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HPV Vaccine & Prevention

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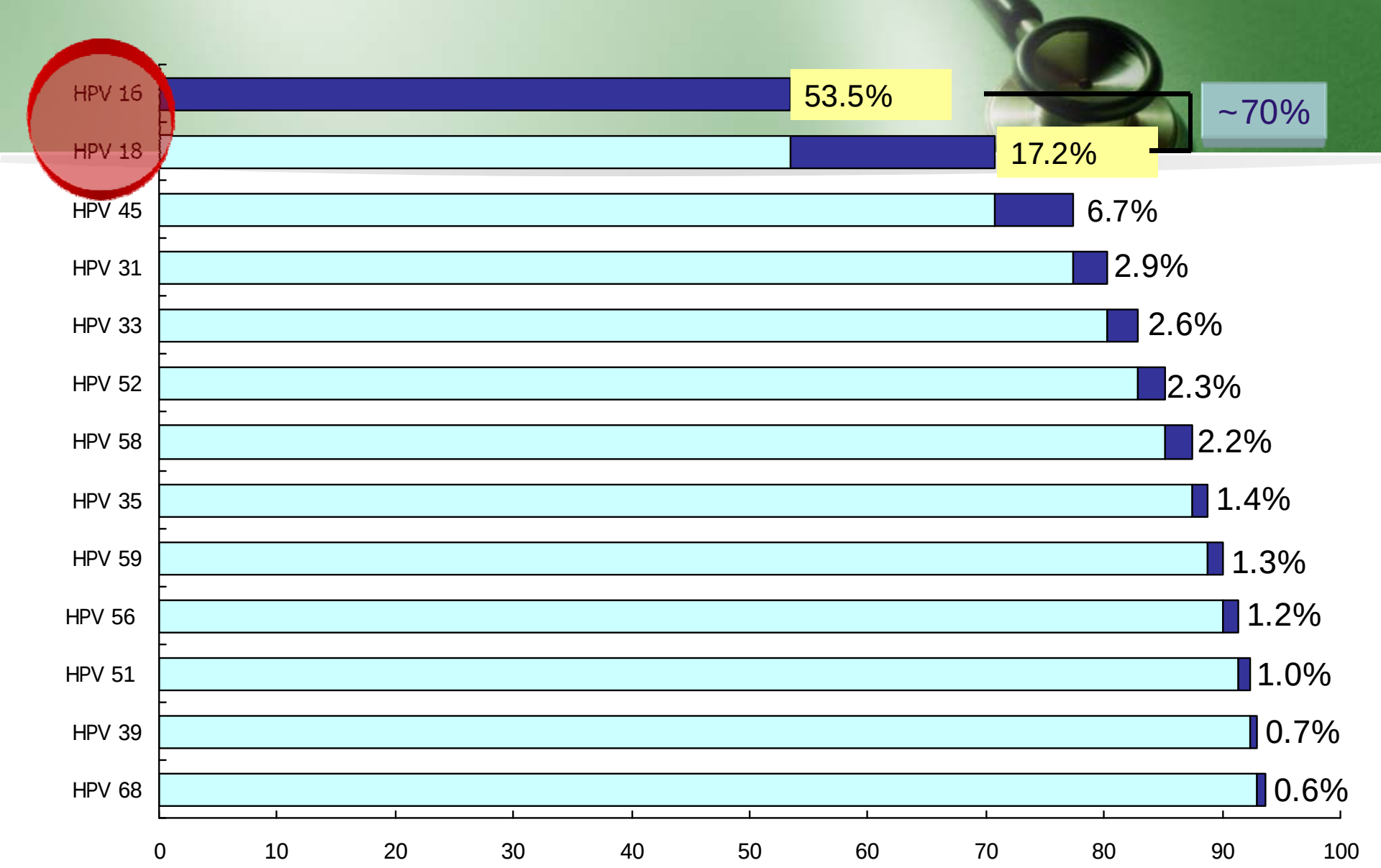
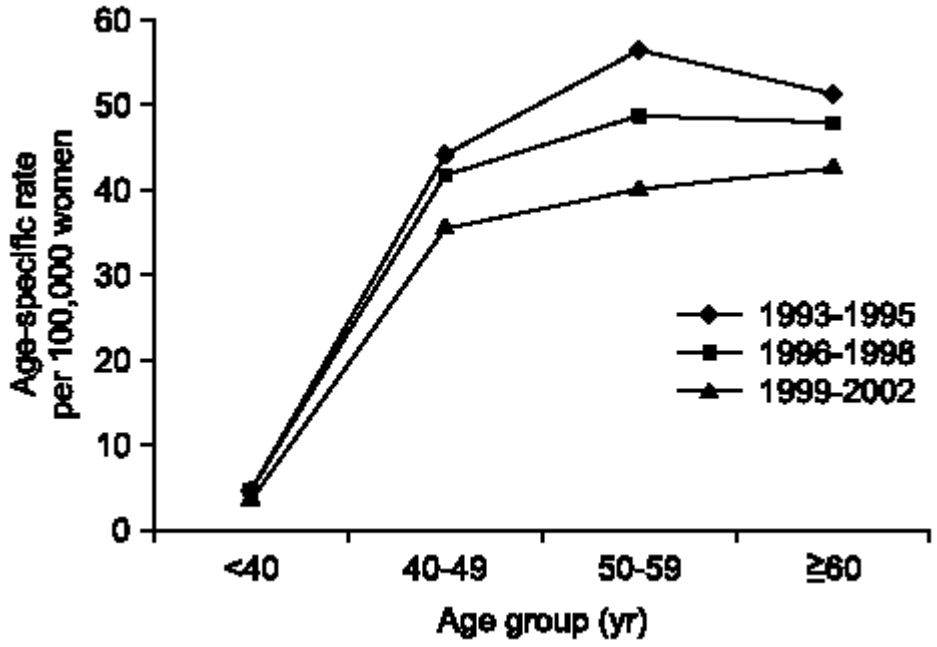
Epidemiology and pathology of HPV infection



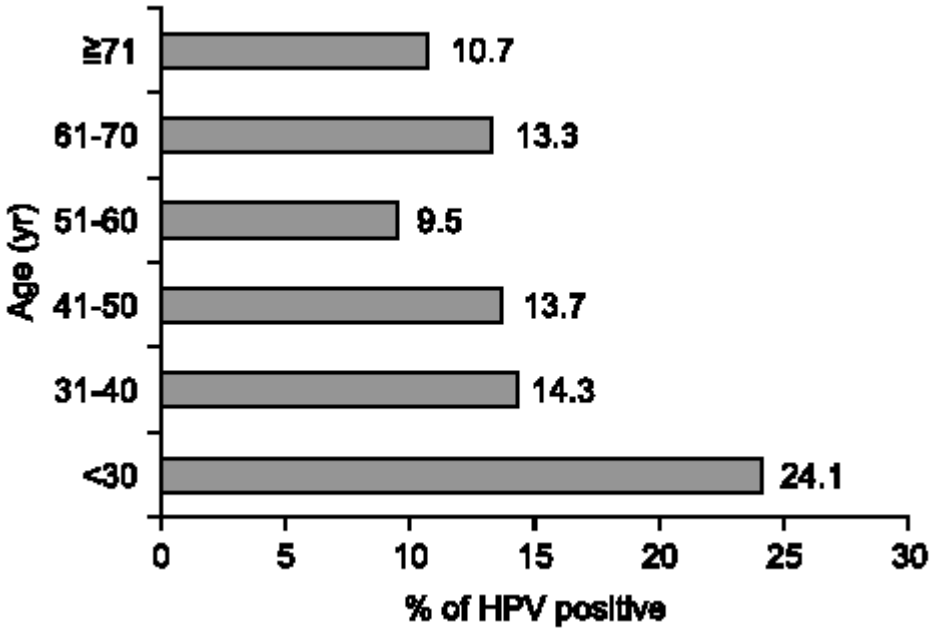
Proportion (%) of Cervical Cancers throughout the World Attributable to Different HPV Types

Franco EL and Harper DM. Vaccine. 2005;23:2388



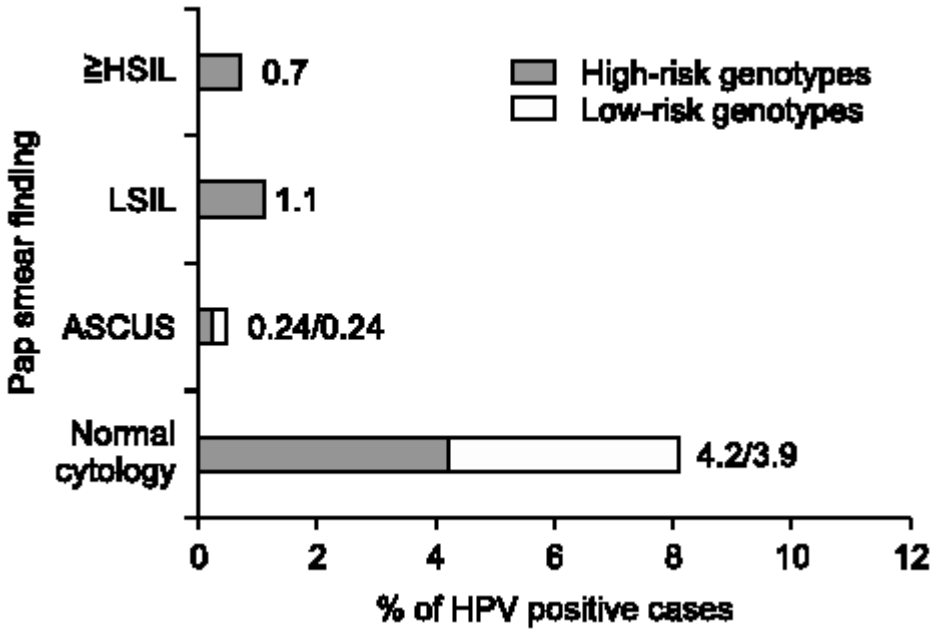
Age-specific incidence of cervical cancer in Korea (1993-2002)

