Review of Data on Duration of Protection after HPV Vaccination

Lauri Markowitz, MD

Division of Viral Diseases

Advisory Committee on Immunization Practices

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Introduction

- HPV vaccination is targeted to young adolescents but protection needed through many years of sexual activity
- Duration of protection from HPV vaccines impacts effectiveness of vaccination programs
- Important to review data on duration of protection for 3-dose HPV vaccination schedule as ACIP considers reducing the number of recommended doses
- Modeling 2 vs 3 doses examines different assumptions of duration of protection

Overview of talk

- Duration of protection data from 3-dose trials
- Immunogenicity data from 3-dose trials
- Persistence of antibody from 2-dose trials

Background

- Three licensed HPV vaccines
  - Bivalent vaccine (2vHPV), quadrivalent vaccine (4vHPV) and 9-valent vaccine (9vHPV)
- Virus-like particle vaccines made from the L1 major capsid protein
- Vaccines differ in their production system and adjuvants
  - 2vHPV adjuvant: AS04, includes MPL (3-O-desacyl-4'-monophosphoryl lipid A)
  - 4vHPV and 9vHPV adjuvant: AAHS, amorphous aluminum hydroxyphosphate sulfate

Data available on duration of protection from long term follow up of randomized clinical trials

- Most efficacy and immunogenicity randomized controlled trials had 3-4 years of follow-up; at end of most trials the control group was vaccinated
- Extended follow-up for infection/disease outcomes and persistence of antibody conducted for some trials after original trial period completed

Duration of Protection
HPV vaccine 3-dose schedules

Long term follow-up for duration of protection HPV vaccine 3-dose schedule

Base Trial				Long term follow-up* available (planned)	
Trial	Participants age (yrs)	Trial duration (yrs)	Reference		
HPV16 phase II efficacy	Females 16–23	4	Koutsky, NEJM 2002 Mao, OBGYN 2007	8.5[+]	
2vHPV Phase II efficacy	Females 15–25	2.3	Harper, Lancet 2004	8.9[+]	
4vHPV immunogenicity	Females/males 9–15	3	Reisinger, PIDJ 2007	10	
4vHPV phase III efficacy	Females 15–26	4	Future II, NEJM 2007	10	(14)
4vHPV phase III efficacy	Males 16–26	3	Giuliano, NEJM 2011 Palefsky, NEJM 2011	8.5	(10)
4vHPV phase III efficacy	Females 24–45	4	Castellsague, Br J CA 2011	7.2	(10)

*Years since first vaccine dose [+]Included an unvaccinated control group

Monovalent HPV 16 vaccine trial in women 16–23 years Final 8.5 years follow-up

- Base RCT enrollment in 1998-1999[1]
  - 2391 participants in the United States
  - Vaccine efficacy for HPV 16 persistent infection = 94% (95% CI, 88 – 98)
  - Vaccine efficacy for HPV 16-related CIN1+ = 100% (95% CI, 84 – 100)
- Final follow-up included participants from Seattle (290/500 enrolled)[2]
  - Exams, swabs for HPV DNA and Pap every 6 months

Results

Outcome	Vaccine	Controls	Vaccine efficacy	
			%	(95% CI)
HPV 16/18 infection	0	6	100%	(29 – 100)
HPV 16-related CIN1+	0	3		

