HPV Vaccine - Update

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Advisory Committee on Immunization Practices
June 21, 2012

Overview of talk

- HPV vaccine monitoring in the United States
- International vaccine introduction
- Vaccine schedules with less than 3 doses
- Future ACIP HPV Vaccine Work Group plans

Post licensure vaccine monitoring in the United States

- Vaccine coverage
- Vaccine safety
- Vaccine impact on infection/disease

Gardasil® Pediatric Utilization and Safety Review for the Pediatric Advisory Committee Meeting, May 8, 2012

- Triggered by 2009 and 2010 approval for prevention of genital warts in males and AIN in males and females
- Data reviewed
  - Vaccine Adverse Event Reporting System (VAERS)
  - Vaccine Safety Data Link (VSD)
  - Manufacturer's Postmarketing Commitments

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM302352.pdf

Gardasil® Pediatric Utilization and Safety Review for the Pediatric Advisory Committee Meeting, May 8, 2012

- Vaccine Adverse Event Reporting System (VAERS)*
  - No new adverse event concerns or clinical patterns identified
- Vaccine Safety Data Link (VSD)*
  - No statistically significant safety signals for the pre-specified events
- Merck's active surveillance program for females in a managed care organization*
  - No safety signals for pre-specified autoimmune diseases
- Merck's Pregnancy Registry, 5th Annual Report
  - Overall rate of congenital anomalies and miscarriages was within estimated background rate; review of congenital anomalies and deaths did not identify any unusual patterns

*Presented to ACIP in October 2011

Gardasil® Pediatric Utilization and Safety Review: Conclusions

- Almost six years of post-marketing safety surveillance in females demonstrating safety of Gardasil
- Syncope still a common adverse event
- Ongoing safety studies
  - Females: VTEs, exposure during pregnancy
  - Males: general safety, autoimmune diseases, and syncope
- FDA recommends continued monitoring of safety with attention to any unexpected differences between females and males

www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM302352.pdf

VTE – venous thromboembolic events

VACCINE IMPACT MONITORING

Monitoring impact on HPV infection and associated disease, United States

- **Type-specific HPV prevalence**
  - National survey*
  - Routine Pap specimens
- **Genital warts**
  - Network of STD clinics
  - Administrative data
- **Cervical pre-cancers**
  - Sentinel projects
  - Administrative data
- **HPV-associated cancer**
  - Established cancer registries
  - HPV typing done at several sites

*Self collected vaginal swabs in females; addition of males being piloted

Baseline (pre-vaccine era) data summarized and published

- **HPV prevalence**
  - Prevalence of genital HPV among females in the National Health and Nutrition Evaluation Survey and screened populations[1,2]
- **Cervical pre-cancer lesions**
  - Incidence and type-specific prevalence in cervical cancer precursor lesions[3]
- **Cancers**
  - HPV-associated cancers - monograph in 2008 and updated MMWR in 2012[4]

[1]Hariri, JID 2011 [1]Dunne, JID 2011 [2]Wheeler, Int J Cancer 2012 [3]Hariri JID, in press [4]Cancer 2008 [4]Watson, MMWR 2012

Analysis of genital warts – *MarketScan® Commercial Claims and Encounters Database*, 2003-2009

