

# HPV Vaccine Update

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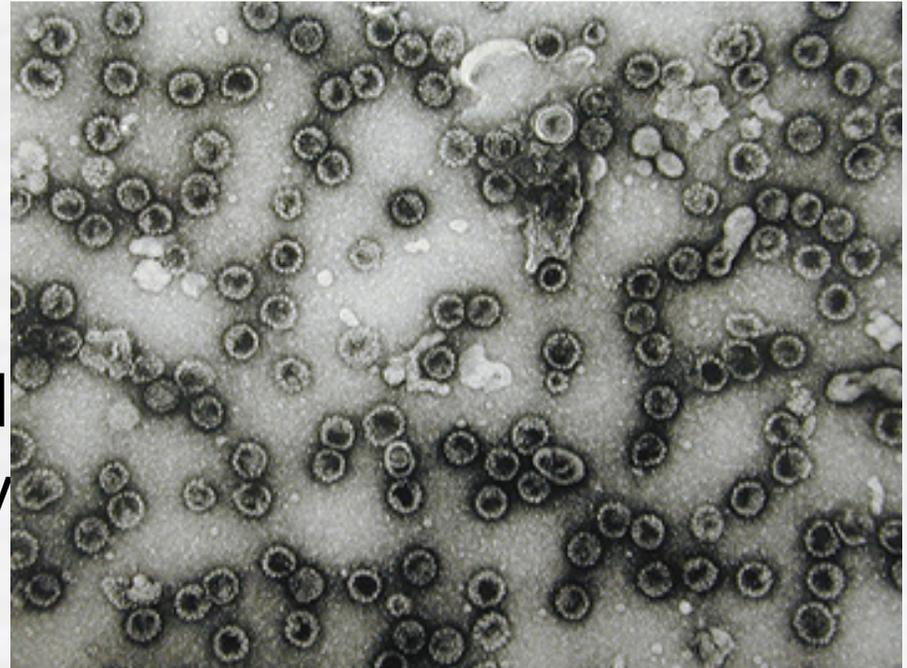
# Overview

- Basic information about the two candidate HPV vaccines
- Efficacy data
- Safety
- Immunogenicity
- Status of the vaccines
  - FDA licensure
  - ACIP recommendations



# Virus-like particles - VLPs

- L1 major capsid protein can self-assemble into structures resembling whole virus
- HPV vaccines are based on type-specific antibody production to VLPs
- L1 protein is not expressed in severe dysplasias



# HPV Vaccines

Vaccine Manufacturer	HPV types (L1 capsid VLPs)	3 dose series	Adjuvant	Ultimate Preventive Outcomes of Vaccine
Merck Quadrivalent	16, 18, 6, 11	0, 2, 6 months	Alum	Cervical Cancer and Genital Warts
GSK Bivalent	16, 18	0, 1, 6 months	Alum and MPL (ASO4)	Cervical Cancer



# HPV Vaccines

Vaccine Manufacturer	Efficacy Trials	Bridging Immunogenicity and Safety Trials	Ongoing and Future Studies
Merck Quadrivalent	Females 16-26 years	Females and males 9-15 years	<ul style="list-style-type: none"> <li>•Efficacy in females 26-45 years</li> <li>•Efficacy in males</li> <li>•Long-term FU</li> <li>•Safety including pregnancy</li> </ul>
GSK Bivalent	Females 15-25 years	Females 10-14 years and 26-55 years	<ul style="list-style-type: none"> <li>•Efficacy in females &gt;25 years</li> <li>•HIV+ women</li> <li>•Co-administration</li> <li>•Long-term FU</li> </ul>



# Quadrivalent HPV Vaccine

## HPV 16/18 Related Cervical CA Precursor Lesions

### Mean 17 Months of Follow-up

Endpoint	Vaccine (n=5301)	Placebo (n=5258)	Efficacy	CI
<b>HPV 16/18-related CIN2/3 or AIS</b>	<b>0</b>	<b>21</b>	<b>100%</b>	<b>76%, 100%</b>
HPV 16-related CIN 2/3 or AIS	0	16	100%	75%, 100%
HPV 18 –related CIN 2/3 or AIS	0	8	100%	42%, 100%

CI=Confidence Interval (for composite endpoint, 97.5% CI; remaining rows, 95% CI)

Merck, unpublished data, as presented at ACIP meeting, February 2006

Per Protocol Population



# Quadrivalent HPV Vaccine

## HPV 6/11/16/18 Related External Genital Lesions

### Mean 20 Months of Follow-up

Endpoint	Vaccine Cases* (n=2261)	Placebo Cases* (n=2279)	Efficacy	CI
<b>HPV 6/11/16/18-EGL</b>	<b>0</b>	<b>40</b>	<b>100%</b>	<b>88%, 100%</b>
HPV 6-related EGL	0	23	100%	83%, 100%
HPV 11-related EGL	0	10	100%	55%, 100%
HPV 16-related EGL	0	10	100%	56%, 100%
HPV 18-related EGL	0	3	100%	<0%, 100%

\*Subjects are counted once per row. Subjects may be counted in more than one row.