CIN1+, cervical intraepithelial neoplasia grade 1 or worse

[1]Koutsky, NEJM 2002; Mao, OBGYN2006 [2]Rowhani-Rahbar, Vaccine 2009

2vHPV phase II trial in women 16–23 years
Final 8.9 year follow-up

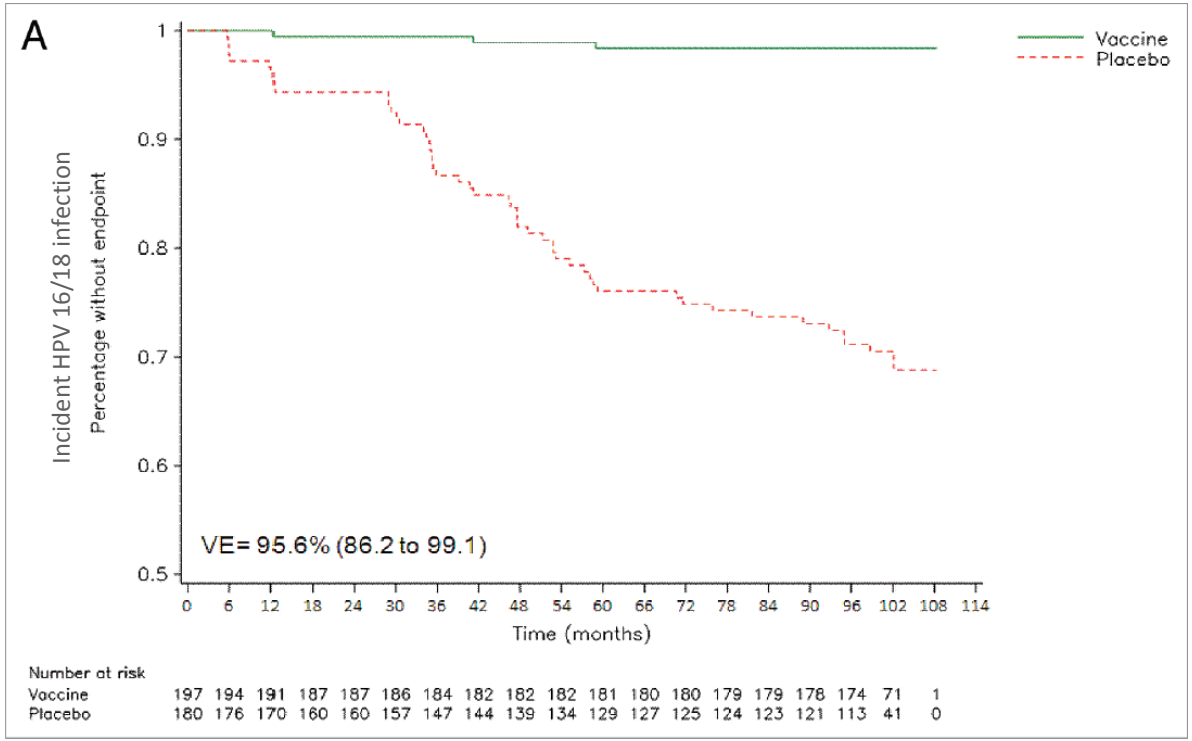
- Base RCT conducted 2001-2003[1]
  - 1113 participants
  - Vaccine efficacy for HPV 16/18 persistent infection = 100% (95% CI, 47 – 100)
- Final follow-up included participants from Brazil (437/506 enrolled)[2]
  - Exams and swabs for HPV DNA every 6 months, Pap every 12 months

Results

Outcome	Vaccine	Controls	Vaccine efficacy	
			%	(95% CI)
HPV 16/18 infection	0	9	100%	(66 – 100)
HPV 16-related CIN1+	0	1		

CIN1+, cervical intraepithelial neoplasia grade 1 or worse [1]Protocol 001. Harper, Lancet 2004 [2]Protocol 023. Naud, Human Vaccin Immunol 2014

2vHPV phase II trial in women 16–23 years
Combined analysis of initial and follow-up studies



Naud, Human Vaccin Immunol 2014

Long term follow-up for duration of protection HPV vaccine 3-dose schedule

Base Trial				Long term follow-up* available (planned)
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*Years since first vaccine dose [+]Included an unvaccinated control group

4vHPV immunogenicity trial in adolescents 9–15 years Final 10 year follow-up

- Base RCT included 1781 sexually naïve boy/girls[1]
  - At end of base trial, placebo group vaccinated (*catch-up vaccine group*)
- Effectiveness follow-up started after age 16[2]
  - Twice yearly evaluation: sexual history, inspection, genital swab (if agreed)
  - 821 in *early vaccine group* (median follow-up 9.9 years)
  - 424 in *catch-up vaccine group* (median follow-up 7.4 years)