Chung HH et al., Int J Gynecol Cancer, 2006



Rate of HPV infection by age group in Korea

Joo WD et al., Kor J Gynecol Cancer Colposc, 2004

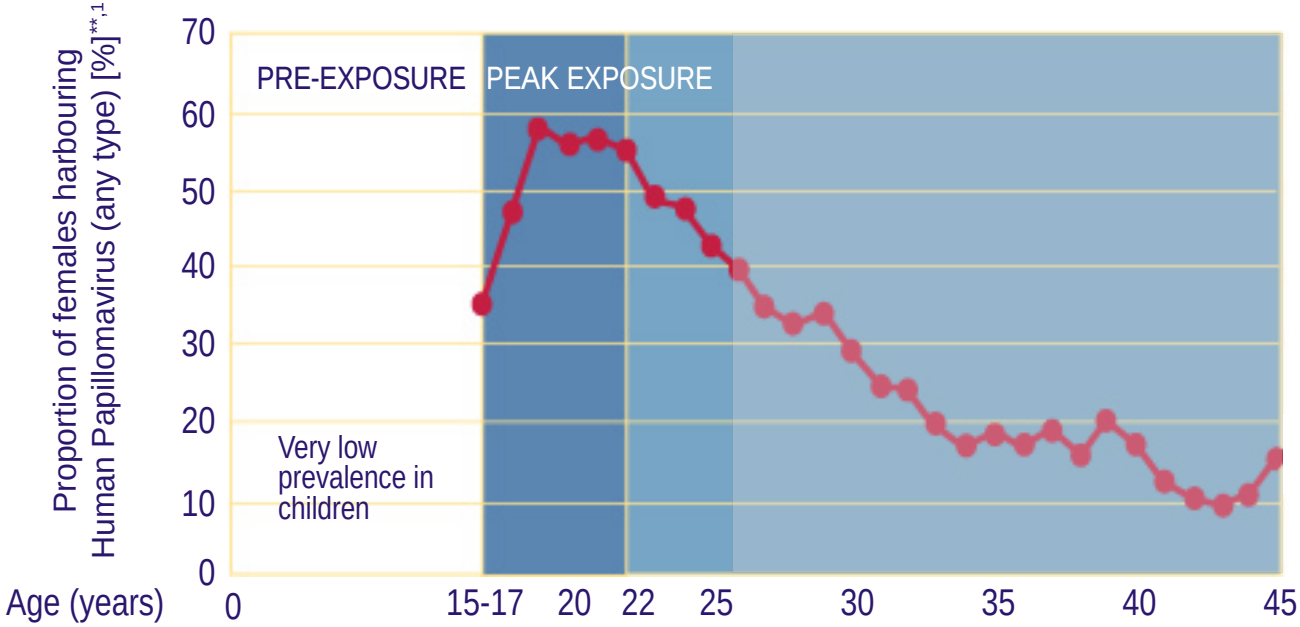


Prevalence of HPV types by cytological findings (1993-2002)

Shin HR et al., Int J Cancer, 2003

Large majority of women become infected with HPV

Age specific prevalence of HPV infection in 11,000 Danish women attending sequentially for routine Pap screening.



* United States' Centers for Diseases Control and Prevention's. Advisory Committee on Immunization Practices

** Cervical smears of Danish women aged 15-93 (n=11,865) collected in 2005

*** For sexually active people

[1] Krüger Kjaer S et al. EUROGIN. 23-26 April 2006. Paris, France

[2] Koutsky LA. Am J Med 1997

[3] Koutsky LA et al. Epidemiology Rev 1988

[4] Syrjänen K et al. Sex Transm Dis 1990

70-80% life time risk to become infected, often as adolescent or young adult***2,3,4**

National cervical cancer screening guideline

	National Cervical Cancer Screening Guideline*	Cervical Cancer Screening Recommendations of Korean Society of Obstetrics and Gynecology†
Test or procedure	Pap smear	Pap smear
Frequency	Every 2 yr	Every 1 yr
Target population	30 yr and over	All women after first intercourse 20 yr and over (excluding virgins)
		Conducted by gynecologists
		Analyzed by pathologists
	Conducted by gynecologists or responsible doctors of the clinic	Reported by The Bethesda System
	Use the brush, not the cotton stick	HPV test, Cervicography, Liquid-based cytology, PC-based system: Reexamine after clinical and economical evidences are accumulated
	Reported by pathologists	The interval is able to be changed by gynecologists according to diagnosis, treatment and requirement of follow-up

*Established in 2001 by The Ministry of Health & Welfare, †Established in 2001 by Korean Society of Obstetrics and Gynecology

HPV infection

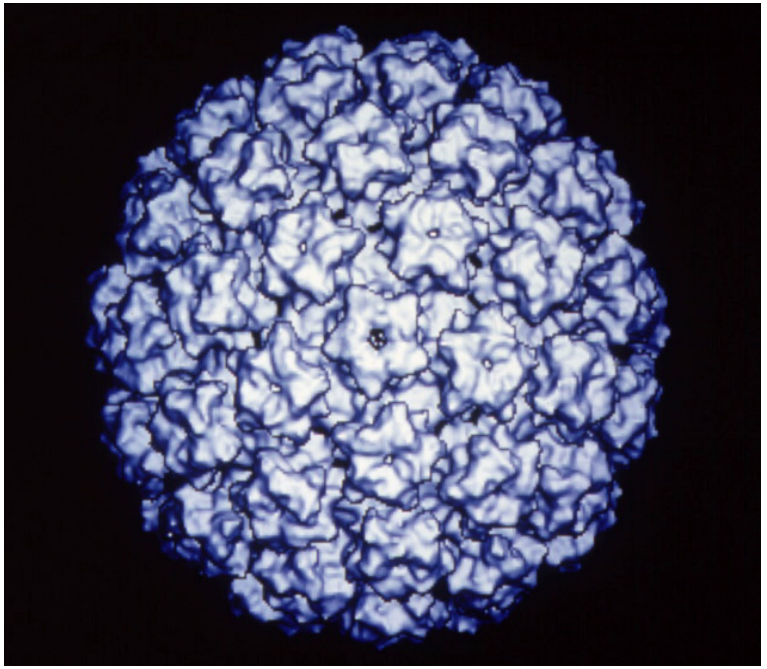
- **HPV: a small DNA virus**
- **Infects deeper layers of the skin and internal lining**
  - (e.g., vagina and mouth)
- **Genital infection: > 40 types**
- **Infections normally resolve spontaneously**
  - 90% within 2 years
- **Persistent HPV infection causes the cell changes**

HPV Risk Factors

- Young age
- Lifetime number of sexual partners
- Early age of first sexual intercourse
- Male partner sexual behavior
- Smoking
- OCP use
- Uncircumcised male partners

HPV transmission

- **Direct physical contact**
- **Any genital contact**
  - not just sexual intercourse
- **Sexually active individuals**
- **No. of sexual partners**



Computerized image of the human papillomavirus

Courtesy of Dept of Pathology, University of Cambridge

Epidemiology of genital HPV infection

- **HPV infection is common**
  - at least **half** of all sexually active women will be infected by a strain of genital HPV strain in their lifetimes
- **Genital HPV infection increases from age 14**
- **Most infection in late teens and early twenties**

Effects of HPV infection

- The HPV virus infects cells and then integrates its DNA into the DNA of the host cell
- Persistent infection leads to cell change
- Eventually cancer occurs after many years
- HPV infections can’t be treated
- Abnormal changes can be detected by screening