CI=Confidence interval (for composite endpoint, 97.5%; for remaining rows, 95% CI)

Merck, unpublished data, as presented at ACIP meeting, February 2006

Per Protocol Population



# Bivalent HPV Vaccine--HPV 16/18

## Incident and Persistent Infection

### Mean 47.7 Month Follow-up

Endpoint	Vaccine (n=414)	Placebo (n=385)	Efficacy	CI
Incident HPV 16/18 Infections	1	28	96.9%	(81.3, 99.9)
Persistent HPV 16/18 Infection (6 month)	1	23	96.0%	(75.2, 100)
Persistent HPV 16/18 Infection (12 month)	0	9	100%	(52.2, 100)

Harper et al, Lancet, 2006.



# Bivalent Vaccine--HPV 16/18

## Cervical Cancer Precursor Lesions

Mean 47.7 Month Follow-up

Endpoint	Vaccine (n=481)	Placebo (n=170)	Efficacy	95% CI
HPV16/18 related CIN 1+	0	8	100.0%	(42.4%, 100%)
HPV 16/18 related CIN 2/3+	0	5	100.0%	(-7.7%, 100%)

CIN 1+ = CIN1, CIN2, CIN3, adenocarcinoma in situ, invasive carcinoma

CIN 2+ = CIN2, CIN3, adenocarcinoma in situ, invasive carcinoma

Harper et al, Lancet, 2006.



# Safety

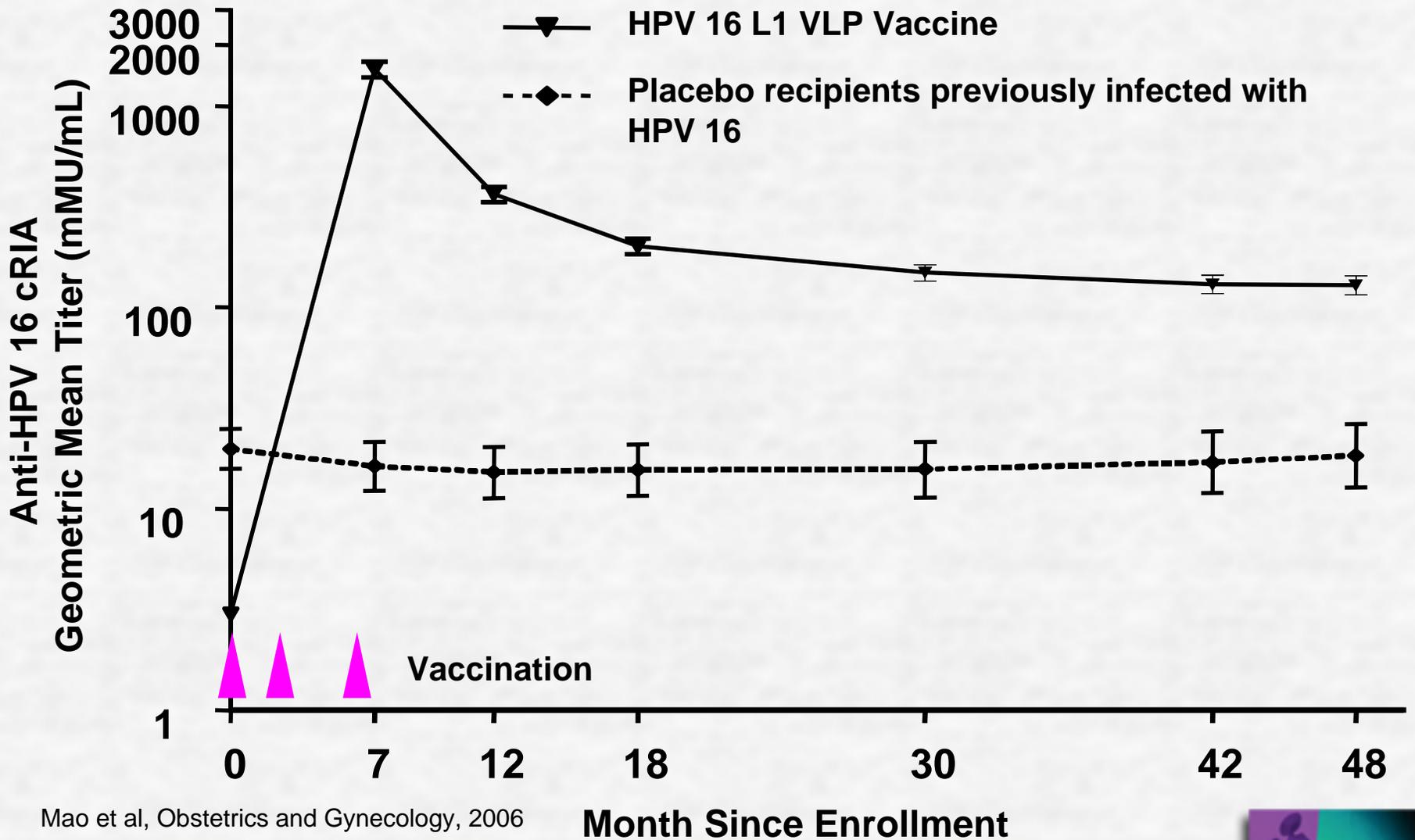
- No serious adverse events related to vaccination were reported to have occurred in either vaccine or placebo groups in studies of both vaccines.
  - There were slightly more injection site symptoms in vaccine groups vs. placebo.