[1]Protocol 018, Reisinger, PIDJ 2007 [2]Das and Saah, EUROGIN 2016 (8 year follow-up published: Ferris, Pediatr 2014)

4vHPV immunogenicity trial in adolescents 9–15 years Final 10 year follow-up

Results

- No cases of HPV 6,11,16,18 disease
- 10 persistent infections ≥6 months
  - 2 persistent infections ≥12 months
- Historical comparison: incidence of persistent vaccine types in placebo group of trials in 16-26 yr-olds
  - Males 6/100 person-years
  - Females 4/100 person-years

Incidence of persistent 6/11/16/18 ≥ 6 months*

Sex	Cases	(types)	Cases/ 100 person-years
males	**6**	(2 HPV 16) (3 HPV 6) (1 HPV 6,16)	**0.4 - 0.6**
females	**4**	(4 HPV 16)	**0.3**

*per protocol population

Das and Saah, EUROGIN 2016

4vHPV efficacy trial in women 16–23 years
Interim 10 year follow-up (14 years planned)

- Base RCT included >12,000 women from 13 international countries[1]
- Follow-up conducted in Nordic Cancer Registries, ~3,800 participants[2]
- Registry searches every 2 years

Results

Endpoint	n Cases/ N Subjects	Person-Years at Risk	Incidence per 100 Person-Years at Risk, % (95% CI)
HPV 6/11/16/18–related CIN and vulvar/vaginal cancer	1/2,171	10,483.2	0.0 (0.0–0.1)
Time since day 1			
≤4 yrs	0/2,050	861.1	0.0 (0.0–0.4)
4 to 6 yrs	0/2,168	4,257.0	0.0 (0.0–0.1)
6 to 8 yrs	1/2,059	3,649.9	0.0 (0.0–0.2)
8 to 10 yrs	0/1,439	1,685.6	0.0 (0.0–0.2)

- One case of CIN1 with HPV types 16,45,52 detected concurrently

CIN1, cervical intraepithelial neoplasia grade 1

[1]Protocol 015. Future II, NEJM 2007 [2]Kjaer, EUROGIN 2015

4vHPV efficacy trial in men 16–26 years
Interim 8 year follow-up (10 years planned)

- Base RCT included 4065 men from 18 countries[1]
- Annual visits among men enrolled in follow-up[2]
  - Inspection, biopsy of external lesions; anal cytology for men in MSM sub-study
  - 936 in *early vaccine group* (median follow-up 8.5 years)
  - 867 in *catch-up vaccine group* (median follow-up 4.2 years)

Results

- No cases of HPV 6,11,16,18 genital warts or external genital lesions in per protocol population in early vaccine group
- One case of AIN1, with HPV types 6 and 58 were detected concurrently
  - Incidence: 0.3/100 person-years
  - Historical comparison: 5.8/100 person-years in placebo group in base study

MSM, men who have sex with men; AIN, anal intraepithelial neoplasia

[1]Protocol 020. Giuliano, NEJM 2011 and Palefsky, NEJM 2011 [2]Das and Saah, EUROGIN 2016

4vHPV efficacy trial in women 24–45 years
Interim 7.2 year follow-up (10 years planned)

- Base RCT included 3817 women from 7 countries[1]
- Follow-up among women enrolled from Columbia[2]
  - Every 2 year evaluation
  - 684 in *early vaccine group* (median follow-up 7.2 years)
  - 651 in *catch-up vaccine group* (median follow-up 2.1 years)

Results

- No cases of HPV 6,11,16,18 external genital lesions or CIN2+ in per protocol population

CIN2+, cervical intraepithelial neoplasia grade 2 or worse

[1]Protocol 019. Castellsague, Br J CA 2011 [2]Das, EUROGIN 2015 (6 year follow-up published: Luna, PLOS One 2013)

Additional studies with planned long term follow-up for duration of protection, HPV vaccine 3-dose schedule