HPV infection in the cervix

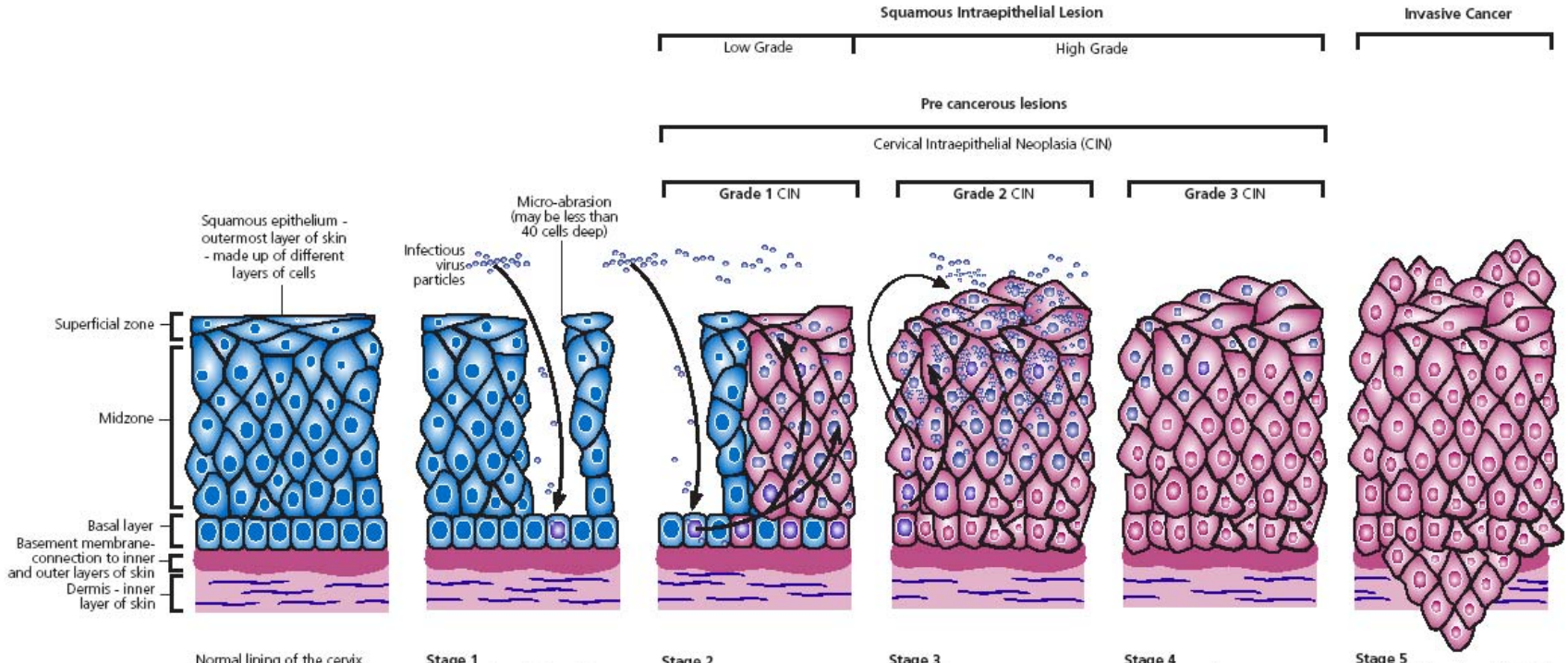
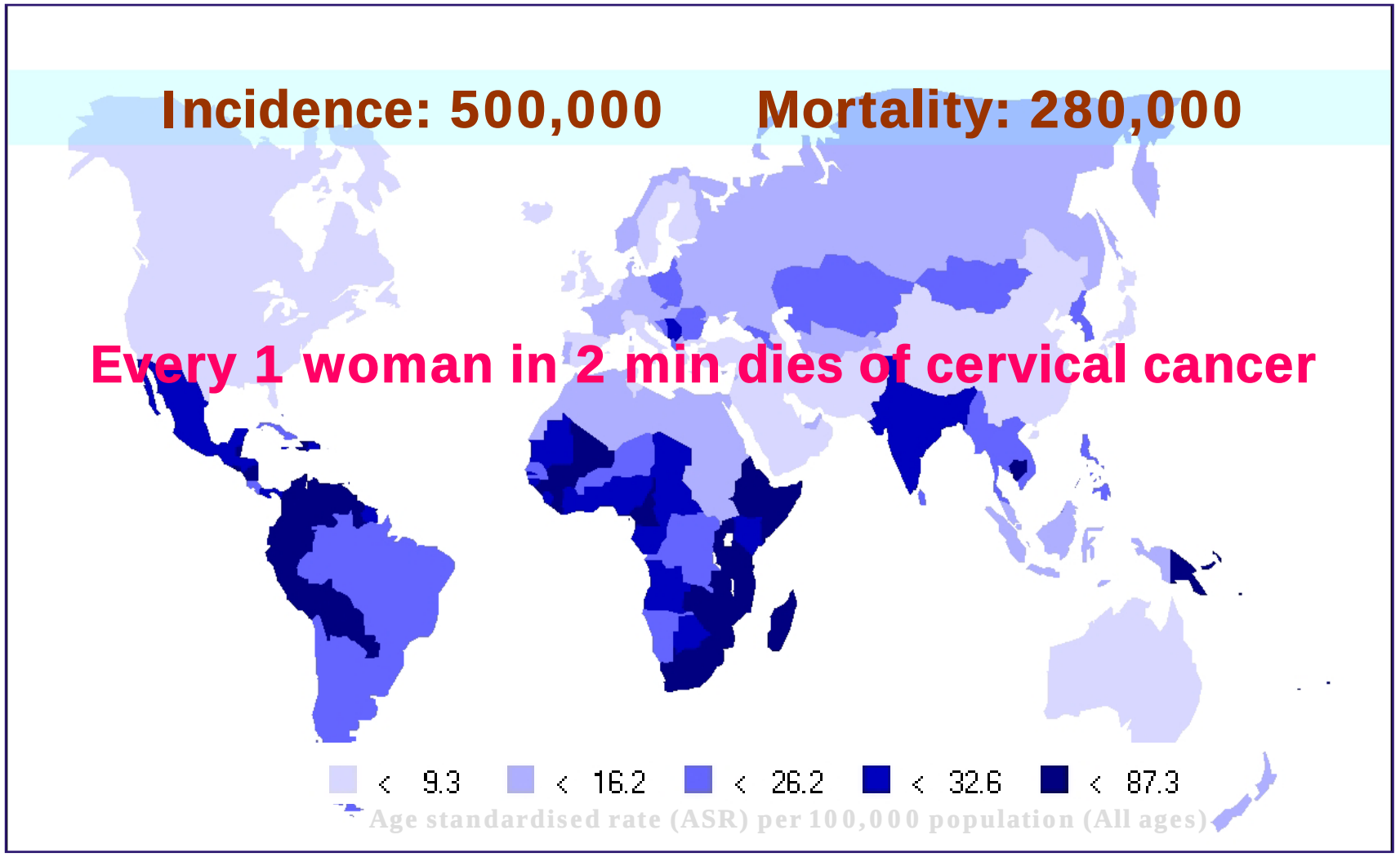


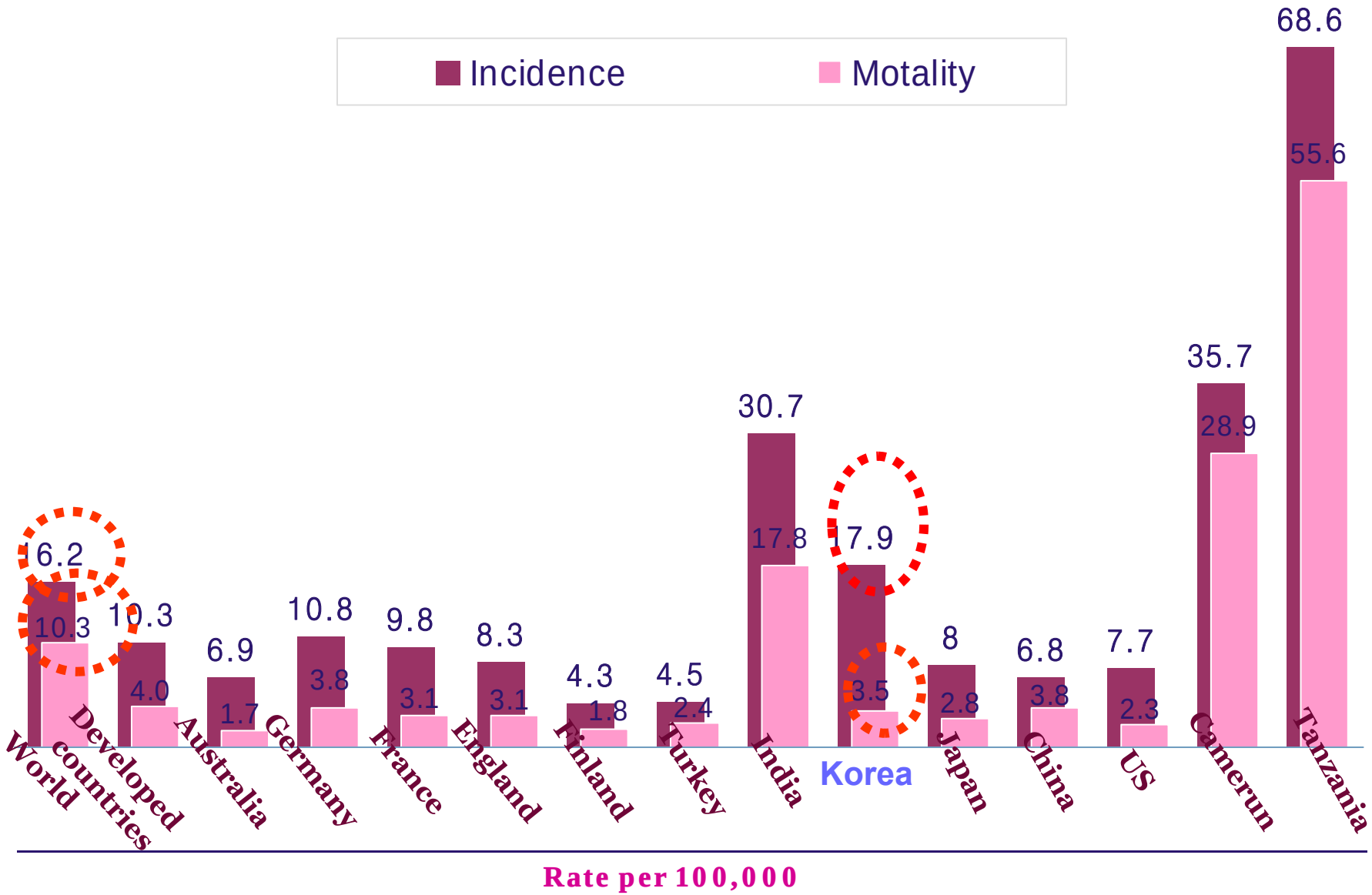
Figure 1 How the human papillomavirus infects the skin of the cervix and produces a cancerous growth.