Harper et al. Lancet, 2004

Villa et al. Lancet, 2005



# Anti-HPV 16 GMTs Through 3.5 Years Postdose 3



Mao et al, Obstetrics and Gynecology, 2006

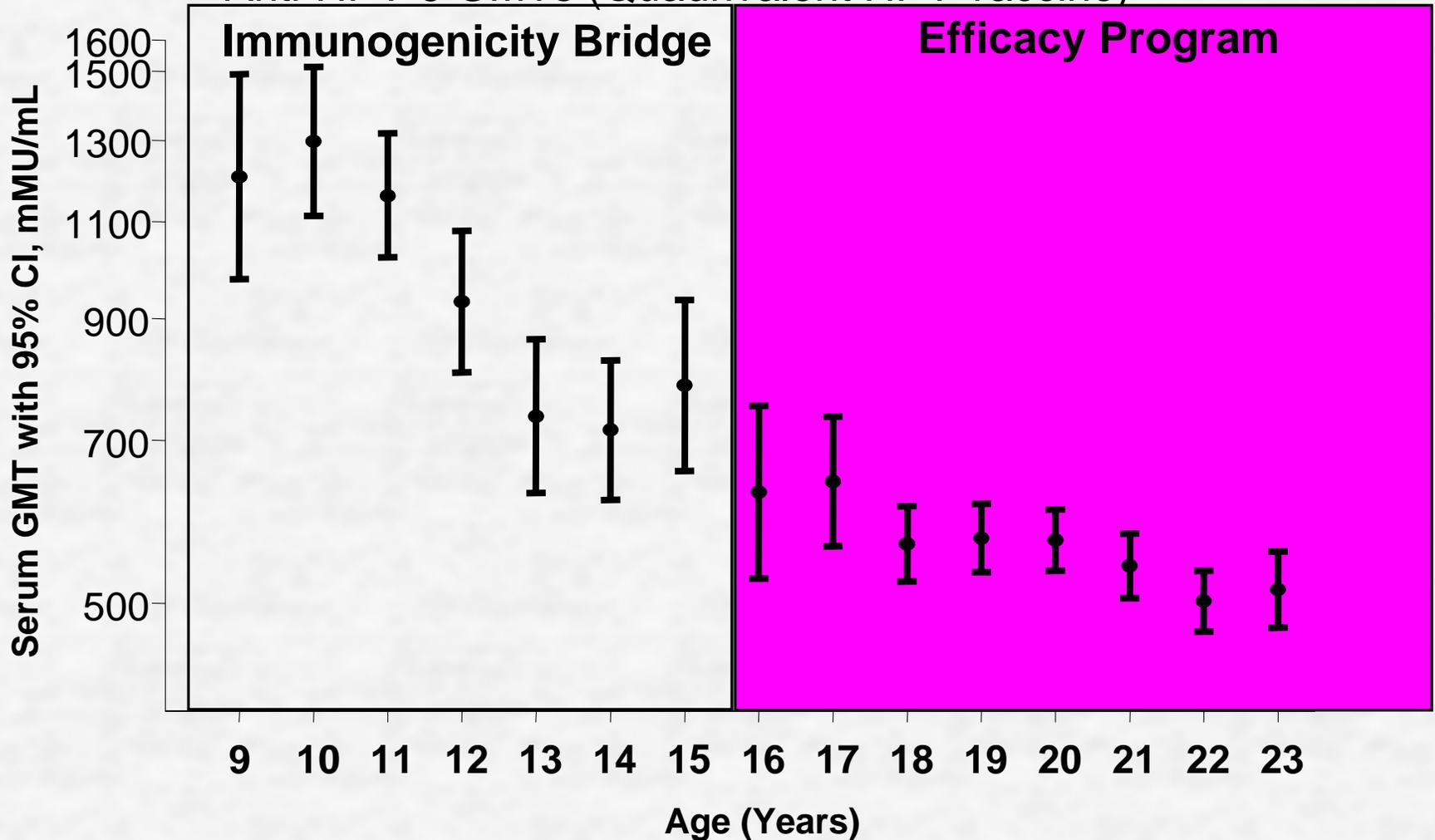
Month Since Enrollment

California HPV Vaccine Summit



# Antibody Titers by Age at Vaccination

## Anti-HPV 6 GMTs (Quadrivalent HPV vaccine)



Merck, unpublished data, ACIP presentation by Eliav Barr, February 2006



# Vaccine Summary

- Both vaccines have been shown to be highly efficacious
  - Quadrivalent vaccine for HPV 16/18 related early cervical cancer precursors and HPV 6/11/16/18 related external genital lesions
  - Bivalent vaccine for HPV 16/18 related infections and early cervical cancer precursors (CIN1+)
- Good safety profile
- Excellent immunogenicity in young adolescents
- Long term protection for 3.5- 4 years to date



# Cost Effectiveness

- Published papers have looked at cost effectiveness of HPV vaccination have suggested that an HPV vaccine would be cost effective using various assumptions
- Models are complicated and use various assumptions
  - Vaccine coverage rates estimated
  - Duration of vaccine protection (booster doses) estimated



# Current Status of Vaccines

Vaccine Manufacturer	FDA Application	FDA Status	Earliest potential US Licensure
Merck Quadrivalent	Filed December 2005 Females 9-26 years and males 9-15 years	Approved for females aged 9 to 26 years of age	Approved June 8, 2006
GSK Bivalent	Pending submission	Pending submission	2007



# ACIP Update

- ACIP Agenda: June 29, 2006
- May consider HPV vaccine for routine immunization of females 11-12 years old (3 dose series) at its June 2006 meeting
- Considering recommendation for females 13-26 years old (or a more limited age range) as catch-up