Base Trial				Long term follow-up* available (planned)
Trial	Participants age (yrs)	Trial duration (yrs)	Reference	
2vHPV Phase III efficacy (PATRICIA)	Females 15–25	4	Lehtinen, Lancet Oncol 2012	- (14)
2vHPV Phase III efficacy (Costa Rica VaccineTrial)	Females 18–25	4	Hildesheim, Vaccine 2014	- (10)
9vHPV phase III efficacy	Females 16–26	4	Joura, NEJM 2015	- (14)
9vHPV immunogenicity	Females/males 9–15	3	Van Damme Pediatr 2015	- (10)

*Years since first vaccine

Persistence of vaccine-induced antibody after a 3-dose schedule

Immunogenicity of HPV vaccines

- **High seroconversion after vaccination (>97%)**
- **Vaccines induce higher antibody titers than natural infection**
  - Peak titer 1 month after last dose, decline and then plateau by 18-24 months
- **Main basis of protection is neutralizing antibody**
  - The minimum protective antibody threshold not known
  - The predominant response to vaccination is neutralizing IgG antibody
- **Clinical trials used different serologic assays**
  - 2vHPV trials used an ELISA
    - Assay detects measure both neutralizing and non neutralizing antibody
  - 4vHPV and 9vHPV trials used a competitive Luminex immunoassay (cLIA)
    - Assay detects antibody restricted to one neutralizing epitope
    - Some 4vHPV vaccinees lost detectable HPV 18 antibody by cLIA but no loss of protection

Long term follow-up for persistence of antibody HPV vaccine 3-dose schedule

Base Trial		Follow-up		
Trial	Participants (yrs)	Yrs available (planned)	Seropositive for 6,11,16,18*	Reference
HPV 16 phase II efficacy	Females 16–23	8.5	86% seropositive for HPV 16 in vaccine group; 9% in placebo	Rowhani-Rahbar, Vaccine 2009
4vHPV immunogenicity	Females/Males 9–15	10	89%, 89%, 96%, 61%	Das and Saah EUROGIN 2016
4vHPV phase III efficacy	Females 16–23	9 (14)	94%, 96%, 99%, 60%	Nygard, Clin Vaccin Immunol 2015
4vHPV phase III efficacy	Males 16–26	6 (10)	84%, 87%, 97%, 48%	Das and Saah EUROGIN 2016
4vHPV phase III efficacy	Females 24-45	8 (10)	89%, 89%, 96%, 61%	Das EUROGIN 2015

*Antibody determinations by cLIA

Long term follow-up for persistence of antibody 4vHPV vaccine 3-dose schedule

- Although some vaccinees lost detectable HPV 18 antibody by cLIA in the 4vHPV clinical trials, there was no breakthrough disease
- Since efficacy remains high, suggests that protective levels are lower than the minimum detectable level by cLIA or that antibodies against additional epitopes can be protective
- Sera in these trials were retested using a total IgG assay; seropositivity to all types increased; seropositivity to HPV 18 reached 78-90%*

*Unpublished data provided by Merck to ACIP HPV Vaccines Work Group

Long term follow-up for persistence of antibody 2vHPV vaccine 3-dose schedule

Base Trial		Follow-up		
Trial	Participants (yrs)	Yrs available (Planned)	Seropositive for 16,18*	Reference
2vHPV Immunogenicity[1]	Females 10–14	10	100%, 100%	Schwarz, WSPID 2015[+]
2vHPV Phase II efficacy[2]	Females 15–25	9	100%, 100%	Naud, Hum Vaccin Imm 2014
2HPV Immunogenicity[3]	Females 15–55	6 (10)	100%, 97%	Schwarz, BJOG 2014

