

Human Papillomavirus (HPV) Vaccination and Implications for Cervical Cancer Screening

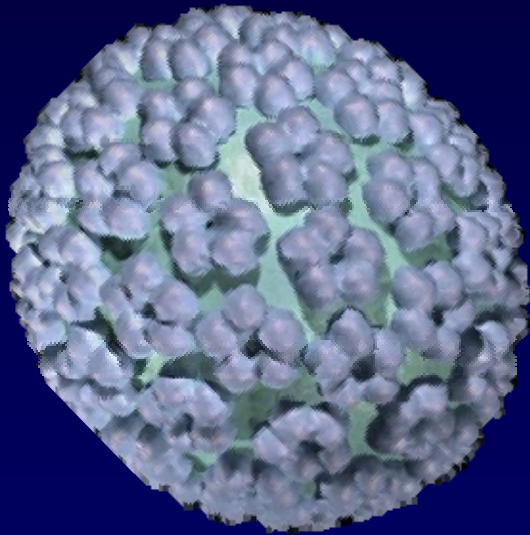
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Current Estimates of the Impact of HPV in Cancer in Women

(Male Estimates Are Similar)

Organ Site	% HPV Related	Estimated Number per Year
Cervical	95% to 98 %	500,000
Vulva	30% to 35%	16,000
Vaginal	65% to 90%	14,000
Anal	80+%	3,000
Oral/larynx	25%	1,000
Oro-pharynx	30% to 75%	534,000
Total		534,000



HPV Vaccines Trials and Results

Current HPV Vaccines

MSD / SPMSD

HPV 6,11,16 & 18

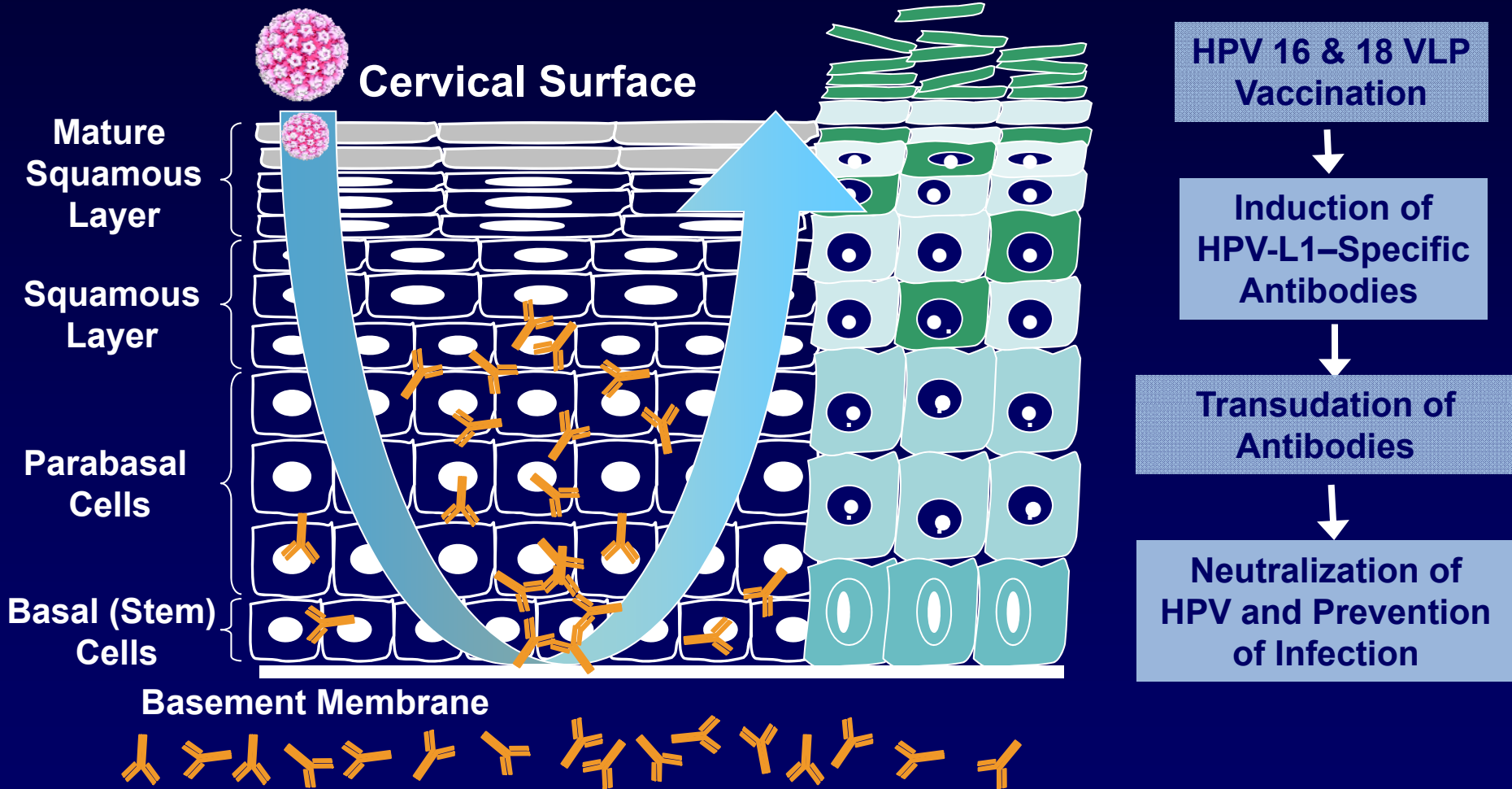
- VLP L1 of four HPV types
- Yeast expressed
- Adjuvant aluminum
- First licensed in 2006 to over 100 countries
- Prequalified June 2009

