HPV Vaccines: A New Approach to Prevention of HPV Related Disease

Satellite Conference and Live Webcast

Produced by the Alabama Department of Public Health
Video Communications and Distance Learning Division

Faculty

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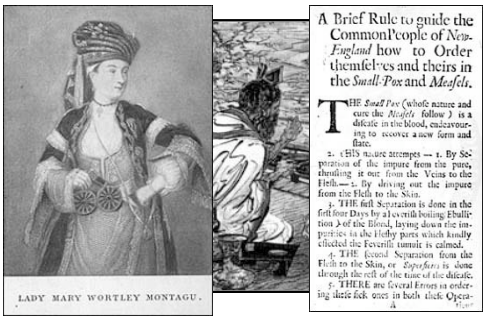
Smallpox

- **The great scourge of mankind**
- **Has crippled, disfigured and/or killed one quarter of all humanity**
- **In the 20th Century alone, nearly 200 million deaths**

Smallpox-Variolation



The Causes and Effects of the Variolae Vaccinae

A Disease Known by the Name of Cow Pox (1798)

- **Edward Jenner (1749-1823), British physician, deliberately inoculated 8-year-old James Phipps with cowpox-infected material from a local milkmaid**

The Causes and Effects of the Variolae Vaccinae

A Disease Known by the Name of Cow Pox (1798)

- **The boy had the expected mild form of the disease and no serious manifestations**
- **Several months later, Dr. Jenner inoculated the boy with smallpox with no adverse reaction**

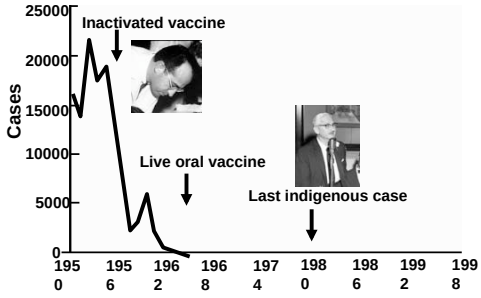
Impact of Vaccines

- Corynebacterium diphtheriae
  - 1900 – Diphtheria killed more Americans than cancer
  - 1990's – Average of only 3 cases per year in the U.S.

Impact of Vaccines

- Poliovirus
  - 1954 – 18,000 cases of paralytic poliomyelitis in the U.S.
  - 1957 – only 2,700 cases of paralytic poliomyelitis
  - 2006 – polio is now eradicated in U.S.

Poliomyelitis U.S., 1950 - 2002



Impact of Vaccines

- WHO and UNICEF provide vaccines against poliomyelitis, measles, diphtheria, tetanus and pertussis
- Prevent 3 million deaths and 750,000 cases of blindness, mental or physical disabilities in children annually

Cancers Caused By Infectious Agents Worldwide

Agent	Site	No. CA	%
H pylori	Stomach	592,000	5.5
HPV	Cervix and Others	561,200	5.2
HBV, HCV	Liver	535,000	4.9
HHV-8	Kaposi's Sarcoma	54,000	0.9
Schistosoma	Bladder	9,00000	0.1
HTLV-1	Leukemia	2,700	
Liver Flukes	Liver/Gallbladder	800	
Total Infection-Related Cancers		1,900,000	18
Total Cancers (for 2002)		10,673,000	

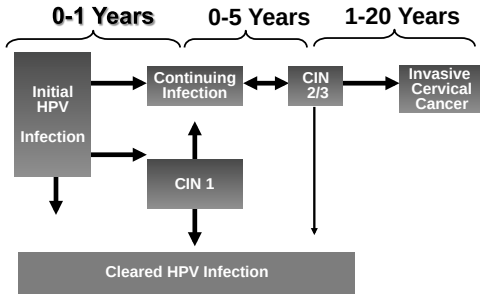
Outline

- Epidemiology and natural history of HPV
- Virus-Like Particles (VLP) as the prototype prophylactic vaccine
- Unanswered questions about VLPs

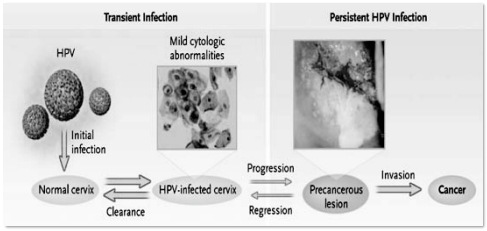
Cervical Cancer

- 450,000 women are newly diagnosed with cervical cancer each year, worldwide
- 250,000 women succumb to this disease each year, worldwide
- In U.S., about 9,710 cases diagnosed in 2006
- In U.S., about 3,700 deaths expected in 2006

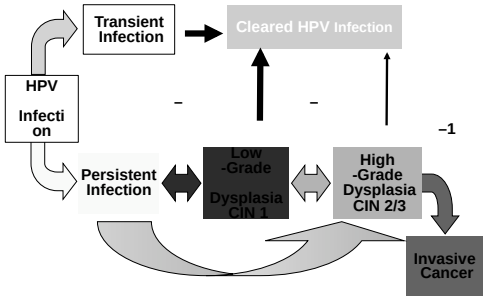
Natural History of HPV Infection and Potential Progression to Cervical Cancer[1]



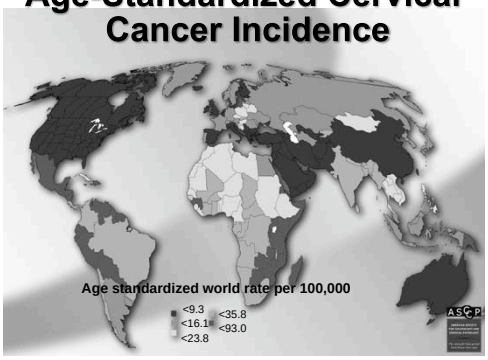
Natural History of HPV Infection and Potential Progression to Cervical Cancer[1]



Natural History of High-Risk HPV Infection and Potential Progression to Cervical Cancer[1,2]

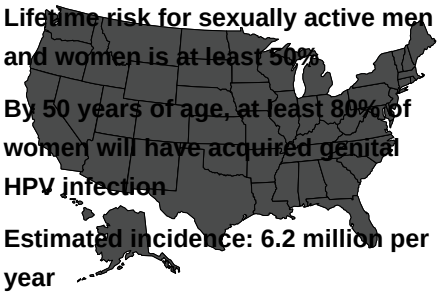


Age-Standardized Cervical Cancer Incidence



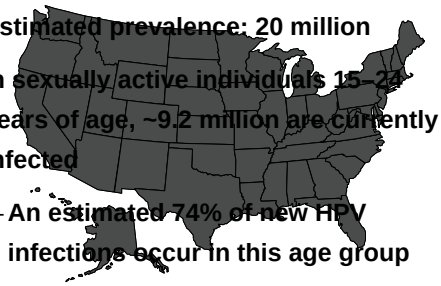
US HPV Statistics

- Lifetime risk for sexually active men and women is at least 50%
- By 50 years of age, at least 80% of women will have acquired genital HPV infection
- Estimated incidence: 6.2 million per year

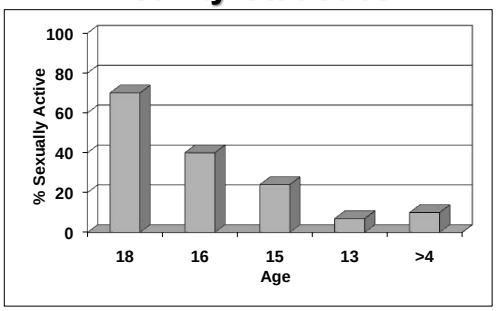


US HPV Statistics

- Estimated prevalence: 20 million
- In sexually active individuals 15–24 years of age, ~9.2 million are currently infected
  - An estimated 74% of new HPV infections occur in this age group



Basic U.S. Sexual Activity Statistics



Mechanisms of HPV Transmission and Acquisition

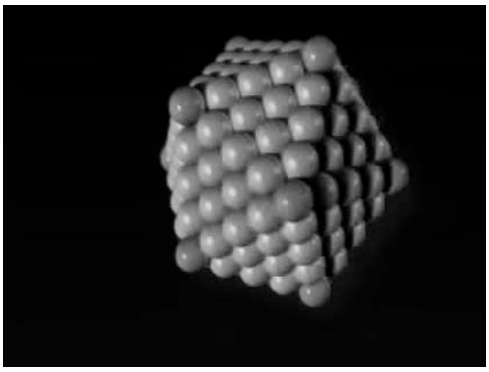
- Sexual contact
  - Through sexual intercourse
    - Including anal intercourse
  - Genital–genital, manual–genital, oral–genital

Mechanisms of HPV Transmission and Acquisition

- Genital HPV infection in virgins is rare, but may result from nonpenetrative sexual contact
- If used correctly, condoms can help reduce the risk of HPV infection

Mechanisms of HPV Transmission and Acquisition

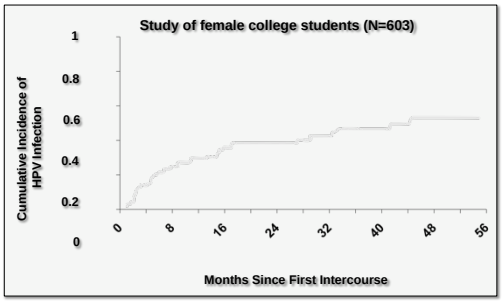
- Nonsexual routes
  - Mother to newborn (vertical transmission; rare)
  - Fomites (eg, undergarments, surgical gloves, biopsy forceps)
- Most infected individuals are unaware that they are infected and may unknowingly spread the virus



Risk Factors for HPV Infection

- Women
  - Young age (peak age group 20–24 years of age)
  - Lifetime number of sex partners
  - Early age of first sexual intercourse
  - Male partner sexual behavior
- Smoking

Infection From Time of First Sexual Intercourse



HPV Clearance

- In women 15–25 years of age, ~80% of HPV infections are transient[1]
  - Gradual development of cell-mediated immune response presumed mechanism

HPV Clearance

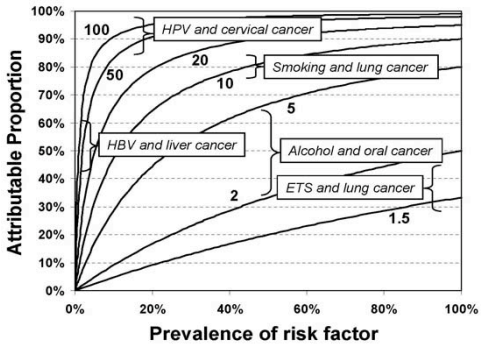
- In a study of 608 college women, 70% of new HPV infections cleared within 1 year and 91% within 2 years
  - Median duration of infection = 8 months
  - Certain HPV types are more likely to persist (eg, HPV 16 and HPV 18)

Link Between HPV and Cervical Cancer

- 99% of cervical cancers and high grade cervical cancer precursors lesions associated with HPV
- Risk for developing cervical cancer with HPV is 50-100x higher than with out HPV infection

Link Between HPV and Cervical Cancer

- Risk of developing lung cancer from smoking is 10 fold
- Risk of high grade precursor lesion with HPV is 300 fold



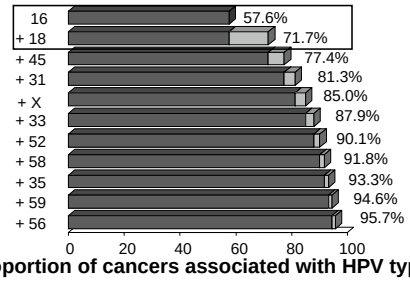
HPV Types

- HPV types 6, 11, 42, 43, and 44 are usually associated with common genital condyloma and thus appear to pose <u>low risk</u> for cancer
- HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 carry a <u>higher risk</u> for cervical cancer

HPV Types

- HPV 16 is detected in about half of all squamous cell cervical cancer
- Hong Kong Study:
  - HPV 16 was the most common type in women with cervical cancer, HPV type 58 was second highest and was detected in 24% of these women

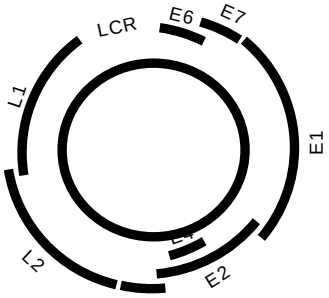
HPV Types in Cervical Cancer



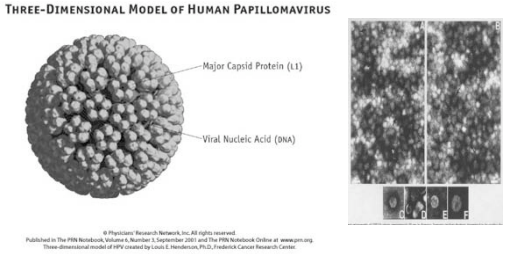
Proportion of cancers associated with HPV types

HPV 16/18 vaccine could prevent > 70% of cervical cancers

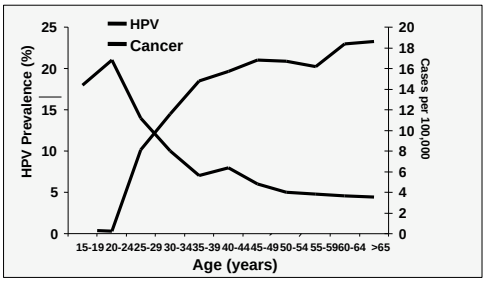
HPV Genome



HPV Virions



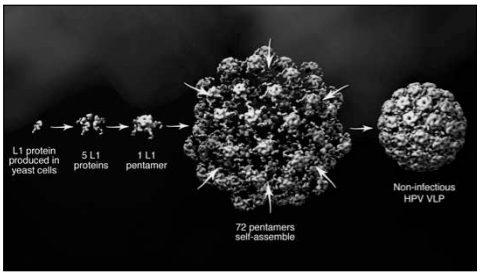
HPV Prevalence And Cervical Cancer Incidence By Age

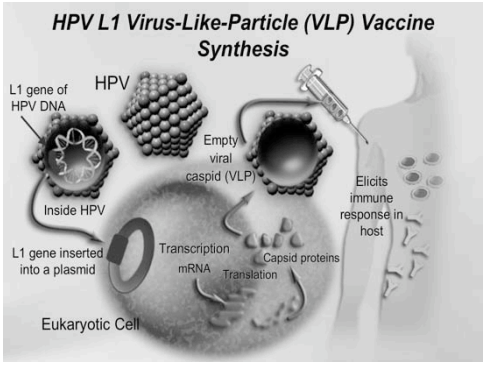


HPV Vaccines

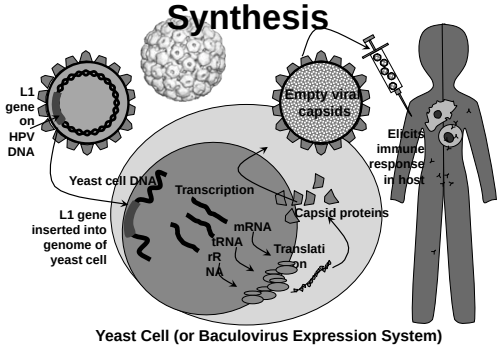
- **Prophylactic**
  - **Target extracellular virus**
  - **Epitopes of native proteins**
  - **Produce antibodies**
- **Humoral Immunity**
  - **CD4+/ MHC II**
- **Therapeutic**
  - **Target viral-infected cells**
  - **Epitopes of MHC processed peptides**
  - **Produce CTLs**
- **Cellular Immunity**
  - **CD8+/ MHC I**

Assembly of VLPs[1–3]





HPV L1 VLP Vaccine Synthesis



Yeast Cell (or Baculovirus Expression System)

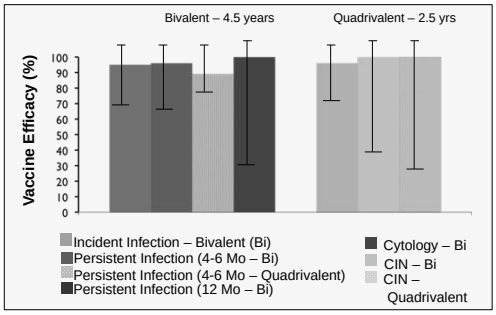
Humoral Immune Response Is Protective Against HPV Infection

- **HPV only infects humans, but animal studies with analogous (animal, not human) papillomaviruses suggest that…**
  - **The efficacy of L1 VLP vaccines is mediated by the development of humoral immune responses**

Phase II Randomized Controlled Trials

	Bivalent Vaccine	Quadrivalent Vaccine
Reference	**Harper DM et al. *Lancet.* 2004;364:1757-1765.**	**Villa LL et al. *Lancet Oncology.* 2005;6:271-278.**
Vaccine Type	Bivalent HPV-16 and HPV-18 VLP ,L1 capsid component	Quadrivalent HPV-6/11/16/18 VLP, L1 capsid component
Concentration	**HPV 6 not included** **HPV 11 not included** 20 µg HPV 16 20 µg HPV 18	**20 µg HPV 6** **40 µg HPV 11** 40 µg HPV 16 20 µg HPV 18
Adjuvant	500 µg aluminum hydroxide w/50 µg 3-deacylated monophosphoryl lipid A (AS04)	225 µg aluminum hydroxyphosphate sulfate

Efficacy for HPV 16/18 Associated Endpoints



Quadrivalent Vaccine

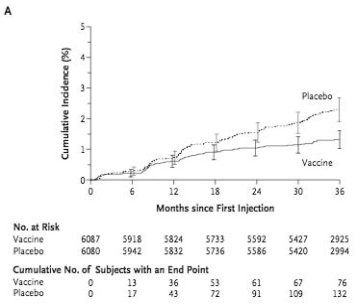
Phase III Trial Efficacy Results in HPV 16/18-Free Women

	Vaccine		Placebo		Efficacy (%)	CI	P Value
End Point	n	Cases	n	Cases			
HPV 16/18: CIN 2/3 or AIS	5,301	0	5,258	21	100	(76–100)	< 0.001
HPV 6/11/16/18: CIN 1	2,240	0	2,258	25	100	(84–100)	
HPV 6/11/16/18: Condy, VIN 1, VAIN 1	2,261	0	2,279	34	100	(89–100)	
HPV 6/11/16/18: VIN 2/3 or VAIN 2/3	2,261	0	2,279	7	100	(30-100)	

Merck - FUTURE II Study (NEJM, 2007)

	VACCINE			PLACEBO			
	Total Subjects	No. of Cases	Rate	Total Subjects	No. of Cases	Rate	Efficacy (95% CI)
Subjects in intention-to-treat population††	6087	83	0.5	6080	148	0.8	44 (26–58)
Lesion type							
Cervical intraepithelial neoplasia grade 2	6087	41	0.2	6080	96	0.5	57 (38–71)
Cervical intraepithelial neoplasia grade 3	6087	57	0.3	6080	104	0.6	45 (23–61)
Adenocarcinoma in situ	6087	5	<0.1	6080	7	<0.1	28 (<0–82)
Lesions associated with any HPV type							
Subjects in intention-to-treat population	6087	219	1.3	6080	266	1.5	17 (1–31)
Lesion type							
Cervical intraepithelial neoplasia grade 2	6087	149	0.9	6080	192	1.1	22 (3–38)
Cervical intraepithelial neoplasia grade 3	6087	127	0.7	6080	161	0.9	21 (<0–38)
Adenocarcinoma in situ	6087	5	<0.1	6080	8	<0.1	37 (<0–84)

Merck - FUTURE II Study (NEJM, 2007)



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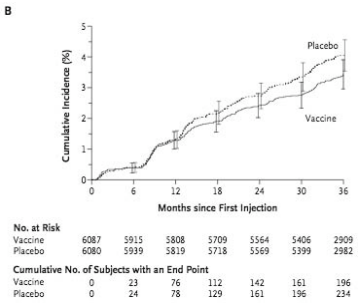
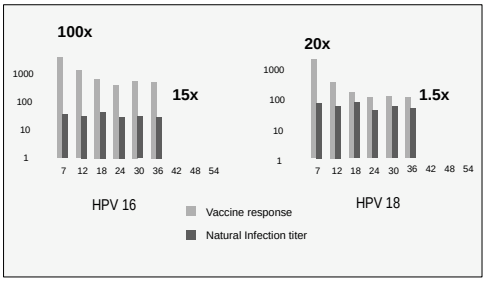


Immunogenicity Over Time (Months)



Immune Response to GARDASIL®

- **Assessed in:**
  - **Women 18 to 26 years of age (GARDASIL N=4,666; placebo N=4,249)**
  - **Female adolescents 9 to 17 years of age (GARDASIL N=1,471; placebo N=583)**

Immune Response to GARDASIL®

- **Individuals who were seronegative and PCR negative to the HPV Types 6, 11, 16, and 18 at enrollment remained HPV PCR negative to the relevant HPV type(s) through 1 month Postdose 3 (Month 7), received all 3 vaccinations, and did not deviate from the study protocol in ways that could interfere with the effects of the vaccine**

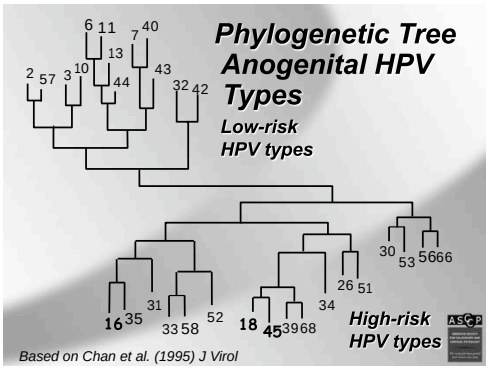
Immune Response to GARDASIL®

- **At least 99.5% of girls and women across all age groups tested, who received GARDASIL became anti-HPV 6-, 11-, 16-, and 18- seropositive by 1 month Postdose 3**

Bivalent Vaccine Protection Against Incident Phylogenetically Related HPV Infections

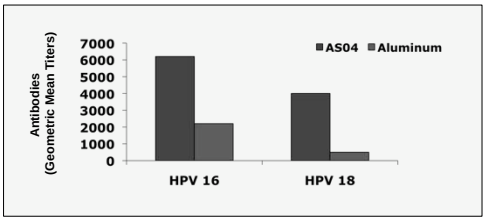
Vaccine				Placebo			
	Total Women	Women w/ Previous HPV Event*	Event Rate (95% CI)	Total Women	Women w/ Previous HPV Event*	Event Rate (95% CI)	Vaccine Efficacy (95% CI)
HPV 45	528	1	0.1 (0-0.4)	518	17	1.2 (0.7-1.9)	**94 (63-100)**
HPV 31	528	14	0.9 (0.5-1.6)	516	30	2.1 (1.4-3.0)	**55 (12-78)**
HPV 33	529	12	0.8 (0.4-1.4)	519	13	0.9 (0.5-1.5)	9 (-117-62)
HPV 52	524	40	2.8 (2.0-3.8)	515	48	3.5 (2.6-4.6)	19 (-27-48)
HPV 58	529	14	0.9 (0.5-1.6)	517	16	1.1 (0.6-1.8)	14 (-88-61)

*Previous HPV event included any self-reported HPV 45, 31, 33, 52, or 58 event.



Role of HPV Vaccine Adjuvants

Antibody Levels at Day 210 after Vaccination with Vaccine + AS04 vs. Same Vaccine with Aluminum Salt Only



Safety of HPV Vaccines

	Bivalent Vaccine[1]	Quadrivalent Vaccine[2]
Injection Site Pain, Erythema, Edema, Fever	Yes	Yes
Acceptable Rate of Adverse Events	Yes	Yes
New Onset of Chronic Diseases after 4.5 Years	No	–
Serious Adverse Events	No	No

Vaccine-Related Experiences

Injection Site (1 to 5 Days Post-Vaccination)			
	GARDISIL (N=5,088)	Placebo (Aluminum) (N=3,470)	Placebo (Saline) (N=320)
Pain	83.9%	75.4%	48.6%
Swelling	25.4%	15.8%	7.3%
Erythema	24.6%	18.4%	12.1%
Pruritus	3.1%	2.8%	0.6%

Systemic Adverse Event(1 to 15 Days Post-Vaccination)		
	GARDISIL (N=5,088)	Placebo (N=3,790)
Fever	10.3%	8.64%

- Few subjects (0.1%) discontinued due to adverse experiences

The vaccine-related adverse experiences that were observed among recipients of GARDASIL were at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients

All-Cause Common Systemic Adverse Experiences*

Adverse Experience (1 to 15 Days Post-Vaccination)	GARDISIL® (N = 5,088) %	Placebo (N = 3,790) %	Adverse Experience (1 to 15 Days Post-Vaccination)	GARDISIL® (N = 5,088) %	Placebo (N = 3,790) %
Pyrexia	13.0	11.2	Cough	2.0	1.5
Nausea	6.7	6.6	Toothache	1.5	1.4
Nasopharyngitis	6.4	6.4	Upper Respiratory Tract infection	1.5	1.5
Dizziness	4.0	3.7	Malaise	1.4	1.2
Diarrhea	3.6	3.5	Arthralgia	1.2	0.9
Vomiting	2.4	1.9	Insomnia	1.2	0.9
Myalgia	2.0	2.0	Nasal Congestion	1.1	0.9

***Greater than or equal to 1% frequency and greater than or equal to the incidence in the placebo group**

Three Phase III Trials Are in Progress

Sponsor	VLP Types	Trial Sites
Merck	HPV 16, 18, 6, 11	Multisite
GSK	HPV 16, 18	Multisite
NCI	HPV 16, 18	Costa Rica

Over 40.000 young women will be followed for several yrs Virologic Endpoint: Persistent cervical HPV DNA Clinical Endpoint CIN 2 and CIN 3

Targeting a High Disease Burden With GARDASIL®

HPV Type	Approximate Disease Burden
16 and 18	• 70% pf cervical cancer, AIS, CIN 3, VIN 2/3 and VAIN 2/3 cases • 50% of CIN cases
6, 11, 16 and 18	• 35-50% of all CIN 1, VIN 1 and VAIN 1 cases • 90% of genital warts cases

AIS = adenocarcinoma *in situ*
CIN = cervical intraepithelial neoplasia
VIN = vulvar intraepithelial neoplasia
VaIN = vaginal intraepithelial neoplasia

Clinical Program for GARDASIL®: Objectives[1]

Demonstrate that GARDASIL:

1.Reduces incidence of vaccine–type-specific:

- **Cervical cancer (via CIN 2/3 + AIS)**
- **CIN**
- **Genital warts and vulvar/vaginal precancers**

2.Reduces overall incidence of HPV-related cervical and genital disease

Clinical Program for GARDASIL®: Objectives[1]

Demonstrate that GARDASIL:

3.Is effective and well tolerated in:

- **Female adolescents aged 9 to 15 years**
- **Young adult females aged 16 to 26 years**

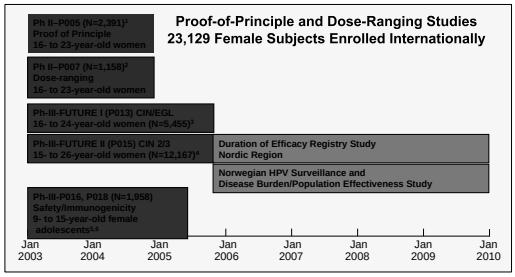
4.Bridges efficacy in adults to efficacy in female adolescents

Clinical Program for GARDASIL®: Selection of Trial End Points[1,2]

Necessary Criteria	Possible End Points		
	HPV Infection	CIN 7	CIN 2/3 or AIS
Required Precursor for Cervical Cancer	√	—	√
Prompts Treatment	—	—	√
Reduction Leads to Cervical Cancer Reduction	—	—	√

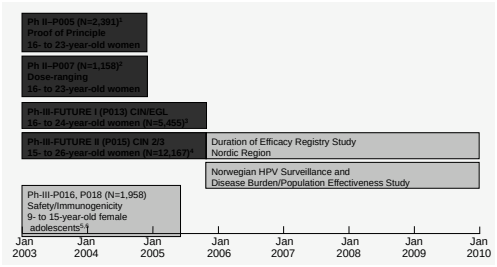
2

Phase II/III Program for GARDASIL®



FUTURE = Females United to Unilaterally Reduce Endo/ Ectocervical Disease; EGL = external genital lesions.

Clinical Program for GARDASIL® Combined Efficacy Analysis



Details of the PPE Population

	PPE Population
Sero (+) and/or PCR (+) to the relevant vaccine HPV type at Day 1	Excluded
PCR (+) to the relevant vaccine HPV type during the vaccination phase	Excluded
Protocol violators	Excluded
<3 Doses	Excluded
Case counting	1 month Postdose 3

Efficacy

100% Efficacious Against HPV 16- and 18-Related Cervical Cancer Precursors[1]

PPE-Combined Population; subjects were naïve to HPV Types 6, 11, 16, and/or 18

End Point: HPV 16/18-related	n	GARDASIL® or HPV 16 L1 VLP Cases*	n	Placebo Cases	Combined Analysis: Efficacy	Combined Analysis: 95% CI
CIN 2/3 or AIS	8,487	0	8,460	53	100%	93–100
CIN 3 or AIS†‡	8,487	0	8,460	32	100%	88–100

- **The efficacy of GARDASIL against HPV 16-, and 18-related VIN 2/3 or VaIN 2/3 was 100%.**

*Analysis of CIN 2/3 and AIS endpoints included protocol 005.
†Defined by FIGO as Stage 0 cervical cancers; FIGO = International Federation of Gynecology and Obstetrics.
‡CIN 3 or AIS analysis was a secondary end point.
1. Data on file.

Efficacy Against HPV

6/11/16/18-Related Lesions[1]

PPE-Combined Population; subjects were naïve to HPV Types 6, 11, 16, and/or 18

End Point: HPV 6/11/16/18-related	GARDASIL® Cases	Placebo Cases	Combined Analysis: Vaccine Efficacy	Combined Analysis: 95% CI
	n=7,858	n=7,861		
CIN or AIS	4	83	95%	87–99

End Point: HPV 6/11/16/18-related	GARDASIL® Cases*	Placebo Cases*	Vaccine Efficacy	95% CI
	n=7,897	n=7,899		
Genital warts	1	91	99%	94–100

- **The efficacy of GARDASIL against HPV 6-, 11-, 16-, and 18-related VIN 1 or VaIN 1 was 100%...**

1. Data on file, MSD.

Subjects Exposed to Any Vaccine HPV Type at Enrollment[1]

Efficacy Studies-Combined Population

Day 1 Composite HPV Status	Combined Analysis: Total (N=18,478)
Negative to HPV 6/11/16/18	73%
By Serology	80%
By PCR Only	85%
Positive to at least 1 HPV type	27%
By Serology	20%
By PCR	15%

- **93% of subjects had one or none of the HPV vaccine types (6, 11, 16, or 18) at enrollment.**

Exclusion criteria: 6 or more sexual partners 1. Data on file, MSD.

Efficacy of GARDASIL® in MITT 2 Population[1]

Ph III–FUTURE I (P013) and FUTURE II (P015)	Vaccine (N=8,799)			Placebo (N=8,800)				
Exposed to ≥1 Vaccine HPV Type at Day 1	n	Number of cases	Rate*	n	Number of cases	Rate*	Observed efficacy	95% CI
HPV 6, 11,16, or 18-Related CIN	2,190	4	0.1	2,184	32	0.8	87.5	(64.8, 96.8)
HPV 6, 11,16, or 18-Related Genital Warts, VIN 1–3, or VaIN 1–3	2,220	3	0.1	2,218	33	0.8	90.9%	(71.1, 98.2)

How Well Do These Vaccines Work In The General Population?

Over 40.000 Young Women Will Be Followed For Several Yrs Virologic

Endpoint: Persistent Cervical HPV DNA Clinical Endpoint CIN 2 And CLN 3

Impact of GARDASIL® Against HPV 6/11/16/18-Related CIN[1]

Seronegative/PCR-negative

End Point	GARDASIL® Cases (N=8,625)	Placebo Cases (N=8,673)
HPV 6/11/16/18-CIN or AIS	9	143

Seronegative/PCR-positive

End Point	GARDASIL Cases (N=797)	Placebo Cases (N=768)
HPV 6/11/16/18-CIN or AIS	70	91

Seropositive/PCR-negative

End Point	GARDASIL Cases (N=1242)	Placebo Cases (N=1283)
HPV 6/11/16/18-CIN or AIS	0	5

Seropositive/PCR-positive

End Point	GARDASIL Cases (N=568)	Placebo Cases (N=580)
HPV 6/11/16/18-CIN or AIS	94	94

1. Data on file, MSD.

MITT Populations Used to Evaluate GARDASIL®[1]

	MITT-2	MITT-3
Sero (-) and/or PCR (-) to the Relevant Vaccine HPV Type at Day 1	Included	Included
Sero (+) and/or PCR (+) to the Relevant Vaccine HPV Type at Day 1	Excluded	Included
PCR (+) to the Relevant Vaccine HPV Type During the Vaccination Phase	Included	Included
Day 1 (+) to non-vaccine HPV type	Included	Included
Day 1 Pap ≥ASCUS	Included	Included
Protocol Violators/< 3 doses	Included	Included
Case Counting	After Day 30	After Day 30

ASCUS = Atypical squamous cells of undetermined significance; those who had a normal Pap at baseline were considered part of a restricted cohort of MITT-3 called R-MITT-3.
1. Data on file, MSD.

Contribution of Subpopulations to Overall Incidence of CIN 2/3 or AIS[1]

Naïve to relevant vaccine HPV types at Day 1 (MITT-2)

- May acquire new infection prior to completion of vaccination regimen
- Takes time for disease to develop

Early on, few disease cases observed

Prophylactic efficacy of GARDASIL is high

MITT-2 + those infected with ≥1 vaccine HPV type or non-vaccine type at Day 1 (MITT-3)

- May have disease at Day 1
  OR
- May develop disease after Day 1

Most disease in clinical trials of GARDASIL® was observed early

Impact of GARDASIL is masked due to early prevalence of disease

1. Data on file, MSD.

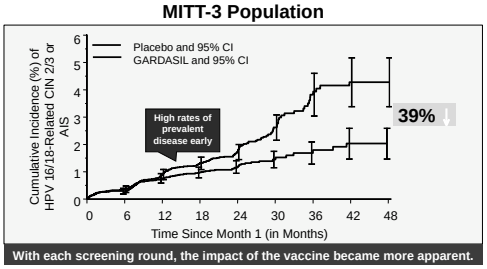
General Population Impact: In Young Women 16–26

End Points	Analysis	GARDASIL or HPV 16 Vaccine Cases	Placebo Cases	% Reduction (95% CI)
HPV 16/18-related CIN 2/3 or AIS	HPV-naïve efficacy	1	81	99 (93, 100)
	HPV 16(+) and/or 18(+) at Day 1	121	120	--
	General population impact	122	201	39 (23, 52)
HPV 6/11/16/18-related CIN or AIS	HPV-naïve efficacy	9	143	94 (88, 97)
	HPV 6, 11, 16, and/or 18 (+) at Day 1	161*	174*	--
	General population impact	170	317	46 (35, 56)
HPV 6/11/16/18-related genital warts	HPV-naïve efficacy	9	136	93 (87, 97)
	HPV 6, 11, 16, and/or 18 (+) at Day 1	49	48†	--
	General population impact	58	184	69 (58, 77)

*Includes 2 subjects who underwent colposcopy for reasons other than an abnormal Pap and 1 subject with missing serology/PCR data at Day 1.
†Includes 1 subject with missing data at Day 1.
1. Data on file, MSD.

General Population Impact: in 16- to 26-Year-Old Females Within 2 to 4 Years[1]

MITT-3 Population



With each screening round, the impact of the vaccine became more apparent.

1. Data on file, MSD.

Should I Give It Women With Abnormal Pap Smears Or Known HPV Disease?

YES

- **No type specific testing currently available**
- **Of those HPV positive, only 60% positive for one type**
- **0.1% of general population positive for both 16 and 18**
- **Based large population based trial, none of the women were positive for 6, 11, 16, and 18**

HOWEVER

- **>19 years of age, 50% have had >4 sexual partners**
- **Cumulative prevalence (2 years) of HPV 16 and HPV 18 in adolescents:**
  - **HPV 16: 31.3%**
  - **HPV 18: 20%**

HOWEVER

- **Merck studies limited maximum number of sexual partners and history of genital abnormalities (<5 partners)**
- **In women 19-26 years, estimates for exposure to high-risk vaccine types is substantial (>50%)**

Clinical Efficacy Studies for GARDASIL®: Study Characteristics

Study Design	Protocol 005*	Protocol 007	FUTURE I	FUTURE II
N	2,391	551	5,442	12,157
Age (years)	16 to 26			
Median duration of follow-up (years)	4.0	3.0	2.4	2.0
Vaccination schedule	Subjects received GARDASIL or placebo on the day of enrollment, and 2 and 6 months thereafter.			

FUTURE = Females United To Unilaterally Reduce Endo/Ectocervical Disease

*Protocol 005 evaluated only the HPV 16 component of GARDASIL

Clinical Program for GARDASIL®: Selection of Trial End Points[1]

Necessary Criteria	End Points		
	HPV Infection	CIN 1	CIN 2/3
Immediate precursor for cervical cancer	√	—	√
Prompts secondary prevention measures	—	—	√
Detection and removal have been shown to prevent cancer	—	—	√

Populations Used to Evaluate GARDASIL®

	PPE Population	General Population Impact
Sero (+) and/or PCR (+) to the Relevant Vaccine HPV Type at Day 1	Excluded	Included
PCR (+) to the Relevant Vaccine HPV Type During the Vaccination Phase	Excluded	Included
Protocol Violators	Excluded	Included
<3 Doses	Excluded	Included
Case Counting	1 Month Postdose 3	1 Month Postdose 1

PPE = Per-protocol efficacy

Clinical Studies for GARDASIL®: Analysis in Per-Protocol Efficacy (PPE) Population

- **Primary analysis of efficacy conducted in PPE population:**
  - **Received all 3 vaccinations within 1 year of enrollment**
  - **Did not have major deviations from the study protocol**

Clinical Studies for GARDASIL®: Analysis in Per-Protocol Efficacy (PPE) Population

  - **Were naïve to the relevant HPV type(s) prior to Dose 1 and through 1 month Postdose 3 (Month 7)**
- **Efficacy measurements started after Month 7 visit**

Prophylactic Efficacy

GARDASIL® Was 100% Efficacious Against HPV 16- and 18-related CIN 2/3 or AIS

Population	n	GARDASIL Cases	n	Placebo Cases	Efficacy	95% CI
Protocol 005*	755	0	750	12	100%	65.1–100
Protocol 007	231	0	230	1	100%	73.9–100
FUTURE I	2,200	0	2,222	19	100%	78.5–100
FUTURE II	5,301	0	5,258	21	100%†	80.9–100
Combined protocols	**8,487**	**0**	**8,460**	**53**	**100%†**	**92.9–100**

*Evaluated only the HPV 16 L1 VLP component of GARDASIL.
†P-values were computed for the prespecified primary hypothesis tests. All p-values were <0.001, supporting the following conclusions: efficacy against HPV 16/18-related CIN 2/3 is >0% (FUTURE II); and efficacy against HPV 16/18-related CIN 2/3 is >25% (combined protocols).

Prophylactic Efficacy

GARDASIL® Was Efficacious Against HPV 6-, 11-, 16-, and 18-related CIN (CIN 1, CIN 2/3) or AIS

Population	n	GARDASIL Cases	n	Placebo Cases	Efficacy	95% CI
Protocol 007	235	0	233	3	100%	73.8-100
FUTURE I	2,240	0	2,258	37	100%*	89.5–100
FUTURE II	5,383	4	5,370	43	90.7%	74.4–97.6
Combined protocols	**7,858**	**4**	**7,861**	**83**	**95.2%**	**87.2–98.7**

*P-values were computed for the prespecified primary hypothesis tests. All p-values were <0.001, supporting the following conclusions: efficacy against HPV 6/11/16/18-related CIN is >20% (FUTURE I).

Prophylactic Efficacy

GARDASIL® Was Efficacious Against HPV 6-, 11-, 16-, and 18-related Genital Warts

Population	n	GARDASIL Cases	n	Placebo Cases	Efficacy	95% CI
Protocol 007	235	0	233	3	100%	93.5-100
FUTURE I	2,261	0	2,279	29	100%	86.4–100
FUTURE II	5,401	1	5,387	59	98.3%	90.2–100
Combined protocols	**7,897**	**1**	**7,899**	**91**	**98.9%**	**93.7–100**

- **The efficacy of GARDASIL against HPV 6-, 11-, 16-, and 18-related VIN 1 or VaIN 1 was 100%.**

Populations Used to Evaluate GARDASIL®

	PPE Population	General Population Impact
Sero (+) and/or PCR (+) to the Relevant Vaccine HPV Type at Day 1	Excluded	Included
PCR (+) to the Relevant Vaccine HPV Type During the Vaccination Phase	Excluded	Included
Protocol Violators	Excluded	Included
<3 Doses	Excluded	Included
Case Counting	1 Month Postdose 3	1 Month Postdose 1

PPE = Per-protocol efficacy

Impact of GARDASIL® in the General Population

- **GARDASIL is a prophylactic vaccine**
- **There was no clear evidence of protection from disease caused by HPV types for which subjects were PCR positive and/or seropositive at baseline**

Impact of GARDASIL® in the General Population

- **Individuals who were already infected with 1 or more vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the remaining vaccine HPV types**

General Population Impact

GARDASIL® Reduced HPV 16- and 18-related CIN 2/3 or AIS

HPV 16- or 18-related CIN 2/3 or AIS	N	GARDASIL or HPV 16 L1 VLP Cases	N	Placebo Cases	% Reduction	95% CI
Prophylactic Efficacy*	9,342	1	9,400	81	98.8%	93–100
HPV 16 and/or HPV 18 Positive at Day 1	--	121	--	120	--	--
General Population Impact†	9,831	122	9,896	201	39.0%	23–52

*Includes all subjects who received at least 1 vaccination and who were naive (PCR (-) and sero (-)) to HPV 6, 11, 16, and /or 18 at Day 1.
Case counting started at 1 Month Postdose 1.
†Includes all subjects who received at least 1 vaccination (regardless of baseline HPV status at Day 1). Case counting started at 1 Month Postdose 1.