[1]NCT00196924, [2]NCT00689741, [3]NCT00196937

*Antibody determinations by ELISA [+]6 year data published: Schwarz, PIDJ 2014

Demonstration of immune memory/anamnestic response HPV vaccine 3-dose schedules

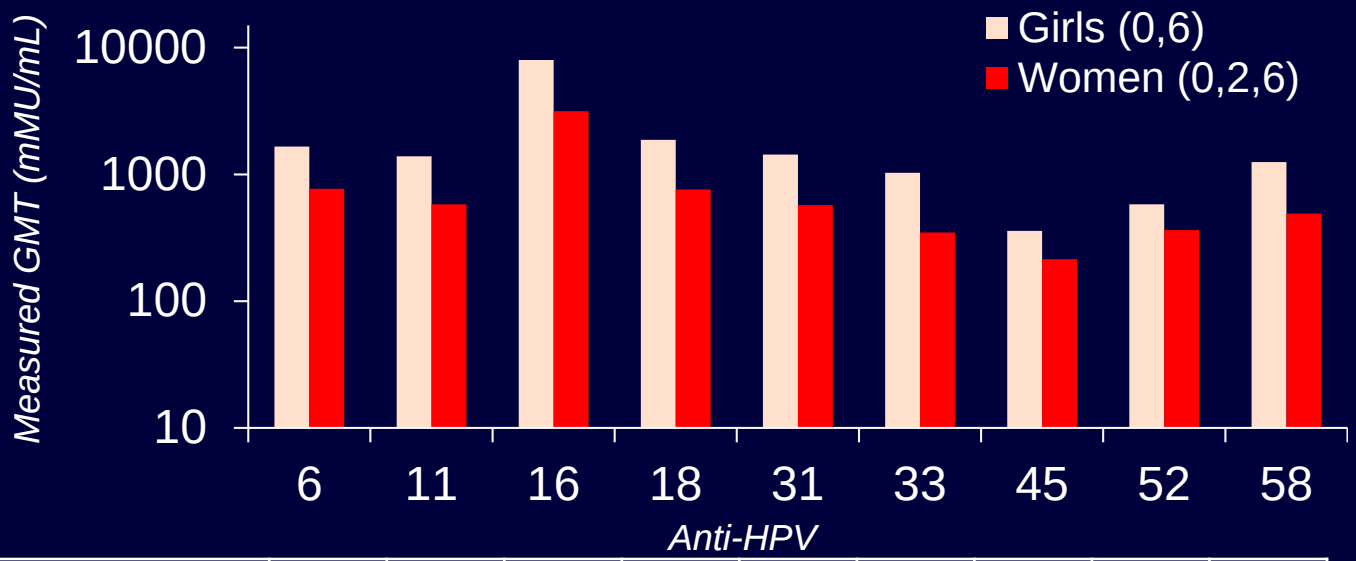
Trial	Participants/ age at first vaccination (yrs)	Challenge (yrs post first dose)	Results
HPV 16 phase II	Females 16–23	8.5	Anamnestic response for HPV 16 after 4vHPV vaccination[1]
4vHPV phase II	Females 16–23	5	Anamnestic response for HPV 6,11,16,18[2]
2vHPV phase II	Females 15–25	7	Anamnestic response for HPV 16,18[3]

[1]Rowhani-Rahbbar, J Clin Virol 2009 [2]Olsson, Vaccine 2007 [3]Moscicki, Vaccine 2002

Persistence of vaccine-induced antibody after a 2-dose schedule

9vHPV 2-dose Trial: Non-inferior GMT at 1 Month Post-Last Dose in 2-dose (0, 6) Girls vs. 3-dose (0, 2, 6) Women

The non-inferiority criterion was met for all 9 HPV types (all p<0.001)



Fold difference (girls/women)	**2.15**	**2.39**	**2.54**	**2.46**	**2.51**	**2.96**	**1.67**	**1.60**	**2.55**
95% CI	*(1.83, 2.53)*	*(2.03, 2.82)*	*(2.14, 3.00)*	*(2.05, 2.96)*	*(2.10, 3.00)*	*(2.50, 3.50)*	*(1.38, 2.03)*	*(1.36, 1.87)*	*(2.15, 3.01)*