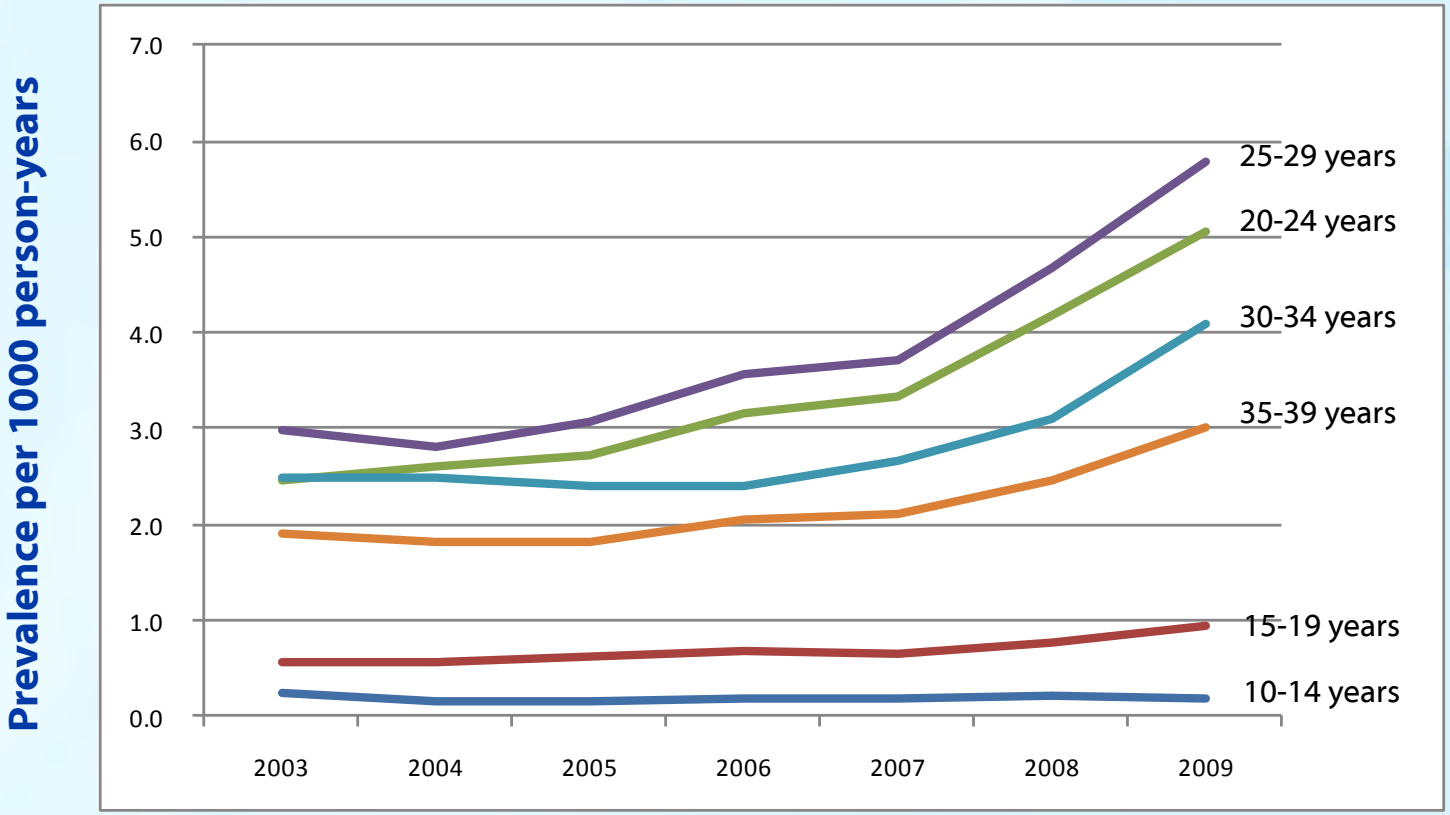
Objectives

- Estimate annual prevalence of anogenital wart diagnoses from 2003 to 2009 in a large group of privately insured US patients
- Identify changes in prevalence that might be attributable to HPV vaccination

Methods

- Persons aged 10-39 years; continuously enrolled within a given year
- 50.5 million person-years of data
- Cases defined using ICD-9-CM codes - viral warts diagnosis or medication combined with diagnosis or procedure specific to anogenital region, excluding cervix