Note: Table does not include disease due to nonvaccine HPV types.

General Population Impact

GARDASIL® Reduced HPV 16- and 18-related VIN 2/3 or VaIN 2/3

HPV 16- or 18-related VIN 2/3 and VaIN 2/3	N	GARDASIL or HPV 16 L1 VLP Cases	N	Placebo Cases	% Reduction	95% CI
Prophylactic Efficacy*	8,641	0	8,667	24	100%	83–100
HPV 16 and/or HPV 18 Positive at Day 1	--	8	--	2	--	--
General Population Impact†	8,954	8	8,962	26	69.1%	30–88

*Includes all subjects who received at least 1 vaccination and who were naive (PCR (-) and sero (-)) to HPV 6, 11, 16, and /or 18 at Day 1.
Case counting started at 1 month Postdose 1.
**Includes all subjects who received at least 1 vaccination (regardless of baseline HPV status at Day 1). Case counting started at 1 month Postdose 1.

Note: Table does not include disease due to nonvaccine HPV types.

General Population Impact

GARDASIL® Reduced HPV 6-, 11-, 16- and 18-related CIN or AIS

HPV 6-, 11-, 16-, 18-related CIN (CIN 1, CIN 2/3) or AIS	N	GARDASIL or HPV 16 L1 VLP Cases	N	Placebo Cases	% Reduction	95% CI
Prophylactic Efficacy*	8,625	9	8,673	143	93.7%	88–97
HPV 6, 11, 16 and/or HPV 18 Positive at Day 1	--	161†	--	174†	--	--
General Population Impact‡	8,814	170	8,846	317	46.4%	35–56

*Includes all subjects who received at least 1 vaccination and who were naive (PCR (-) and sero (-)) to HPV 6, 11, 16, and /or 18 at Day 1.
Case counting started at 1 month Postdose 1.
†Includes 2 subjects (1 in each vaccination group) who underwent colposcopy for reasons other than an abnormal Pap and 1 placebo subject with missing serology/PCR data at Day 1.
‡Includes all subjects who received at least 1 vaccination (regardless of baseline HPV status at Day 1). Case counting started at 1 month Postdose 1.

Note: Table does not include disease due to nonvaccine HPV types.

General Population Impact

GARDASIL® Reduced HPV 6-, 11-, 16- and 18-related Genital Warts

HPV 6-, 11-, 16-,18-related Genital Warts	N	GARDASIL or HPV 16 L1 VLP Cases	N	Placebo Cases	% Reduction	95% CI
Prophylactic Efficacy*	8,760	9	8,786	136	93.4%	87–97
HPV 6, 11, 16 and/or HPV 18 Positive at Day 1	--	49	--	48†	--	--
General Population Impact‡	8,954	58	8,962	184	68.5%	57–77

*Includes all subjects who received at least 1 vaccination and who were naive (PCR (-) and sero (-)) to HPV 6, 11, 16, and /or 18 at Day 1.
Case counting started at 1 month Postdose 1.
†Includes 1 subject with missing serology/PCR data at Day 1.
‡Includes all subjects who received at least 1 vaccination (regardless of baseline HPV status at Day 1). Case counting started at 1 month Postdose 1.

Note: Table does not include disease due to nonvaccine HPV types.

Immunogenicity

- **Because there were few disease cases in subjects naïve (PCR negative and seronegative) to vaccine HPV types at baseline in the group that received GARDASIL®, it has not been possible to establish minimum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 antibody levels that protect against clinical disease caused by HPV 6, 11, 16, and/or 18**

Immunogenicity

- **Type-specific competitive immunoassays with type-specific standards were used to assess immunogenicity to each vaccine HPV type. These assays measured antibodies against neutralizing epitopes for each HPV type. The scales for these assays are unique to each HPV type; thus, comparisons across types and to other assays are not appropriate**

Immune Response to GARDASIL®: PPI Population

*Number of subjects randomized to the respective vaccination group who received at least 1 injection

**Number of subjects in the per-protocol analysis with data at the specified study time point

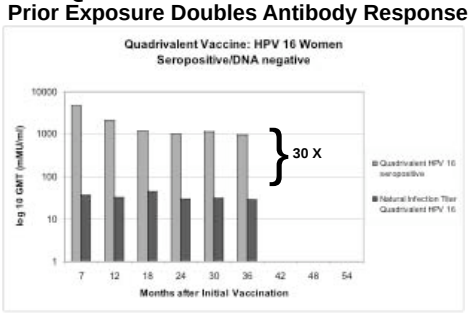
†mMU = milli-Merck units

Note: These data are from Protocol 007

Study Time	GARDASIL (N* = 276)		Aluminum-Containing Placebo (N = 275)	
	n**	GMT (95% CI) mMU/mL†	n	GMT (95% CI) mMU/mL
Anti-HPV 6				
Month 07	208	582.2 (527.2, 642.8)	198	4.6 (4.3, 4.8)
Month 24	192	93.7 (82.2, 106.9)	188	4.6 (4.3, 5.0)
Month 36	183	93.8 (81.0,108.6)	184	5.1 (4.7, 5.6)
Anti-HPV 11				
Month 07	208	696.5 (617.8, 785.2)	198	4.1 (4.0, 4.2)
Month 24	190	97.1 (84.2, 112.0)	188	4.2 (4.0, 4.3)
Month 36	174	91.7 (78.3, 107.3)	180	4.4 (4.1, 4.7)
Anti-HPV 16				
Month 07	193	3889.0 (3318.7, 4557.4)	185	6.5 (6.2, 6.9)
Month 24	174	393.0 (335.7, 460.1)	175	6.8 (6.3, 7.4)
Month 36	176	507.3 (434.6, 592.0)	170	7.7 (6.8, 8.8)
Anti-HPV 18				
Month 07	219	801.2 (693.8, 925.4)	209	4.6 (4.3, 5.0)
Month 24	204	59.9 (49.7, 72.2)	199	4.6 (4.3, 5.0)
Month 36	196	59.7 (48.5, 73.5)	193	4.8 (4.4, 5.2)

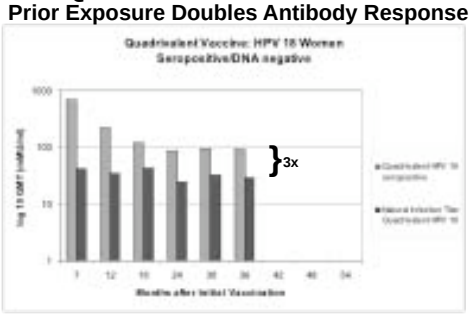
Immunogenicity of Quadrivalent Vaccine

Prior Exposure Doubles Antibody Response



Immunogenicity of Quadrivalent Vaccine

Prior Exposure Doubles Antibody Response



When Will HPV Vaccines Be Available?