Luxembourg, presented to ACIP, February 2016

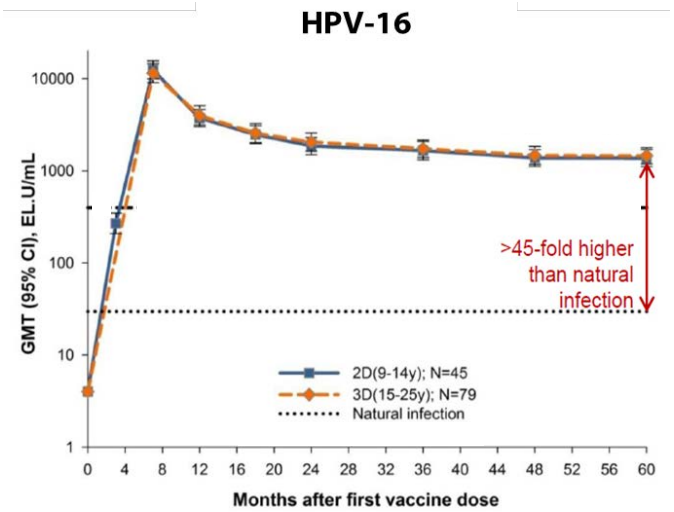
9vHPV 2-dose immunogenicity trial

- Immunogenicity data 1 month after last dose presented to ACIP in February 2016
- Trial to continue for 2 more years for assessment of antibody persistence
- 1 additional dose to be given at month 36 to assess immune memory
- Separate long-term effectiveness study planned

Luxembourg, presented to ACIP, February 2016

2vHPV 2- vs 3-dose immunogenicity trial

- **Follow-up through month 60**
  - 2 doses (0,6 months) in 9–14 yrs
  - 3 doses (0,1,6 months) in 15–25 yrs
- **Antibody kinetics similar in two groups**

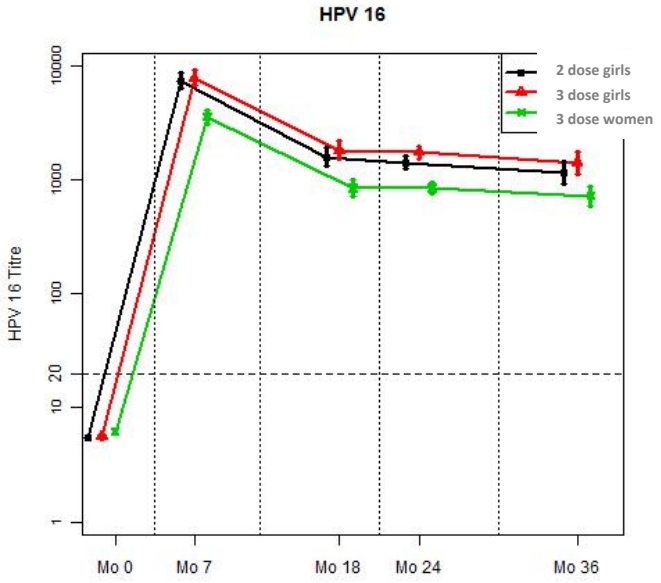


Romanowski, Hum Vaccin 2016

Antibody measured by ELISA

4vHPV 2- vs 3-dose immunogenicity trial

- **Follow-up through month 36**
  - 2 doses (0,6 months) in 9–13 yrs
  - 3 doses 0,2,6 months in 9–13 yrs
  - 3 doses (0,1,6 months) in 16–26 yrs
- **Antibody kinetics similar in three groups**



Dashed line is serostatus cut-off
Antibody measured by cLIA

Adapted from: Dobson, JAMA 2013

Summary

- No evidence of waning protection after a 3-dose schedule
  - Data available through ~ 10 years for 2vHPV and 4vHPV
  - Longer follow-up, through 14 years, ongoing in some studies
- Antibody responses maintained over time after a 3-dose schedule
  - Data available through ~10 years for 2vHPV and 4vHPV
  - Longer follow-up, through 14 years, ongoing in some studies
  - Waning of detectable antibody to HPV 18 by cLIA in 4vHPV vaccinees not associated with loss of protection

Summary

- Long term protection data not available yet from 2-dose trials
- Antibody kinetics similar with 2vHPV and 4vHPV 2-dose schedules (interval ≥ 6 months between doses) in adolescents compared with standard 3-dose schedule in women

Acknowledgements

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Thank you

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov