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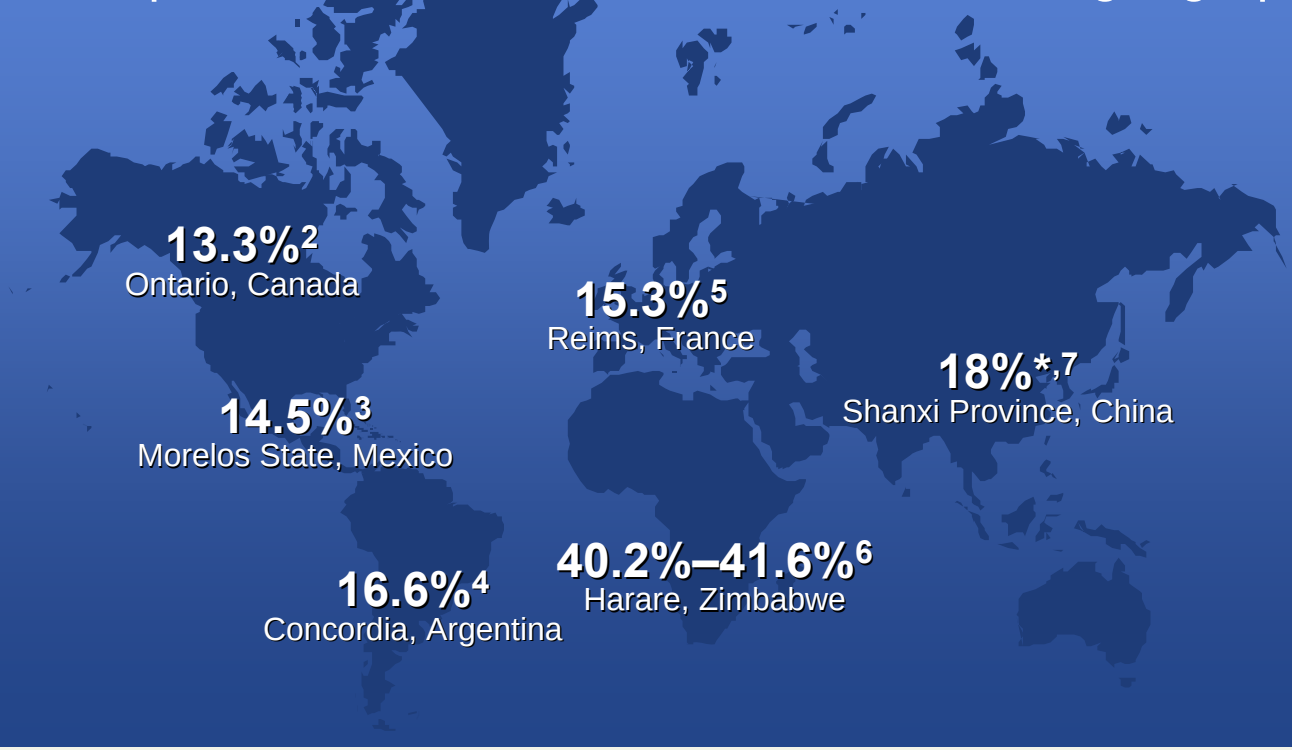
Vaccines for Viral Infections in Developing Countries

Human Papillomavirus Vaccination for Cervical Cancer Prevention

Focus on Asia

Global HPV Statistics

- Worldwide prevalence of HPV infection is estimated to be between 9% and 13%: ~630 million infected individuals.[1]
- Estimated prevalence of HPV infection in selected geographic areas:



*Among women 30–45 years of age

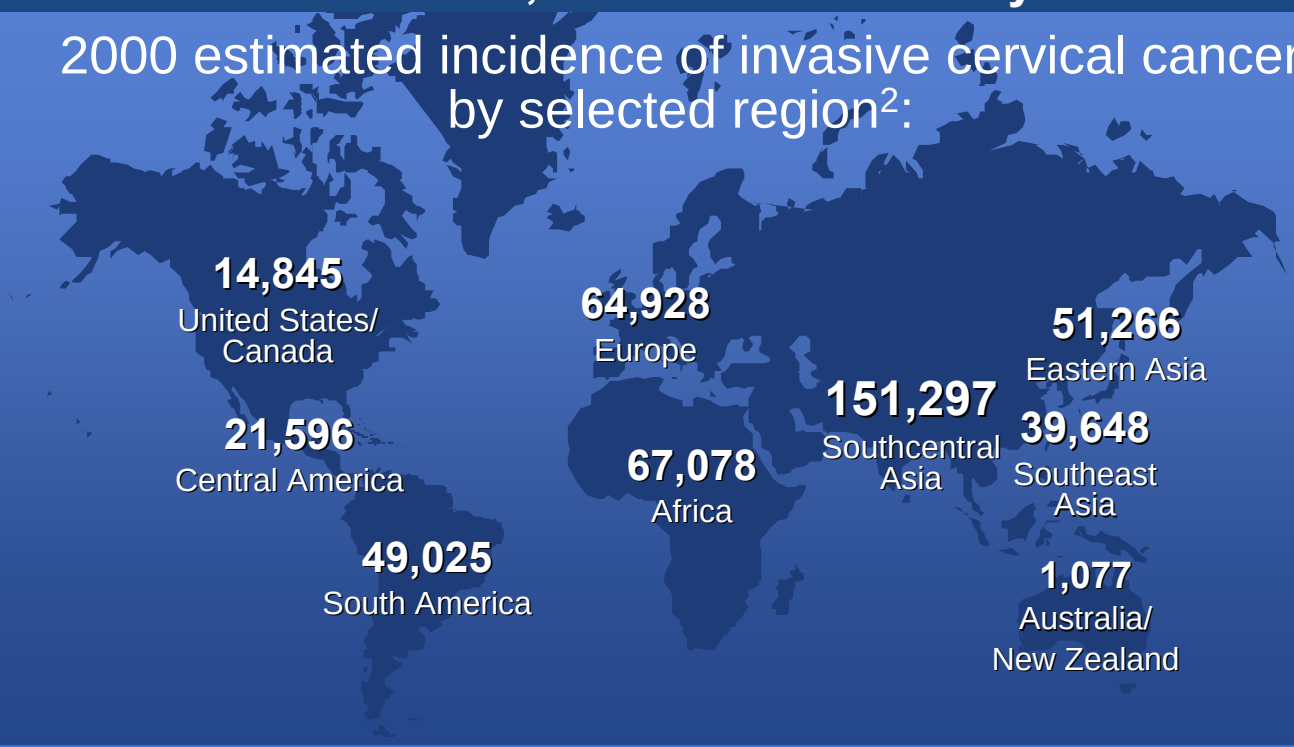
1. World Health Organization; 2001. Available at: http://www.who.int/vaccines/en/hpvrd/shtml. Accessed July 12, 2004.
2. Sellors JW, Mahony JB, Kaczorowski J, et al. *CMAJ*. 2000;163:503–508. **3.** Lazcano-Ponce E, Herrero R, Muñoz N, et al. *Int J Cancer*. 2001;91:412–420. **4.** Matos E, Loria D, Amestoy GM, et al. *Sex Transm Dis*. 2003;30:593–599. **5.** Clavel C, Masure M, Bory JP, et al. *Br J Cancer*. 2001;84:1616–1623. **6.** Blumenthal PD, Gaffikin L, Chirenje ZM, McGrath J, Womack S, Shah K. *Int J Gynecol Obstet*. 2001;72:47–53. **7.** Belinson J, Qiao YL, Pretorius R, et al. *Gynecol Oncol*. 2001;83:439–444.

slide courtesy of Merck & Co., Inc.