- Merck filed with the FDA for approval of its quadrivalent vaccine (Gardasil™) in December 2005

When Will HPV Vaccines Be Available?

- On May 18th 2006, the FDA Vaccines and Related Biological Products Advisory Committee voted 13 to 0 that the data from Phase II and Phase III clinical trials support the efficacy and safety of quadrivalent HPV vaccine for the prevention of cervical cancer, CIN, VAIN, VIN and genital warts[1]

When Will HPV Vaccines Be Available?

- On June 8, 2006, the FDA approved the vaccine for clinical use
- Cost: $120 per dose
- Advisory Committee on Immunization Practices (ACIP) recommend that Gardasil™ be administered to 11 and 12 year old females and to females age 13 to 26 who have not been previously vaccinated

Dosage and Administration of GARDASIL®

- GARDASIL should be administered intramuscularly as 3 separate 0.5-mL doses according to the following schedule:
  - First dose: at elected date
  - Second dose: 2 months after the first dose
  - Third dose: 6 months after the first dose

Dosage and Administration of GARDASIL®

- Administer intramuscularly
  - In deltoid region of upper arm or in higher anterolateral area of the thigh
- Do not inject intravascularly

Dosage and Administration of GARDASIL®

- Subcutaneous and intradermal administrations have not been studied
  - Therefore they are not recommended
- Use as supplied
  - No dilution or reconstitution is necessary

Unanswered Questions

Unanswered Questions

Unanswered Questions

How will the public respond to a cancer vaccine?

Particularly, one caused by a STI?

Christian conservatives fear that new, amazingly effective cervical-cancer vaccines will spur promiscuity and **undermine abstinence.** Let the lobbying wars begin. BY JANET GUYON

Unanswered Questions

Should men be vaccinated?

Data on HPV vaccine efficacy in men not yet available

What man would want to get a "cervical cancer" vaccine??

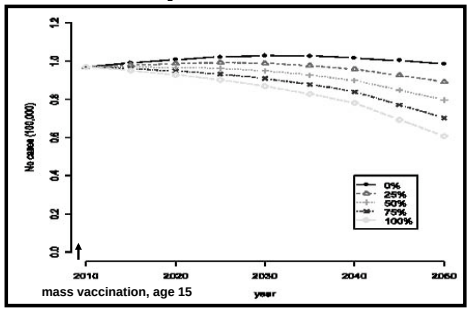
Unanswered Questions

What will happen to screening?

Screening practices will not change and any impact will not be seen for decades

.

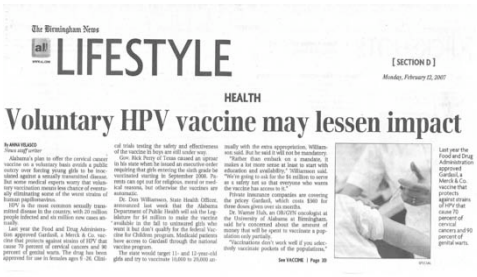
HPV Vaccine for Prevention Minimal Impact in Near Future



Unanswered Questions

Unanswered Questions

- **Will other 'high risk' types replace 16/18?**
- **Who will pay for the vaccine?**
  - **If there are only 10K cases, is the vaccine in the U.S. worth it?**
- **May not significantly decrease cervical cancer in the U.S. over the next 50 years?**



The Birmingham News
al LIFESTYLE
[SECTION D]
Monday, February 12, 2007

HEALTH

Voluntary HPV vaccine may lessen impact

by ANNA VILLAGO
News staff writer

Alabama's plan to offer the cervical cancer vaccine on a voluntary basis avoids a public backlash but could limit the number of girls shielded against a sexually transmitted disease. But some medical experts worry that voluntary vaccination means less chance of eventually eliminating some of the worst strains of human papillomavirus.

HPV is the most common sexually transmitted virus in the U.S., infecting 6.2 million people infected and six million new cases annually.

Last year the Food and Drug Administration approved Gardasil, a Merck & Co. vaccine that protects against strains of HPV that cause 70 percent of cervical cancers and 90 percent of genital warts. The drug has been approved for use in females ages 9 -26. Clinical trials testing the safety and effectiveness of the vaccine in boys are still under way.

Gov. Rick Perry of Texas caused an uproar in his state when he issued an executive order that would require all girls entering sixth grade vaccinated starting in September 2008. Parents can opt out for religious, moral or medical reasons, but otherwise the vaccines are automatic.

Dr. Don Williamson, State Health Officer, announced last week that the Alabama Department of Public Health would ask the Legislature for $2 million to make the vaccine available in the fall to uninsured girls who want it but don't qualify for the federal Vaccine for Children program. Medicaid patients have access to Gardasil through the national immunization program.

The state would target 11- and 12-year-old girls and try to vaccinate 16,000 to 20,000 annually with the extra appropriation, Williamson said. But he said it will not be mandatory.

"Rather than embark on a mandate, it makes a lot more sense at least to start with a voluntary program," Williamson said. "We're going to ask for the $2 million to serve as a safety net so that everyone who wants the vaccine has access to it."

Private insurance companies are covering the private Gardasil, which costs $360 for three doses given over six months.

Dr. Jeffrey Peipert, an OB/GYN oncologist at the University of Alabama at Birmingham, said he's concerned about the amount of money that will be spent to vaccinate a population only partially.

"Vaccinations don't work well if you select mostly vaccinate pockets of the population,"

See VACCINE | Page 2D

Last year the Food and Drug Administration approved Gardasil, a Merck & Co. vaccine that protects against strains of HPV that cause 70 percent of cervical cancers and 90 percent of genital warts.

Why Voluntary Vaccination Won't Work

- **Most adolescents do not receive annual health examinations**
- **Most successful regimens are based on <u>required</u> immunizations for infants**
  - **Example: Hepatitis B Vaccine**

Why Voluntary Vaccination Won't Work

- **Sporadic, voluntary immunization in the state unlikely to dramatically reduce rates of cervical cancer and abnormal pap smears**
- **No one likes having something "rammed down their throat" but the success of vaccination is based on widespread and compulsory use (i.e., Smallpox and Polio)**

Unanswered Questions

- **Who will give it?**
  - **Pediatricians**
  - **Family Medicine**
  - **Adolescent Medicine Specialists**
  - **Gynecologists**

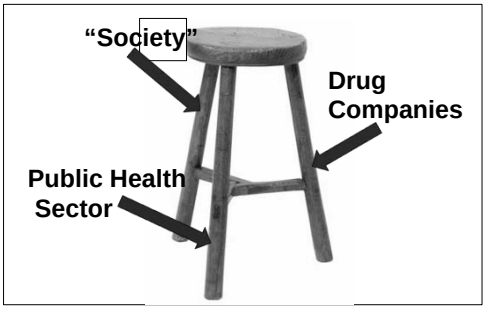
Unanswered Questions

- Will a booster be necessary?
- How do we counsel patients without type specific assays?

Summary

- HPV is very common
- Cervical cancer should be completely preventable
- VLP vaccines demonstrate impressive immunity and protection against HPV and pre-invasive lesions
- Significant issues still need to be addressed

Vaccine Implementation: The "Rickety" 3-legged Stool



Questions?