GSK

HPV 16 / 18

- VLP L1 of two HPV
- Baculovirus expressed in insect cells
- AS04 adjuvant :
 - Aluminum salts and monophosphoryl lipid A
- First licensed in 2007 to over 90 countries
- Prequalified 2009

Protection from HPV Infection by Vaccination



Key Results from Phase III Trials of HPV Vaccines

Vaccine Name	Gardasil®	Cervarix®
Time of follow up	Final	Final
HPV types included	6, 11, 16, 18	16, 18
Efficacy HPV 16 or 18 CIN2+	Proven	Proven
Efficacy HPV 16 CIN2+	Proven	Proven
Efficacy HPV 18 CIN2+	Proven	Proven
Efficacy 16 or 18 CIN2	Proven	Proven
Efficacy 16 or 18 CIN3	Proven	Proven

* Proven in combined analysis of phase II and III trials

Key Results from Phase III Trials of HPV Vaccines

Vaccine Name	Gardasil®	Cervarix®
Therapeutic effect	No	No
Safety/tolerability	Safe	Safe
Efficacy VIN; VAIN 2/3	Proven	Not reported
Cross protection (infection)	Reported	Reported
Cross protection (lesions)	Reported	Reported
Immunogenicity bridging 9-14, 15-26, 26-45, & boys	Proven	Proven
Immune memory	Booster with 4 th dose at year 5	Enhanced AB titers and B cell production

Key Results and Speculations from Phase III Trials of HPV Vaccines

Vaccine Name	Gardasil®	Cervarix®
Efficacy genital warts (6/11)	Proven females / males	Not in target
Efficacy RRP	Likely	Not in target
Efficacy VIN; VAIN 2/3	Proven	Not reported*
Efficacy anal cancer*	Likely	Likely
Efficacy penile cancer**	Likely	Likely
Efficacy oral /pharynx cancer	Likely	Likely

* Analogy with cervical cancer results in Gardasil trials

** Indirect analogy with GW results

**NEW CLINICAL DATA:
25th INTERNATIONAL
PAPILLOMAVIRUS CONFERENCE
Malmö 2009**

***Gardasil*[®]: HPV 6 & 11, 16, & 18**

*Efficacy in males (GW)