# Unanswered questions

- Specific ACIP recommendations? Catch-up ages?
- Target population? Benefits/risks post sexual debut?
- Duration of protection? Booster dose?
- Outcome of long term safety?
- Long term effect on Pap screening?
- Effectiveness against anal cancer?
- Cost-effectiveness of vaccinating males?
- Addition of more high-risk types to later vaccines?
- Will there be gaps in funding?
- Acceptance – parental, health care provider?



# Barriers

- Access to the pre-adolescent target population for a three dose immunization series
- Cost--\$360 for the 3-dose series
- Controversy and discomfort about a vaccine for a virus that is sexually transmitted
- Lack of public knowledge about HPV
- Potential for miscommunication about HPV, vaccine effects, need for Pap screening
- Female-only vaccine currently
- General distrust of immunization



# Opportunities

- Create collaboration across different branches of state government
- Promote adolescent health
- Promote immunization for adolescents
- Promote sexual health
- Increase awareness of cervical cancer and role of Pap screening
- Create partnerships between state government and advocacy, professional, and healthcare organizations



# Summary

- Two HPV vaccines have high efficacy as a preventive vaccine for cervical cancer precursors (HPV 16 & 18 cause ~70% of cervical cancer cases) and one for genital warts (HPV 6 and 11 cause ~90% of genital warts)
- Cervical cancer screening will still be important as approximately 30% of cancers not covered by the two candidate vaccines
- Vaccine is prophylactic with greatest benefit prior to sexual debut
- Most likely initial recommendations for 11-12 year olds with a catch-up for females (13 up to 26 years possibly)
- Importance of collaboration