Cervical Cancer: Worldwide Prevalence, Incidence, and Mortality Estimates

Prevalence: 2,274,000 women have cervical cancer[1]
Incidence: 510,000 new cases each year[1]

2000 estimated incidence of invasive cervical cancer by selected region[2]:

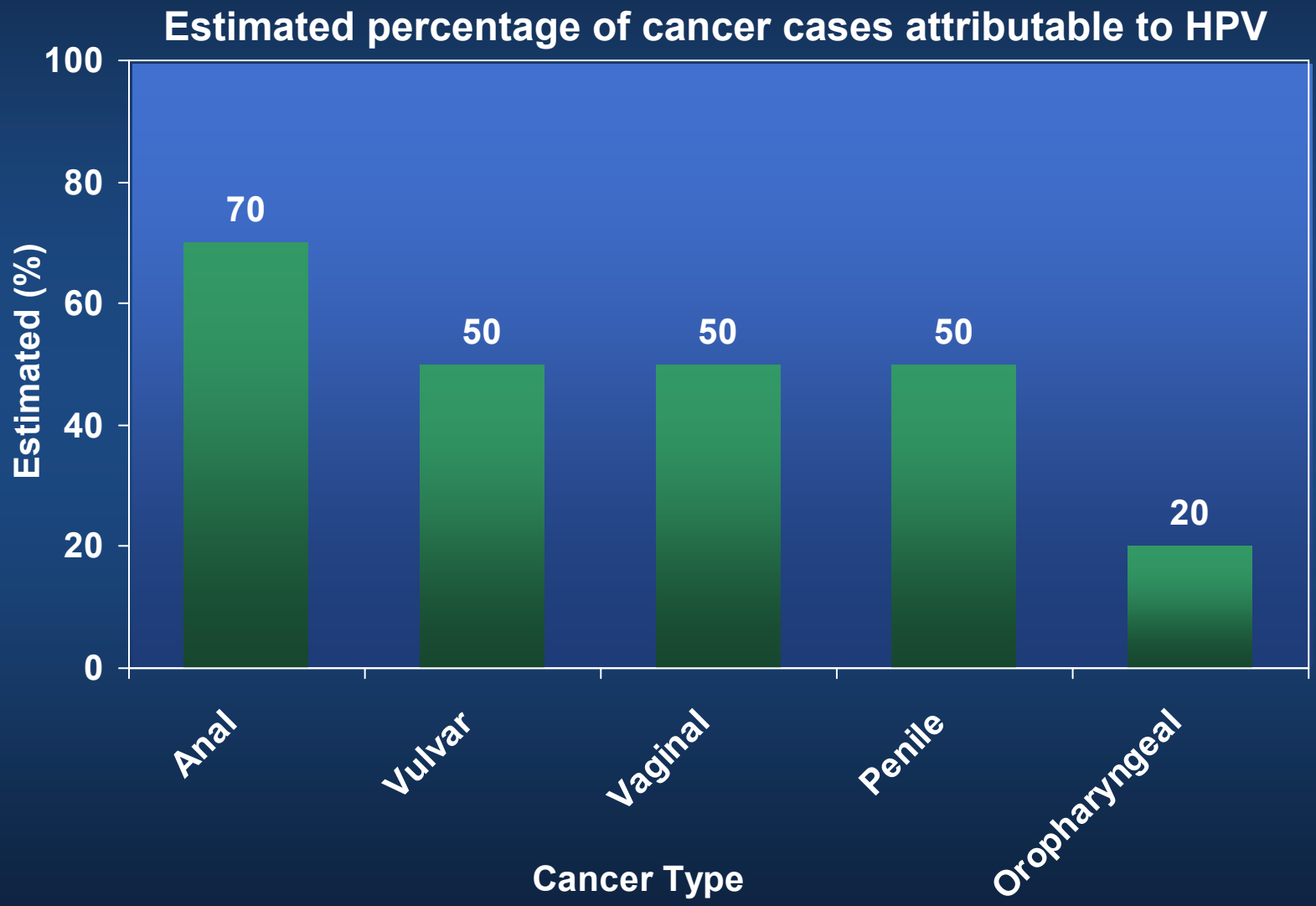


Mortality: Second leading cause of female cancer-related deaths (288,000 annually)[1]

1. World Health Organization. Geneva, Switzerland: World Health Organization; 2003:1–74. **2.** Bosch FX, de Sanjosé S. *J Natl Cancer Inst Monogr.* 2003;31:3–13.

slide courtesy of Merck & Co., Inc.