Prevalence of anogenital warts by age 2003-2009, males



Flagg E. National STD Prevention Conference, May 2012

Prevalence of anogenital warts by age 2003-2009, females

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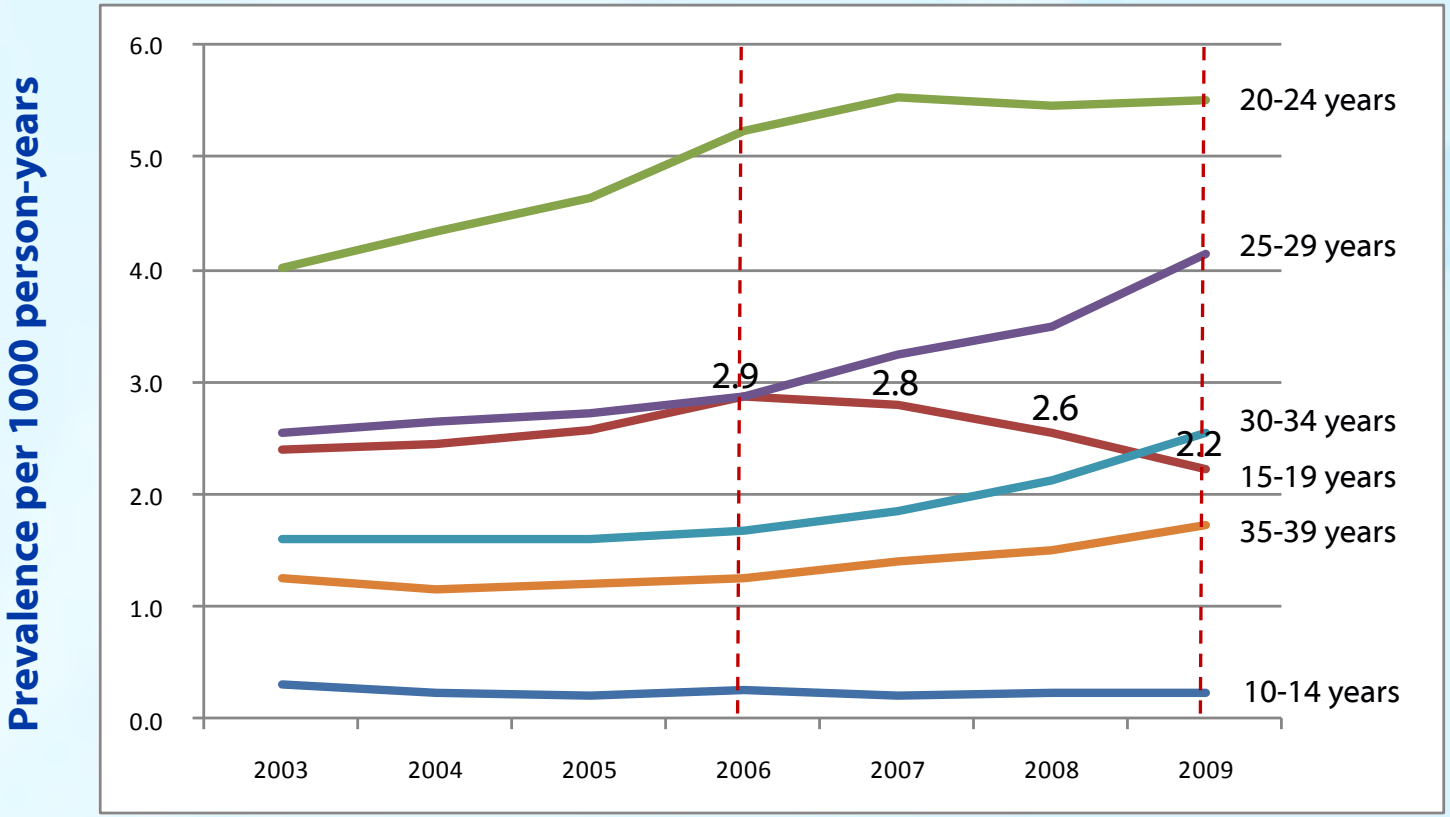

Flagg E. National STD Prevention Conference, May 2012

INTERNATIONAL ISSUES

HPV vaccine: International progress

- 2009 - WHO recommended HPV vaccination inclusion in national immunization programs if*
  - Cervical cancer/HPV-related disease is public health priority, introduction is programmatically feasible, sustainable funding can be secured, cost-effectiveness has been considered
- 2009-2011 - Few middle/low income countries introduced
  - Private donations led to demonstration projects; national introductions in 2 countries
  - Tiered pricing allowed introduction in some middle income countries

* Weekly Epidemiologic Record No. 1-2, January 2009

HPV vaccine: International progress

- November 2011 - GAVI Alliance Board announced opening a funding window for introduction of HPV vaccine
  - GAVI eligible countries can apply for national introduction based on demonstrated ability to reach target age group, or
  - Demonstration projects followed by national introduction

* Weekly Epidemiologic Record No. 1-2, January 2009

Interest in HPV vaccine schedules with less than 3 doses

- Could facilitate implementation
- More convenient for providers, parents and vaccinees
- Cost saving