*Herd immunity

*Efficacy in women to age 45 years

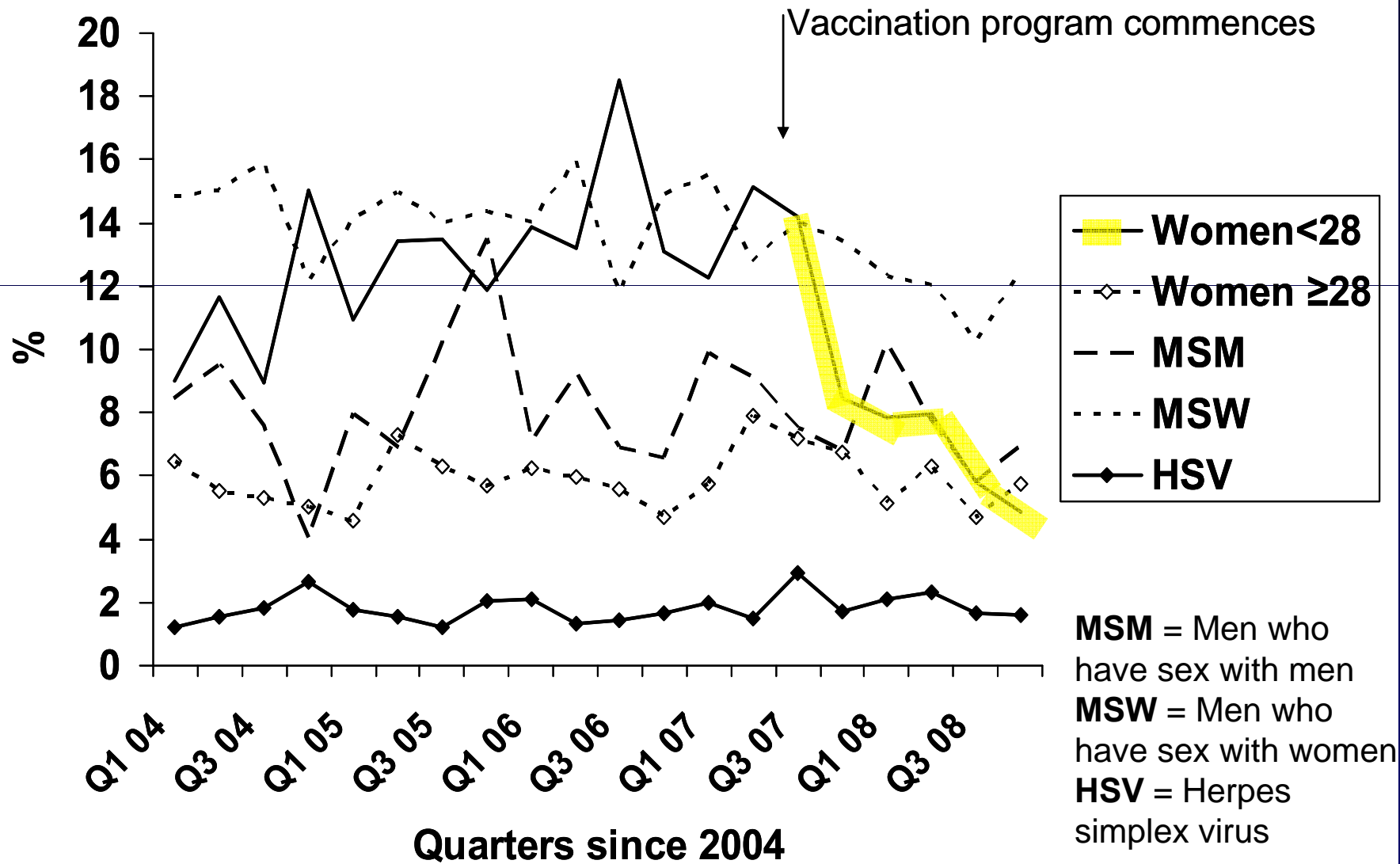
Efficacy Against HPV 6/11/16/18–Related External Genital Lesions in Males

HPV 6/11/16/18–Related	Efficacy, %	95% CI, %
All EGLs	90.4	69.2-98.1
Condyloma	89.4	65.5-97.9
PIN	100	<0-100

Impact of HPV 6/11/16/18 Vaccination on External Genital Warts (EGW): Melbourne Sexual Health Centre

- 36,055 new visits in interval January 2004 – December 2008:
EGWs diagnosed in 10.6%
- Vaccine uptake in Australian females 12-26 years ~ 70% since 2007
- In 2008, the number of new EGW cases was compared to the expected average
 - 48% reduction in genital warts in women <28 years of age
 - 17% reduction in genital warts in heterosexual males
 - No change in homosexual males
 - There was no change in the incidence of herpes simplex

Percentage with Presentation of Warts



Gardasil Trials: Per Protocol Efficacy in Women Aged 24-45 Years. Incidence of HPV 6,11,16,18– Related Persistent Infection/Disease; Cervical/External