Burden of Cervical Cancer

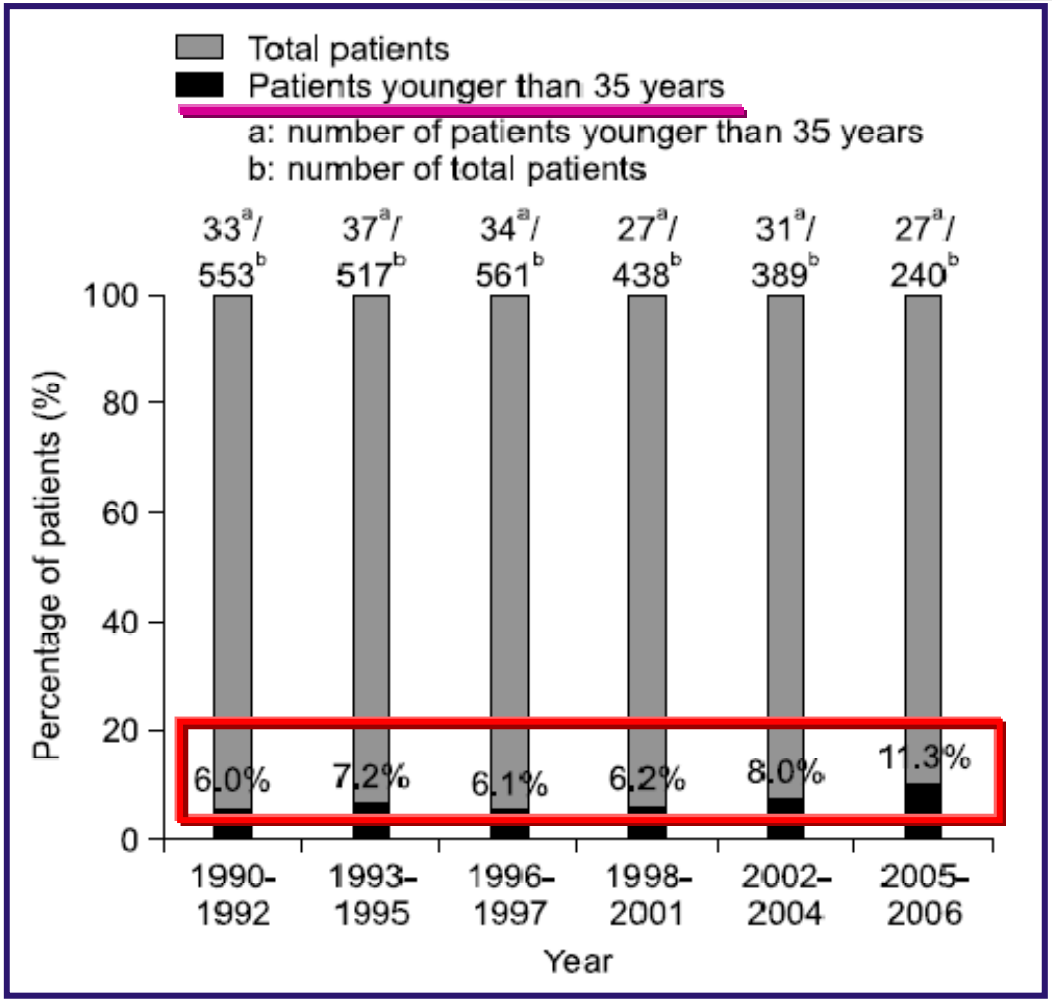


Globocan, WHO 2006 report

Incidence & mortality (2002)



Cervical cancer in young adults (< 35y)



Increasing proportion of patients younger than 35 years old with cervical cancer (p=0.033).

Study period: 1990-2006

2,698 Cervical cancer patients

- **Increasing incidence**
- **More aggressive form**
- **HPV infection: 94.0%**

CH Han, et al. Caner Res Treat 2008; 40(1): 1-5

Conditions caused by HPV

Percentage of cancers caused by HPV

Cancer site	Percentage of cervical cancer cases caused by HPV
Cervix	> 99%
Penis	40%
Vulva & vagina	40%
Anus	90%
Mouth	3%
Oropharynx	12%

Courtesy of Margaret Stanley, Univ of Cambridge

Current approaches to preventing HPV infection

- **Condoms reduce the risk of acquiring HPV**
  - Transmission by contact of areas not covered by condoms
- **Cervical screening does not prevent HPV infection**
- **Cervical screening remains important as:**
  - Vaccination will take several years to reduce cancer
  - Vaccination does not protect against all HPV types
  - Unvaccinated women will not be protected

HPV Vaccination

Composition of *Cervarix™* and *Gardasil®*

Cervarix™

Antigens

HPV 16 VLPs HPV 18 VLPs

+

AS04 adjuvant

Aluminium salt ($Al(OH)_3$) + **MPL** Immunostimulant

AS04-containing vaccine

Gardasil®

Antigens

HPV 16 VLPs HPV 18 VLPs HPV 6 VLPs HPV 11 VLPs

+

Adjuvant

Aluminium salt (amorphous aluminium hydroxyphosphate sulphate [AAHS])

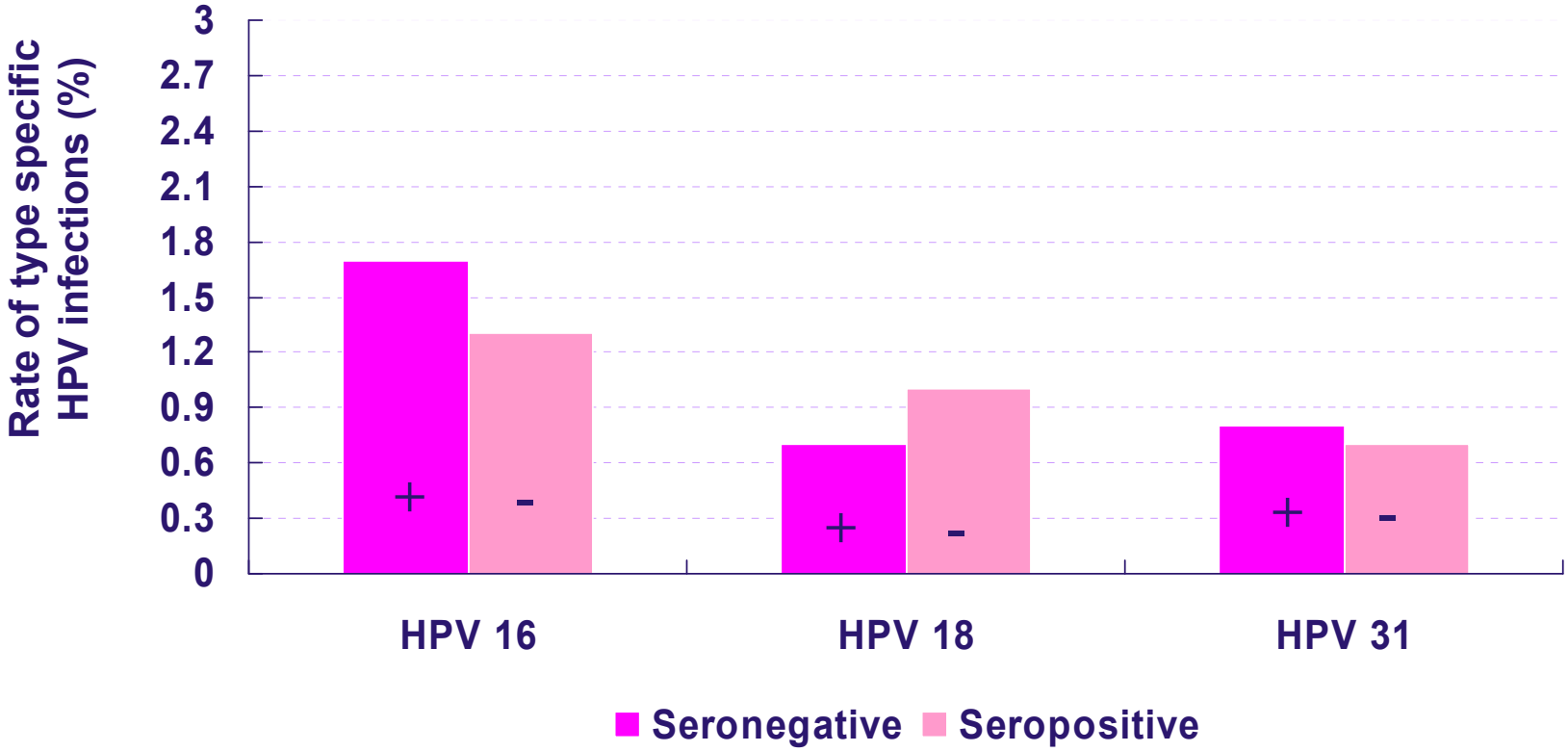
AAHS-containing vaccine

Limitation of immunity after natural infection

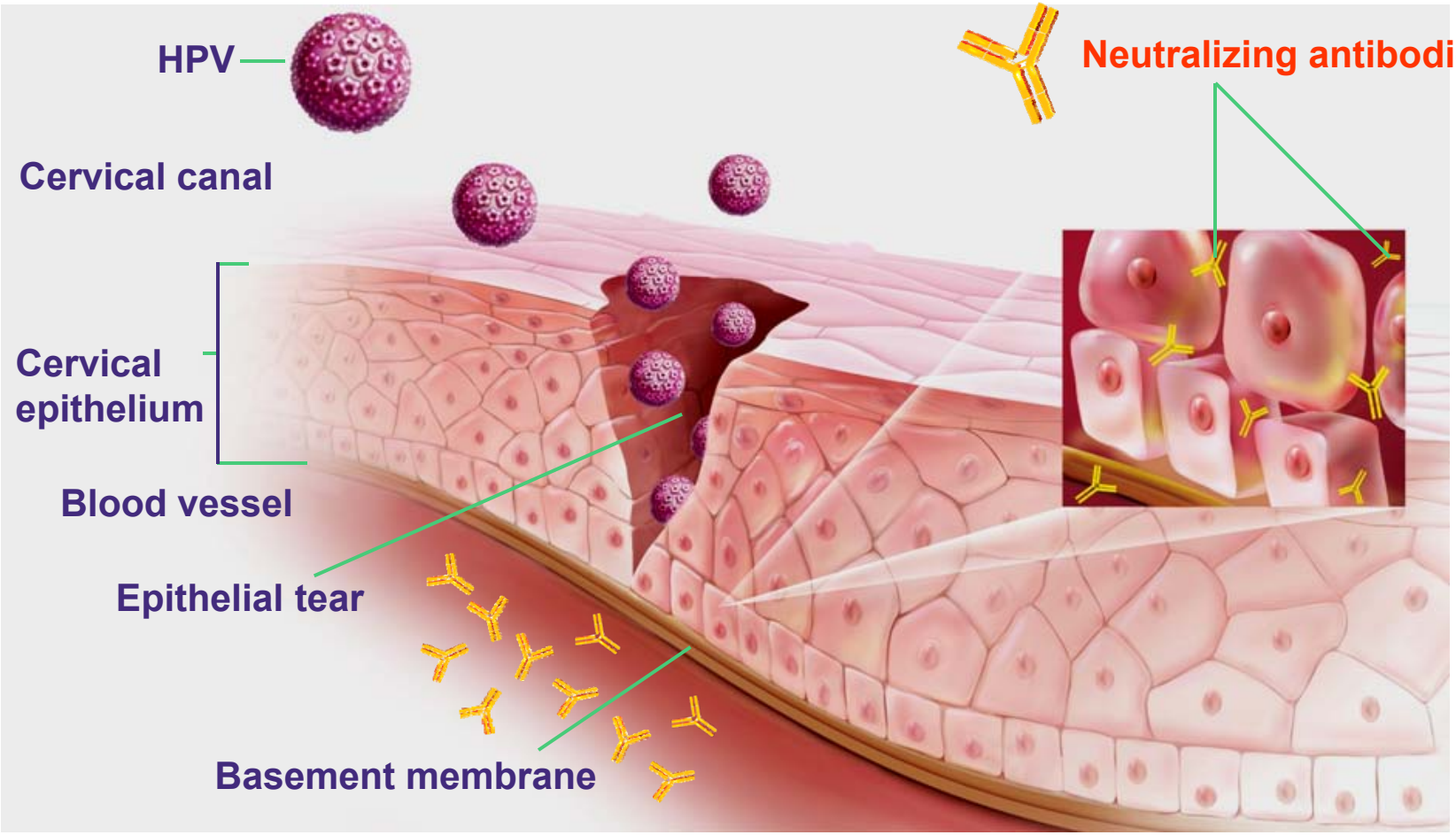
- **Late** formation of Ab after natural HPV infection
- Ab formation rate: **< 50%** in natural infection[7,9,10]
- **Low** Ab titer after natural infection
- Cannot prevent re-infection of HPV[1,9,10]
- Cell-mediated immunity: proposed mechanism of HPV clearance in natural infection HPV[1-7]

1. Stanley M. Vaccine 2006; 24: S16-22, 2. Bontkes HJ et al. Int J Cancer 2000; 88, 92, 3. Scott M et al. Clin Diagn Lab Immunol 2001; 8, 209, 4. Passmore J-AS et al., Immunology 2006; 119, 507, 5. Passmore J-AS et al. J Med Virol 2002; 67, 234, 6. Shepherd PS. J Gen Virol 1996; 77, 593, 7. Stanley M. HPV Today 2007; 11, 1-16, 8. Carter J. et al. J Infect Dis. 2000; 181:1911-19, 9. Viscidi R et al. Cancer Epidemiol Biomarkers Prev 2004; 13: 324-27, 10. Ho et al. Cancer Epidemiol Biomarkers Prev 2004; 13, 110.

Repeat HPV type-specific natural infections occur equally in women after 5-7 years FU regardless serostatus



Neutralizing Antibody



1.Stanley M. *Vaccine* 2006; **24:**S16–S22; 2. Giannini S, *et al. Vaccine* 2006; **24:**5937–5949; 3. Nardelli-Haefliger D, *et al. J Natl Cancer Inst* 2003; **95:**11281137; 4. Poncelet S, *et al.* IPC 2007(poster).

HPV vaccination

- Sexually active women may still remain susceptible to HR-HPV infection and might benefit from vaccination
- The vaccine cannot protect against HPV-related disease with an active HPV infection
- The vaccine may protect a woman who has already been exposed to HPV infections
- Vaccination will not harm a girl who has been infected with HPV previously

Vaccine strategy

- Importance of HPV 16/18 (>70% of cervix cancer)

Targeting vaccine

- Weak immune reaction after natural infection

Strong vaccine

- Life-long risk of HPV infection after sexual debut

Long-acting vaccine

1. Bosch et al. J Natl Cancer Inst Monogr 2003; 3.
2. Stanley et al. Vaccine 2006; 24 Suppl 1, S16.
3. Baseman et al. J Clin Virol 2005; 32 Suppl 1, S16.

Vaccine effectiveness

- Vaccination has been shown to be **99%** effective in preventing CIN caused by HPV types 16 and 18

- **Cross-protective** effect against other HR-HPV types

FUTURE TRIAL
Vaccine Efficacy

End Point	Vaccine n	Vaccine Cases	Placebo n	Placebo Cases	Efficacy (%)	CI
HPV 16/18: CIN 2/3 or AIS	5,305	1	5,260	42	98	(86–100)
HPV 6/11/16/18: VIN 2/3 or VAIN 2/3	2,261	0	2,279	9	100	(49–100)

N Engl J Med 356; 19 (2007) 1915-1925

N Engl J Med 356; 19 (2007) 1928-1942

FUTURE TRIAL
Vaccine Efficacy

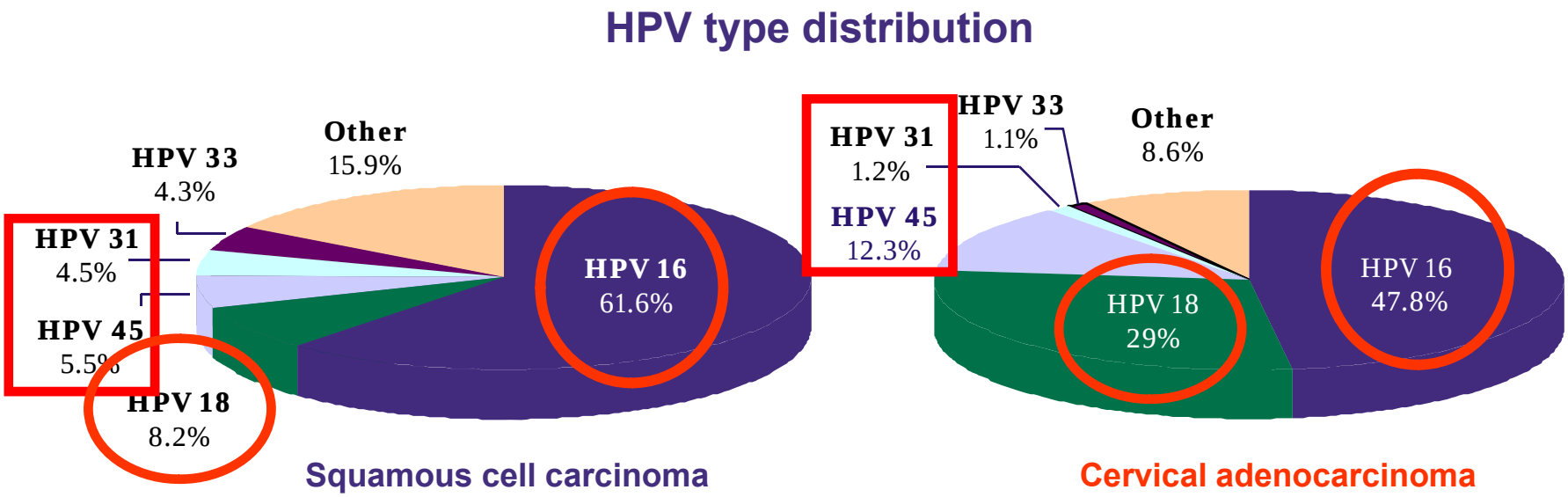
End Point	Vaccine n	Vaccine Cases	Placebo n	Placebo Cases	Efficacy (%)	CI
HPV 6/11/16/18: CIN 1	2,241	0	2,258	65	100	(94–100)
HPV 6/11/16/18: Condy, VIN 1, VAIN 1	2,261	0	2,279	57	100	(94-100)

N Engl J Med 356; 19 (2007) 1915-1925

N Engl J Med 356; 19 (2007) 1928-1942

HPV type distribution in cervical cancer

- The most common HPV types in all cervical cancers
  - **HPV 16, 18, 45 and 31**[1]
- **HPV 16 and 18**: >70% of cervical cancer cases[1,2]
- **HPV 16, 18, 45 and 31**: >90% of cervical adenoca cases[2,3]



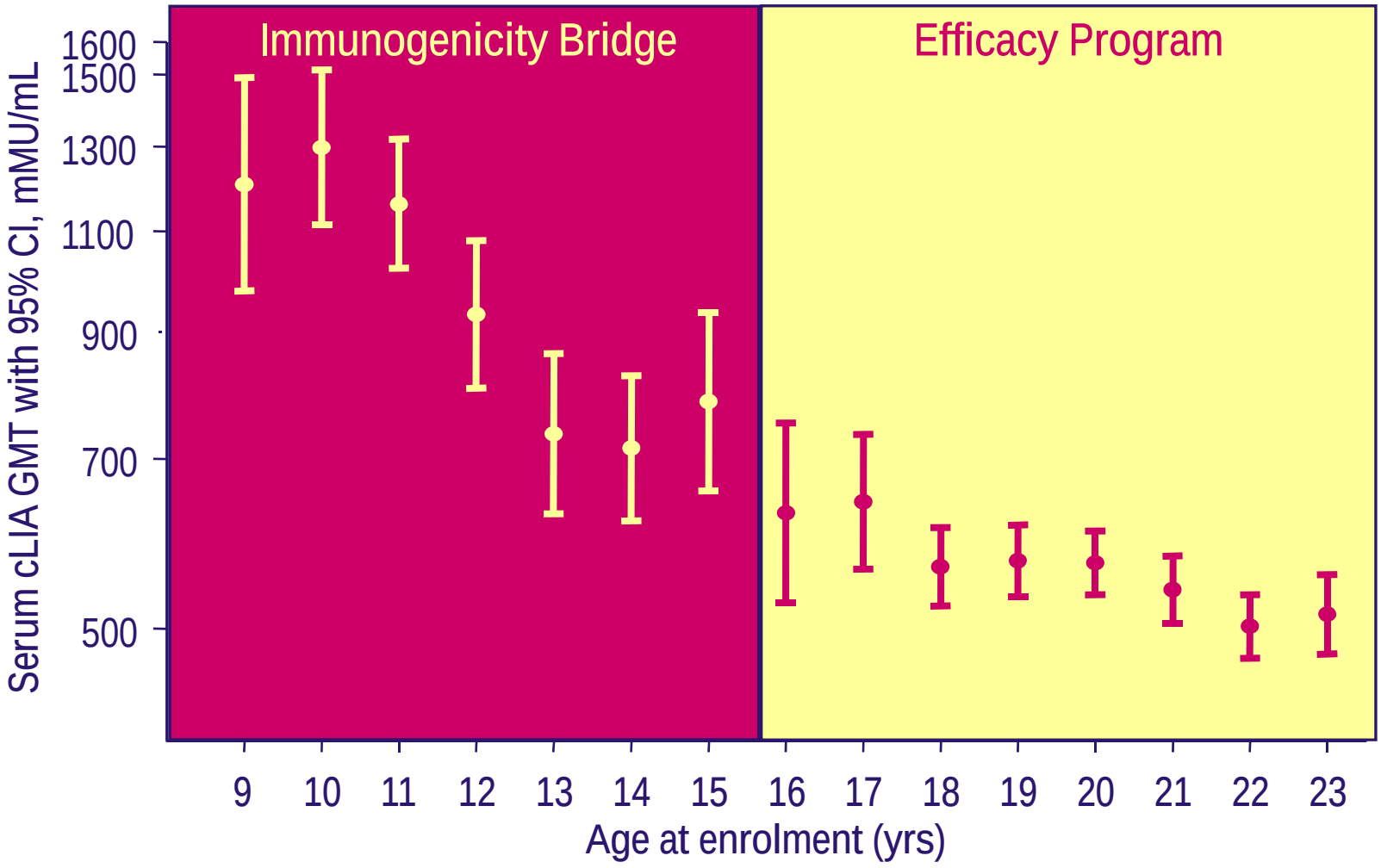
1. Munoz N, et al. Int J Cancer. 2004; 111:278–285.
2. Bosch FX *et al. Vaccine.* 2008; 26S:K1–K16.
3. Smith JS, *et al. Int J Cancer.* 2007; 121:621–632.

Duration of immunity

- The immune response to HPV vaccination lasts at least six years

- Ab levels have been shown to be higher from vaccination than from natural infection after 5 years

Immune response in adolescents even better than in adults (100% efficacy)



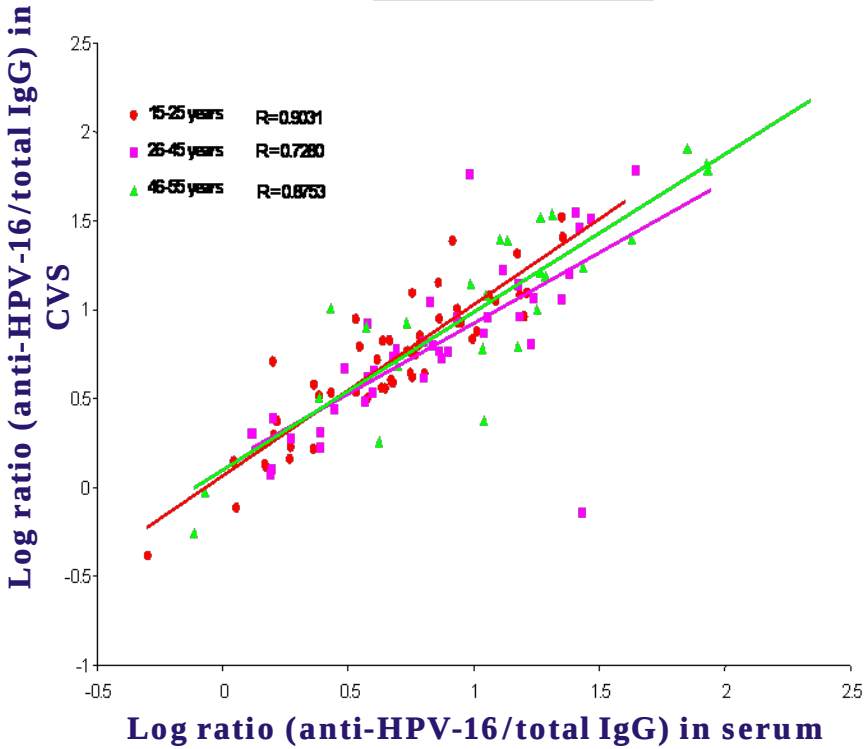
Correlation between Serum & CVS Ab titers

HPV-014 (women 15-55 yrs)

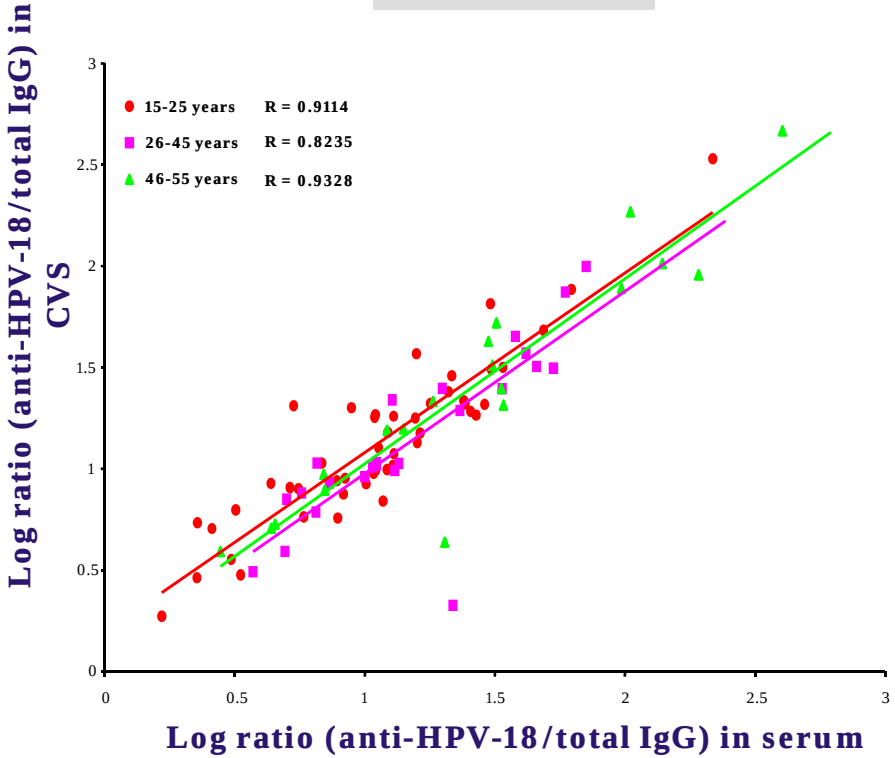
(ELISA)

Month 24

Anti-HPV-16



Anti-HPV-18



High serum Ab titer: High CVS Ab titer

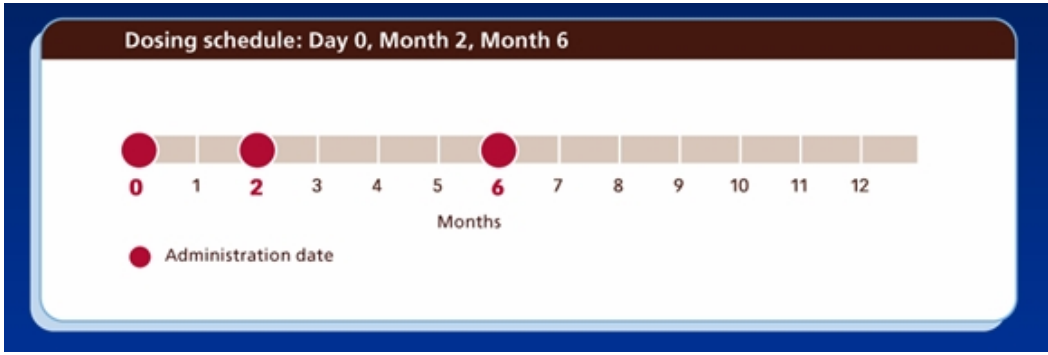
Poncelet et al. 24th International Papillomavirus Conference and Clinical Workshop 2007; PS19-25.Stanley et al. Vaccine 2006; 24 Suppl 3, S106. Giannini et al. Vaccine 2006; 24, 5937.

