  - Regulatory approval in 50+ countries
  - US FDA approval likely based on expert committee approval in September of 2009
- Quadrivalent HPV6/11/16/18, HPV4
  - Gardasil® Merck
  - Regulatory approval in 100+ countries including the US
- Recommendations
  - Prioritize routine vaccination of females 9 to 15 years of age



Phase III Randomized Clinical Trials of HPV6/11/16/18 (Merck) or HPV16/18 (GSK) L1 VLP Vaccines in Susceptible Women (~16 to 25 Yrs)

	Merck (*NEJM* 2007;357:19)		Vaccine Efficacy	GlaxoSmithKline (*Lancet* July 7, 2009)		Vaccine Efficacy
	Vaccine	Placebo	(95% CI)	Vaccine	Placebo	(96% CI)
	5865	5863		8040	8080	
HPV 16/18-CIN2+	3	62	**95%** (85-99)	5	91	**95%** (86-98)
	2723	2732				
HPV6/11/16/18-Genital warts	3	67	**96%** (86-99)			

Merck Vaccine: HPV6/11/16/18 L1 VLP with injections 0, 2, 6 mo. (3 years FU)

GSK Vaccine: HPV16/18 L1 VLP with injections 0, 1, 6 mo. (3 year FU)

Additional RCT Findings

- Neither vaccine acts therapeutically to induce regression of established lesions
- Protection is HPV-type restricted
  - Both vaccines show partial protection against HPV-31
- Duration of protection is unknown although current evidence supports durability
  - Strong protection 6 to 8 years after VLP antibody levels have reached a plateau
  - The few vaccine failures not related to low antibody titers
  - Antigen challenge at 5 years stimulates an anamnestic response (characteristic of vaccine with long-lasting protection)

Prophylactic Efficacy Against HPV 6/11/16/18-Related Genital Lesions in Susceptible Men (15-27 years old)

Giuliano A. presented at EUROGIN, Nice France, November 2008

Endpoint	HPV6/11/16/18 Vaccine (n = 1,397)	Placebo (n = 1,408)	Vaccine Efficacy (95% CI)
Genital Warts	3	28	**89%** (66, 98)

Safety

U.S. Data for Monitoring Vaccine Safety after Licensure

- Vaccine Adverse Events Reporting System (VAERS)
  - Passive surveillance system
- Vaccine Safety Datalink (VSD)
  - Collaboration between CDC and 8 managed care organizations
  - Data from 8.8 million members captured annually (3% of US population)
  - Tests hypotheses based on pre- and post-licensure data
    - Rapid Cycle Analysis (RCA)
- Clinical Immunization Safety Assessment Network (CISA)
  - Clinical investigations of adverse event reports
  - Develop strategies to eliminate adverse events
- Vaccine Manufacturers – RCT and surveillance data

October 2008 U.S. Advisory Committee on Immunization Practices (ACIP) Meeting

- Post-vaccination syncope (fainting) happens with all adolescent vaccines, not just the HPV4 vaccine
- Available data do not support a causal relationship Between HPV4 vaccine and death, Guillain-Barre Syndrome (GBS), Transverse Myelitis (TM), or venous thromboembolism
- No confirmed reports of anaphylaxis
- Pregnant women and those with reactions to vaccine components should not be vaccinated
- Surveillance and study of outcomes ongoing in VAERS, CISA, and VSD
- CDC and FDA continue to consider the HPV4 vaccine, Gardasil®, to be a safe and effective vaccine

Population-level Effectiveness

Population-level Effectiveness

- Coverage of US adolescent females is <40%
- Coverage in countries with school-based vaccination programs:
  - Scotland (12-18 yr old females) - 90%
  - England (12-13 yr old females) - 80%
  - Australia (12-18 yr old females) - 80%
- Preliminary efficacy data from Australian STD Clinic:
  - ~50% ↓ genital wart prevalence in young women, ~ 20% ↓ in young men, and no ↓ in young MSM
- Need for sentinel surveillance systems in the US
  - SEER for CIN2-3, AIS, cancer
  - VSD for CIN2-3, AIS, cancer, and genital warts

Next Generation Vaccines

- 9-valent HPV L1 VLP – Merck (results of efficacy VS HPV4 in ~August 2013)
- HPV L2 Vaccine (early development)
- HPV L1 recombinant Ty21a *Salmonella typhi* (early development)
- HPV L1 recombinant measles (early development)

Controversies

Challenges for Implementing HPV Vaccination Programs in the U.S.

- Cost
  - >$360 for the 3-dose series
  - >$300 for public health (Vaccine for Children program)
- Consensus
  - Poor understanding of HPV link with ano-genital cancers and warts
  - Selective presentations of the risk: benefit profile
  - Denial of adolescent sexual activity
- Coverage
  - Limitations of marketing and lobbying
  - 3 doses of the same vaccine
  - Importance of school-based immunization programs

Vaccination Strategy Objectives

Feudtner and Marcuse *Pediatrics* 2001:107;1158

	Policy Alternatives		
Objectives	Mandatory	Recommended	Elective
Minimize deleterious disease consequences	Best		
Minimize deleterious vaccine consequences			Best
Maximize just distribution of benefits and burdens	Best		
Optimize personal liberty to refuse or choose			Best
Promote family duty to protect child		Best	
Promote societal duty to protect children	Best		
Use health care resources prudently	Best		

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