Endpoint	GARDASIL	Placebo	Efficacy	IC 95%	<i>P</i>
VPH 6/11/16/18	4	41	91%	74, 98	<.001
VPH 16/18	4	23	83%	51, 96	<.001
VPH 6/11	0	19	100%	79, 100	<.001

Population	GARDASIL	Placebo	Efficacy	IC 95%	<i>P</i>
All ages	4	41	91%	74, 98	<.001
24-34 y	2	24	92%	67, 99	<.001
35-45 y	2	17	89%	52, 99	<.001

**NEW CLINICAL DATA:
25th INTERNATIONAL
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Malmö 2009**

***Cervarix*[®]: HPV 16 & 18 + ASO4 Adjuvant**

Impact of type specific cross protection
Duration of antibody titers

Type-Specific Cross-Protection Beyond HPV-16/18 TVC-Naïve

HPV	6 Month Persistence					CIN2+				
	n HPV	n Control	VE%	LL	UL	n HPV	n Control	VE%	LL	UL
HPV-31	32	140	77.5	66.1	85.5	0	20	100	78.3	100
HPV-33	53	93	43.5	18.6	61.2	5	18	72.3	19.1	92.5
HPV-45	12	64	81.4	64.3	91.2	0	5	100	-19.5	100

 Values with LLCI >0 statistically significant

Skinner R, et al. Presented at: 25th International Papillomavirus Conference; 8-14 May 2009: Malmö, Sweden. Abstract O-29.01.

Efficacy Against CIN2+ Irrespective of HPV Type in the Lesions

TVC-Naïve—Two Different Studies

	Vaccine	Control	VE, %	Confidence Interval
CIN2+ (any HPV type)				
Gardasil*	NA	NA	42.7	23.7 - 57.3

*<http://www.emea.europa.eu/humandocs/PDFs/EPAR/gardasil/H-703-PI-en.pdf> - page 9.

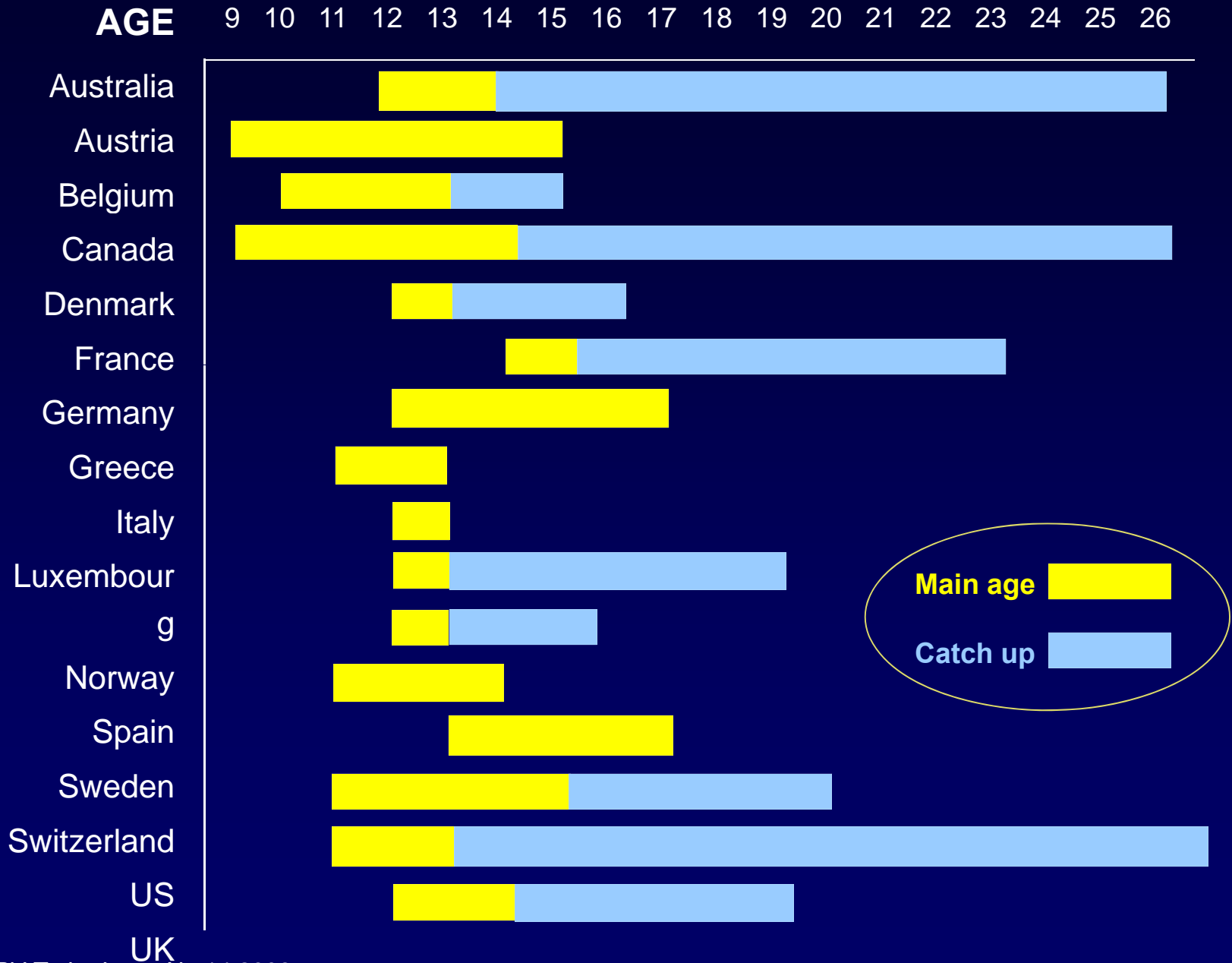
Includes 17,599 subjects enrolled in protocols 013 & 015