Potential benefits of vaccination

- **Better to prevent CIN than to treat it**
  - Reduce No. of women receiving additional cytology & colposcopy
  - Reduce the cost of treatment associated with screening program
  - Reduce the anxiety and discomfort during treatment of abnormal lesions

KSGOC Recommendation: Gardasil

- Quadrivalent HPV vaccine (HPV 6, 11, 16, 18)
- Prophylaxis for
  - Cervical cancer
  - Condyloma
  - AIS, CIN, VIN, VaIN
- 3-time vaccination (0, 2, 6m)
- Age
  - Range: 9-26 years (women)
  - Best: 15-17 years
  - Catch-up: 18-26 years
- Screening should be continued irrespective of HPV vaccination



KSGOC Recommendation: Cervarix

- **Bivalent HPV vaccine (HPV 6, 11)**
- **Prophylaxis for**
  - Cervical cancer
  - CIN
- **3-time vaccination (0, 1, 6m)**
- **Age**
  - Range: 10-25 years (women)
  - Best: 15-17 years
  - Catch-up: 18-25 years
  - Possible age: 26-55 years

Comparison table

	Gardasil™ Al(OH)3	Cervarix™ ASO4
Efficacy	Prevention of HPV 6/11/16/18 related cervical cancer	Prevention of HPV 16/18 related cervical cancer
	CIN 1,2,3	CIN 1,2,3
	Persistent infection	Persistent infection
	AIS	Abnormal cytology
	External genital lesions	
Schedule	0.5mL, 0, 2, 6M IM	0.5mL, 0, 1, 6M IM
Routine vaccination	Female, 9-26 yr	
	(optimal age 15-17 yr)	Female, 10-25 yr
	Male, 9-15 yr	(optimal age 15-17 yr)
	(prevention of genital warts)	
Catch-up vaccination	Female, 18-26 yr	Female, 18-25 yr
Vaccination of old-aged	-	Possible for 26-45 yr
Therapeutic effect	-	-
Effect of cross-protection		HPV 31, 45-related persistent infection
Cervical cancer screening	Same as cervical cancer screening program	

Vaccination in older group

Risk of infection still significant in sexually-active women aged > 26Y

Why women > 25 still be at risk?

- Limited immunological protection with risk for re-infection
  - Oncogenic HPV down-regulation
  - Prior infection: not induce immunity
- Reactivation of latent infection
  - Gradual loss of type-specific natural immunity
- Woman's sexual behavior
  - Divorce, partner change etc.
- Sexual behavior of male sexual partner

Do Exposed Women Benefit from the Vaccine?

Women with prior HPV infection

HPV vaccines have no therapeutic effect

- No evidence of hazardous effects of vaccine
- Vaccine may decrease the risk of auto-inoculation or transmission
- Further analysis warranted

Male HPV vaccination

Men & women both share the responsibility

- **Non-cervical HPV-related cancers**
  - Skin, oral pharynx, esophagus, anus, penis
- **Modeling study**
  - Relatively small effect on cervical cancer incidence

Current problems of vaccination

- No protection against 30% of cervical cancer
- Duration of efficacy
- Single-dose, heat-stable, needle-free formula
- Optimum age of vaccination
- Effects of vaccine on public health
  - Cost effectiveness
  - Ethical concern

HPV Vaccine Controversy

- **Should it be mandated?**
  - Undermines abstinence-based prevention messages
  - Intrusion on individual and parental rights
  - Conflict with religious or personal beliefs

N Engl J Med 355; 23 (2007) 2389-2391

Updated data from FIGO, 2009

- Analysis in a subset of women from 4 Phase III clinical trials(recruitment age: 10–56 years, N=350)
- Serum and CVS samples were collected at pre-specified time points ranging from 7 to 36 months after first vaccine dose

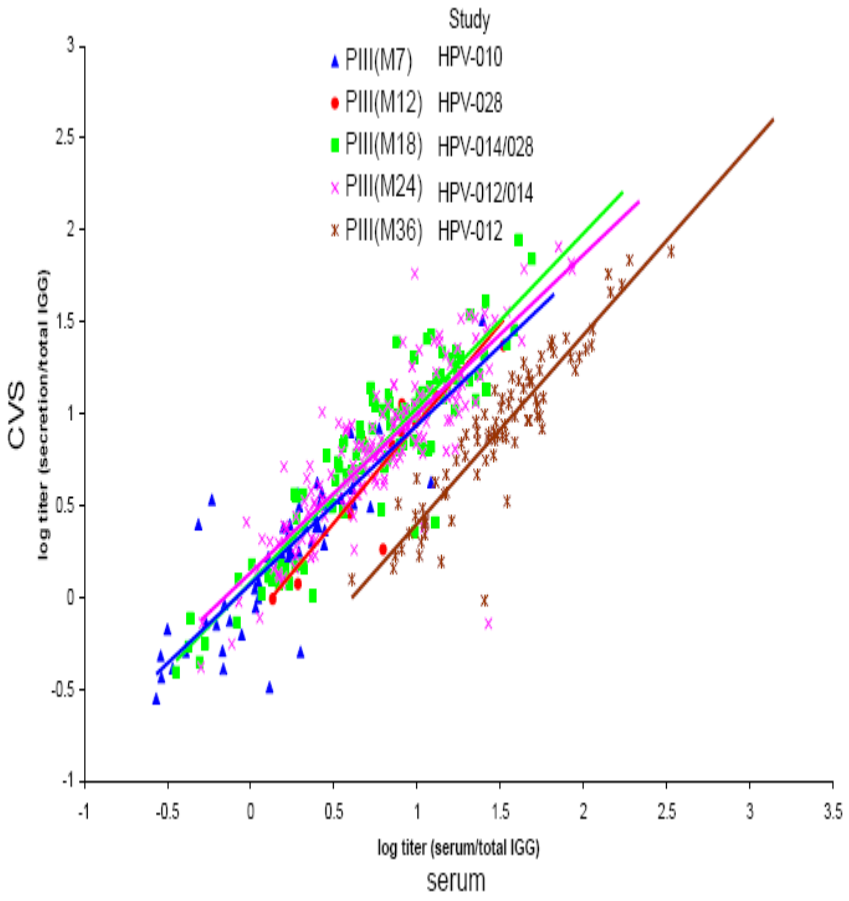
Sampling time (month)	Study	N
Month 7	**HPV-010 (NCT00423046)**	**65**
Month 12	**HPV-028 (NCT00456807)**	**12**
Month 18	**HPV-014 (NCT00196937), HPV-028**	**153**
Month 24	**HPV-012 (NCT00337818), HPV014**	**220**
Month 36	**HPV-012**	**108**

Courtesy from TF Schwarz.. TF Schwarz et al. presented at 26th FIGO, Capetown, Oct 4-9, 2009

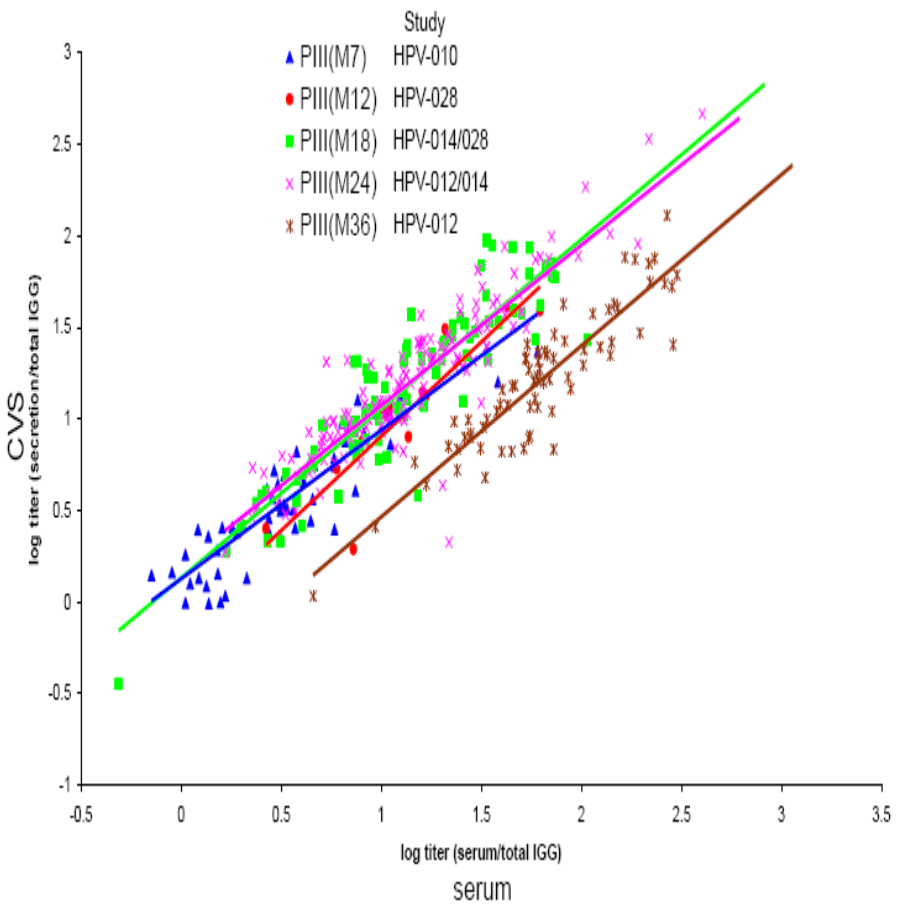
High correlation between CVS and serum for HPV-16/18 antibodies at different time points