Jurisdictions with 'extended' 3 dose* or 2 dose schedules

- Quebec, Canada
- British Columbia, Canada
- Mexico
- Switzerland

*Dose 1 and 2 in early adolescence, 6 months apart; dose 3 given 5 years later (0,6,60 months)

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*Dose 1 and 2 in early adolescence, 6 months apart; dose 3 given 5 years later (0,6,60 months)

British Columbia changed from a 3 dose to 'extended' 3 dose schedule in 2010 after immunogenicity study results; plan to evaluate need for third dose

Switzerland changed from 3 dose to 2 dose schedule for those younger than 15 years (2 doses at interval of 4-6 months) in 2012

Studies of less than 3 doses of HPV vaccine

- Bivalent vaccine
  - Immunogenicity studies
  - Efficacy from trial in Costa Rica
- Quadrivalent vaccine
  - Immunogenicity studies
  - Efficacy trial of 2 vs 3 doses, India

Bivalent vaccine trial, Costa Rica
Efficacy against persistent infection

	Arm	N	Events	%	VE	(95% CI)
3 doses	HPV	2957	25	0.9%	**80.9%**	(71.1, 87.7)
	Control	3010	133	4.4%		
2 doses	HPV	422	3	0.7%	**84.1%**	(50.2, 96.3)
	Control	380	17	4.5%		
1 dose	HPV	196	0	0.0%	**100.0%**	(66.5, 100)
	Control	188	10	5.3%		

- Among women enrolled in trial, 20% received less than 3 doses
- Excludes women DNA positive to HPV 16/18 and those with no follow-up
- Median time of follow-up post first dose, 4.2 yrs
- Endpoint was incident infection that lasted at least 10 months

Kreimer A et al. JNCI 2011

Quadrivalent HPV vaccine 2 dose immunogenicity study, Canada

- **Randomized controlled trial**
- **3 arm study** (~200/arm)
  - 9-13 yrs – 2 dose: 0, 6 months
  - 9-13 yrs – 3 dose: 0, 2, 6 months
  - 16-26 yrs – 3 dose: 0, 2, 6 months
- **Main analysis: 2 doses at 9-13 yrs vs 3 doses at 16-26 yrs**
  - Non inferiority declared if lower bounds of adjusted 95% CI of GMTs ratios for HPV 16 and 18 are >0.5 at month 7

Quadrivalent HPV vaccine 2 dose immunogenicity study, Canada
(36 month results)

HPV Type	Comparison			
	Group 1/Group 3*		Group 1/Group 2+	
	GMT ratio	(95% CI)	GMT ratio	(95% CI)
HPV 6	1.38	(0.99, 1.94)	0.65	(0.46, 0.92)
HPV 11	1.45	(1.04, 2.02)	0.74	(0.53, 1.05)
HPV 16	1.70	(1.15, 2.50)	0.82	(0.55, 1.21)
HPV 18	1.47	(0.88, 2.44)	0.44	(0.26, 0.74)

***Main analysis comparing 2 doses at 9-13 yrs with 3 doses at 16-26 yrs**

- Non inferiority criteria met

+Analysis comparing 2 doses at 9-13 yrs with 3 doses at 9-13 yrs

- Non inferiority at 7 months; lost for HPV 18 by 24 months and HPV 6 by 36 months

Dobson et al, 27th IPV Conference, Berlin 2011

HPV vaccine schedules with less than 3 doses

- Limited efficacy data available
- If efficacy against early endpoints is demonstrated in additional studies, there will be further questions
- Will there be differences in duration of protection for 2 vs 3 dose schedules?
- Will there be differences for special populations (immunocompromised)?

- Data from ongoing trials, post licensure effectiveness studies and monitoring data will provide more information

Ongoing work of ACIP HPV vaccine WG

- Continue to review data on vaccination program, vaccine impact, effectiveness, safety and other data
  - Post marketing manufacturer commitments
  - Post licensure monitoring projects
  - Other ongoing studies

Acknowledgements

Elaine Flagg
Eileen Dunne
Susan Hariri
Mona Saraiya
Julianne Gee
Claudia Vellozzi
Andrea Sutherland

Thank you

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