NA= not available

	Vaccine	Control	VE, %	Confidence Interval
CIN2+ (any HPV type)				
Cervarix**	33	110	70.2	54.7 - 80.9

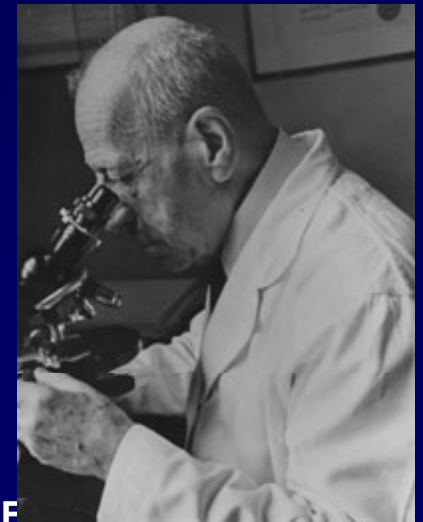
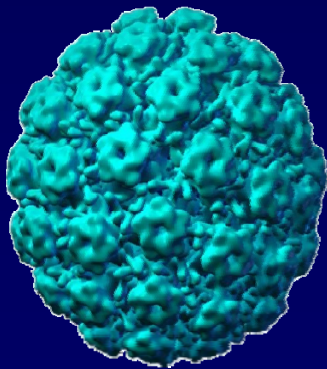
**Paavonen J, et al. Presented at: 25th International Papillomavirus Conference; May 8-14, 2009: Malmö, Sweden. Abstract O-29.06.

Recomendations For HPV Vaccination October 2007



HPV DNA Tests in Screening:

**The present and the future of primary screening
with a secondary triage test to screen for treatment:
Cytology, biomarkers, VIA, VIAM...**