Pearson correlation coefficients

0.73–0.93 for HPV-16



0.82–0.93 for HPV-18



Courtesy from TF Schwarz.. TF Schwarz et al. presented at 26th FIGO, Capetown, Oct 4-9, 2009

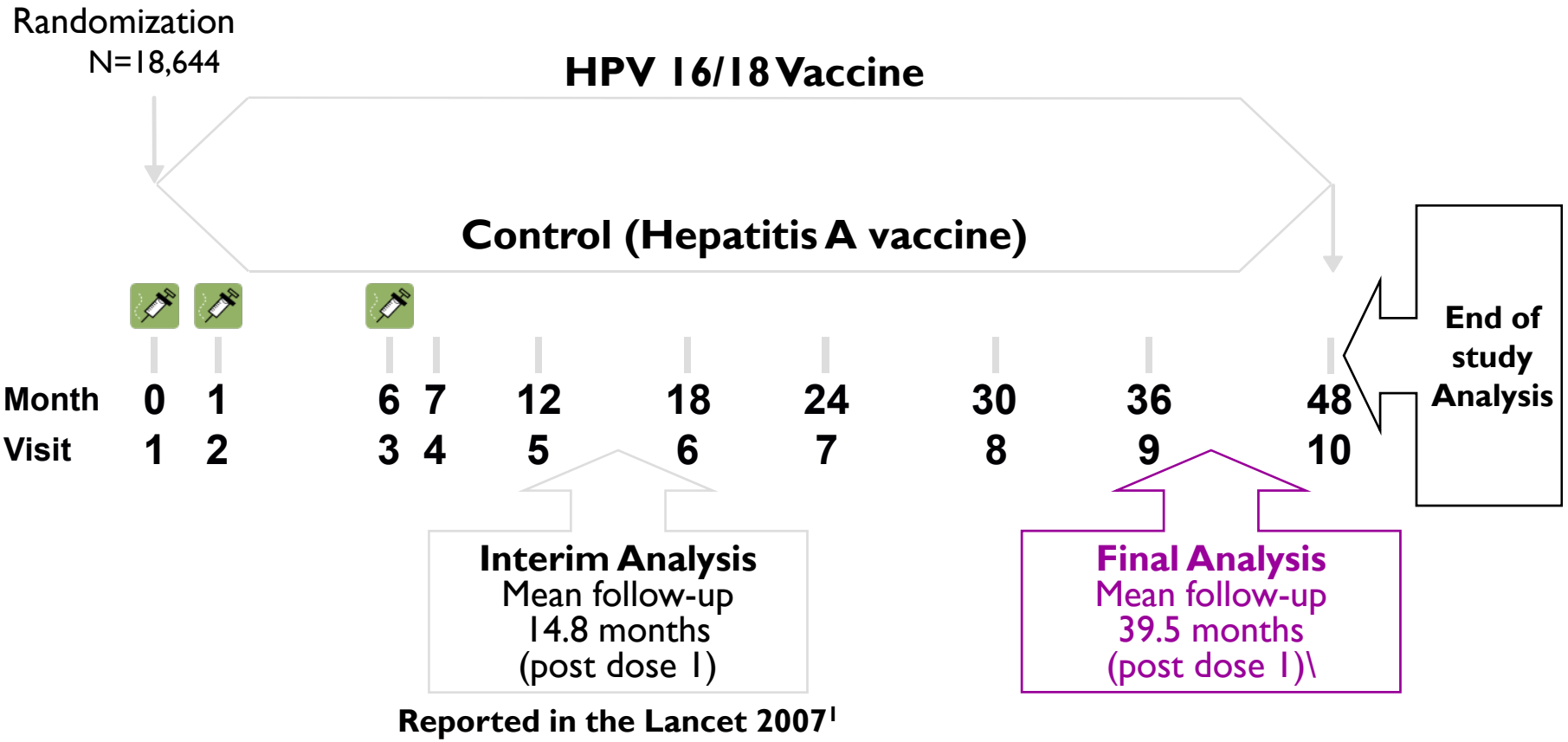
Antibody titers do not predict protection

- **The more antibody, the more efficacy? NO**
  - **Case 1) MMR vaccine (Triviraten, Berna, Switzerland):**
    - **The higher antibody than previous MMR vaccines → Outbreaks among vaccinees → withdrawal from market**
  - **Case 2) HSV vaccine:**
    - **No serological difference between males and females → Vaccine Efficacy was observed only in females**
- **The less antibody, the less efficacy? NO**
  - **Case 3) Guidelines for HBV vaccine has been changed:**
    - **Booster every 5 years → no booster**

No immune correlate of protection!

PATRICIA (HPV-008) Study Design

18,644 women enrolled (15–25 years)
Double-blind; randomized 1:1; *Cervarix*® vs control (Hep A vaccine)
Event triggered interim and final efficacy analyses



* 1. Paavonen J et al. Lancet 2007; 369: 2161-70 2. Paavonet J et al. Lancet 2009; 374 (9686): 301 - 314

Vaccine efficacy against ASCUS+, CIN1+ and CIN2+ associated with HPV-16/18 or irrespective of HPV type (TVC-naive)

Endpoint	HPV type	HPV (N= 5449) (n)	Control (N= 5436) (n)	VE % (96.1% CI)	p-value
ASCUS+	HPV-16/18	37	362	90.0 (85.8, 93.2)	< 0.0001
	Irrespective of HPV type	870	1098	22.2 (14.5, 29.2)	< 0.0001
CIN1+	HPV-16/18	3	85	96.5 (89.0, 99.4)	< 0.0001
	Irrespective of HPV type	106	211	50.1 (35.9, 61.4)	< 0.0001
CIN2+	HPV-16/18	1	63	98.4 (90.4, 100)	< 0.0001
	Irrespective of HPV type	33	110	70.2 (54.7, 80.9)	< 0.0001
CIN3+	HPV-16/18	0	13	100 (64.7, 100)	< 0.0001
	Irrespective of HPV type	3	23	87.0 (54.9, 97.7)	< 0.0001

Adaptef from 1. Paavonen J et al. Lancet 2009; 374(9686): 301-14

2. Tjalma W et al. 16th ESGO, Belgrade, Serbia, Oct 11-14, 2009.

Head to Head Trial (HPV-010)

Comparison of the immunogenicity and safety of *Cervarix*® and *MSD vaccine* in healthy women aged 18–45 years

MSD vaccine: licensed HPV 6,11, 16, 18 vaccine by MSD Korea

Method

- Phase: IIIb, observer-blind, randomized, multicenter
- Study Region: US
- Stratified by age (18–26, 27–35, 36–45 years) (N=1,106)
- Duration of study: 48m
- Vaccination schedule:

Month 0	Month 1	Month 2	Month 6
Cervarix®	*Cervarix®*	Placebo ($Al(OH)_3$)	*Cervarix®*
MSD Vaccine	Placebo ($Al(OH)_3$)	*MSD Vaccine*	*MSD Vaccine*

MSD vaccine: licensed HPV 6,11, 16, 18 vaccine by MSD Korea

Results

- Similar efficacy

- Excellent rate of vaccination completion (≥84% of subjects received all three doses)

1. Einstein MH, on behalf of the HPV-010 study group. Human vaccine 2009; 5(10): 705-19

2. Einstein MH, et al. Presented at 16th ESGO, Oct 11-14, 2009.

WHO Guideline (April, 2009)

Since the immunological correlates of vaccine protection are unknown, CIN2/3 or AIS needs to be used as clinical end-points to prove vaccine efficacy.

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

10 APRIL 2009, 84th YEAR / 10 AVRIL 2009, 84e ANNÉE
No. 15, 2009, 84, 117–132
http://www.who.int/wer

Clinical efficacy and duration of protection

Since the immunological correlates of vaccine protection are unknown and the development of cervical cancer may occur decades after HPV infection, regulatory authorities have accepted the use of CIN grade 2 or 3 (CIN2–3) and AIS as clinical end-points in vaccine efficacy trials instead of invasive cervical cancer.[11] Also,

Considerations for public health

- Country's disease burden
- Health care infrastructure
- Capacity for immunization program
- Cost-effectiveness
- Cultural acceptability
- Public support

Summary

- HPV infection is highly prevalent
- Certain HPV-related lesions can be prevented
- Vaccinate before the onset of sexual activity
- Long-term F/U will address unanswered questions


"What's Up? South!" World Map
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ARCTIC OCEAN
AUSTRALIA
INDONESIA
CHINA
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RUSSIA
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ALGERIA
TUNISIA
SUDAN
ETHIOPIA
NIGERIA
CHAD
NIGER
MALI
MAURITANIA
SOUTH AFRICA
NAMIBIA
ZAMBIA
ANGOLA
TANZANIA
KENYA
MADAGASCAR
BRAZIL
ARGENTINA
CHILE
PERU
BOLIVIA
VENEZUELA
COLOMBIA
MEXICO
UNITED STATES
CANADA
GREENLAND
NORWAY
SWEDEN
FINLAND
POLAND
BELARUS
UKRAINE
FRANCE
SPAIN
PORTUGAL
GERMANY
ITALY
GREECE
JAPAN
PHILIPPINES
VIETNAM
THAILAND
MALAYSIA
PAPUA NEW GUINEA
NEW ZEALAND
SAID "NORTH" WAS "UP"?
WHAT'S UP? SOUTH! WORLD


Thank you!