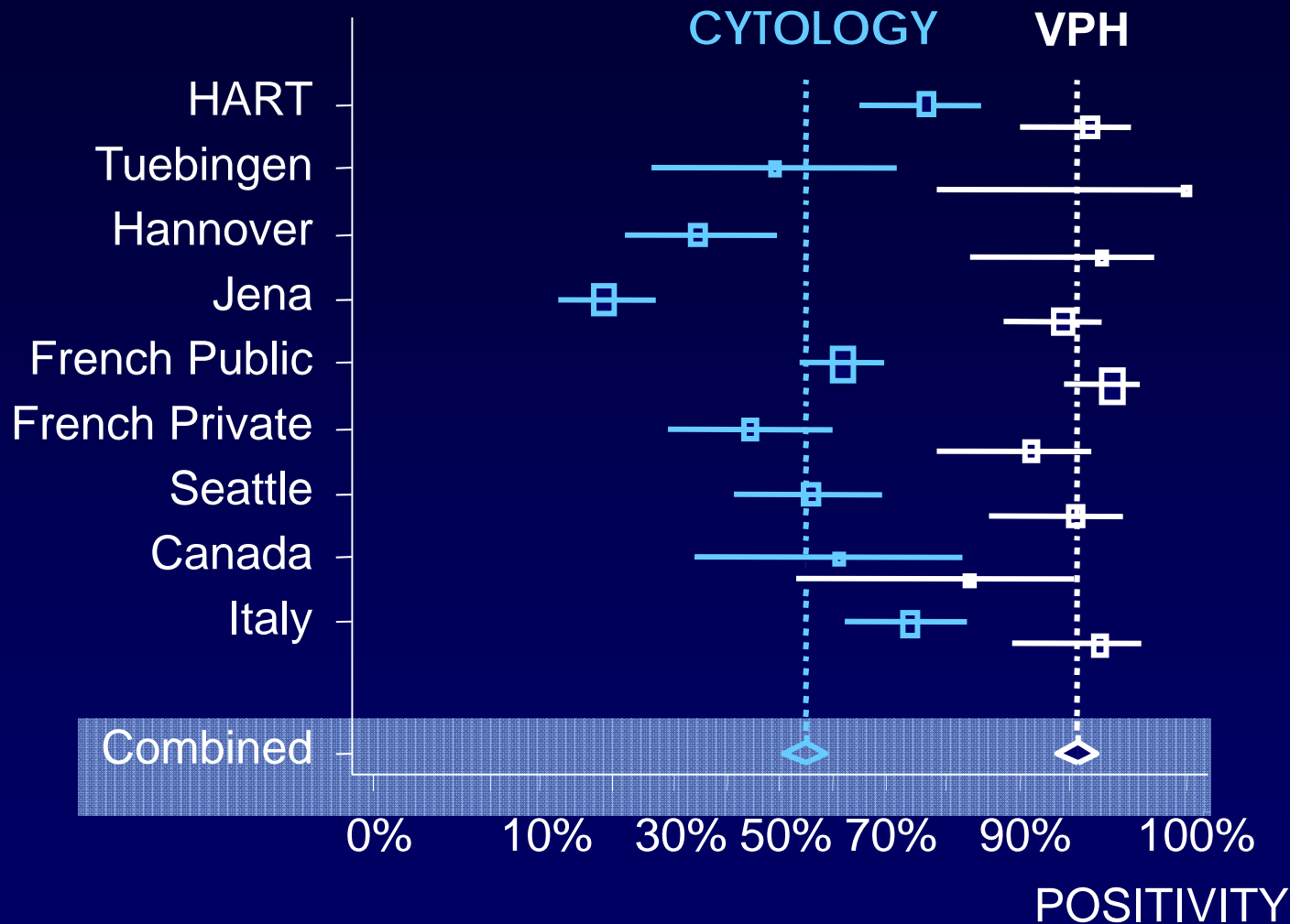
Essential Traits Of HPV Screening as Compared With Standard Cytology

GAIN IN SENSITIVITY 30% to 40%

LOSS IN SPECIFICITY 5% to 8%

**HIGH REPRODUCIBILITY &
AUTOMATIZATION**

Sensitivity for Histology Confirmed CIN 2+ of HPV Tests and Cytology in Studies in Europe and North America



- Point estimates and 95% CI. The size of the box is proportional to the size of the study.
- ◇ Summary estimates of all studies

HPV Test vs Cytology: Summary of 16 Controlled Trials

	SENSITIVITY CIN2+	SPECIFICITY CIN2+
HPV-DNA	96%	92%
CYTOLOGY	53%	97%

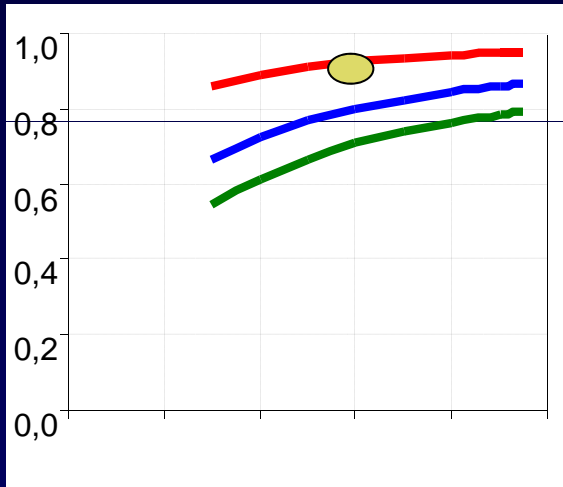
Loss of Screening Performance Due to Vaccination

- *As successive cohorts of women are vaccinated, we will achieve a significant (50% +) reduction in the prevalence of the most significant cytologic abnormalities resulting in:*
 - Decrease in positive predictive value of cytology
 - Increase in false positive rates will lead to over-diagnosis and over-treatment
 - Negative impact on technician training and quality assurance (largely avoided by HPV tests)

Joint Effects of Changes in Sensitivity, Specificity, and Lesion Prevalence on the PPV of a Screening Test

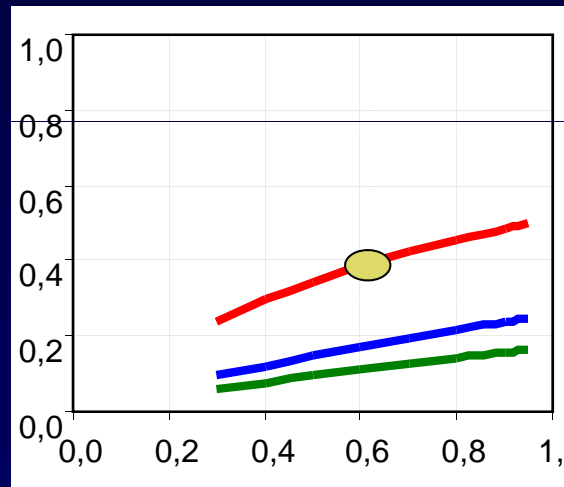
TRIAGE

Prevalence 50%



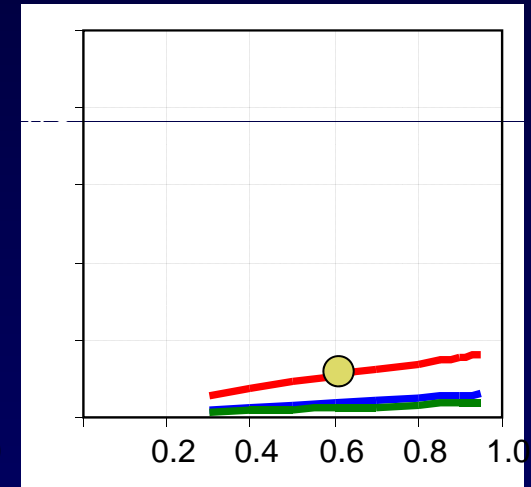
CURRENT

Prevalence 5%



POST VACCINATION

Prevalence 1%



Positive Predictive Value

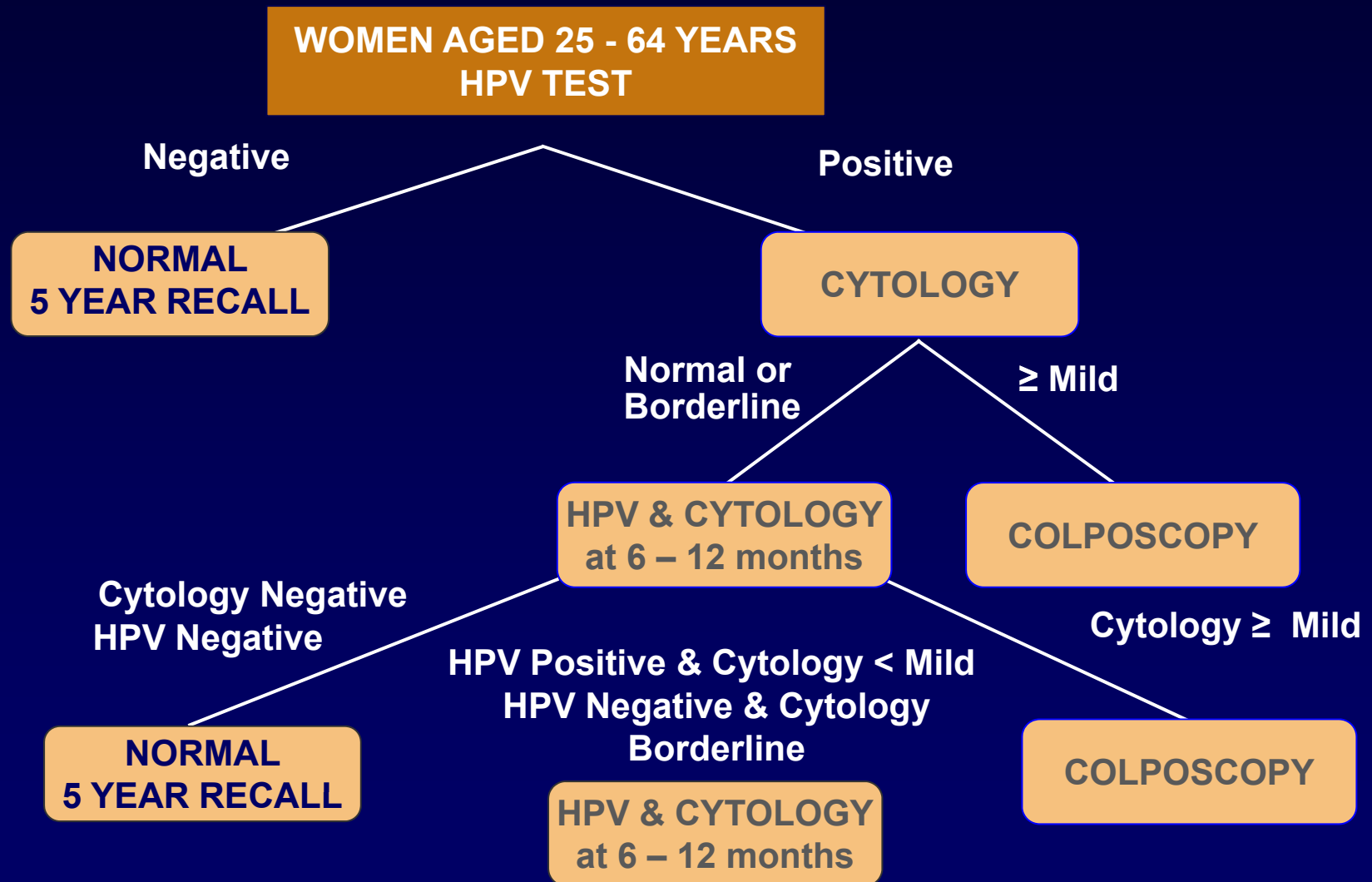
Sensitivity of the Screening Test

● Sensitivity: 60% and specificity 95%

Specificity: blue: 85%, and green: 75%

Proposed New Screening Algorithm

Use of HPV TESTING as the primary screening test and of CYTOLOGY to triage HPV-positive women



Suggested Cost-Effectiveness Strategies

		Screening	Triage	Cost x Qualy
Unvaccinated women	At 21	Cytology x 3 y	HPV Test	78,000
	At 30	HPV Test	Cytology	
Girls vaccinated at 12	At 25	Cytology	HPV Test	41,000 If x 5 years
	At 35	HPV Test	Cytology	

- **More effective and more cost-effective than screening women all ages with PAP or PAP + HPV TRIAGE annually or bi-annually**

Conclusion

- The epidemiology and the causality of HPV infections and cervical cancer—and other—has been largely described
- HPV-based screening tests have been validated
- Excellent vaccines are available
 - *Cervical (and other) cancers can potentially be eradicated*

Conclusions: Vaccines for Cancer Prevention

Non 16 & 18–exposed women:
95% + (70% of cancer) (independent of age)

Cross protection impact: 6% to 12% additional (76% to 82%)

- **Previous exposure resolved** (DNA neg; Sero pos) protection against other types & possible booster impact on exposed vaccine types
- **HPV carriers** (DNA pos) no change in prognosis and protection against re-infections & other types

VACCINATION IS SAFE IN ALL GROUPS

Conclusions: Screening for Cervical Cancer Prevention

Nonvaccinated women:

Continue program / change to HPV screening

Vaccinated women while sexually active:

HPV screening/continue program

Vaccinated women while presexually active:

HPV screening

Screening transition time:

T0: First adolescent cohort fully vaccinated

T1: Their 25th birthday