Cancer Types Attributable to HPV Other Than Cervical Cancer[1]



1. González Intxaurraga MA, Stankovic R, Sorli R, Trevisan G. *Acta Dermatovenerol*. 2002;11:1–8.

slide courtesy of Merck & Co., Inc.

HPV prevalence and cervical cancer incidence by age

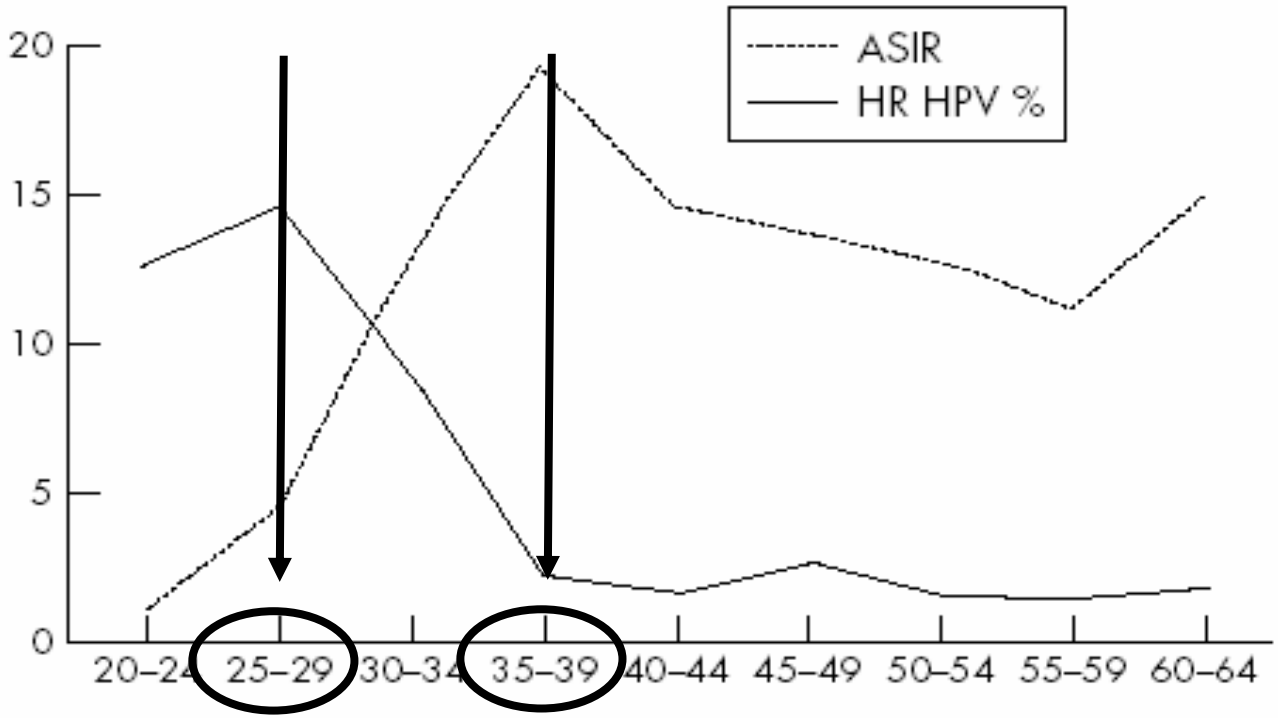


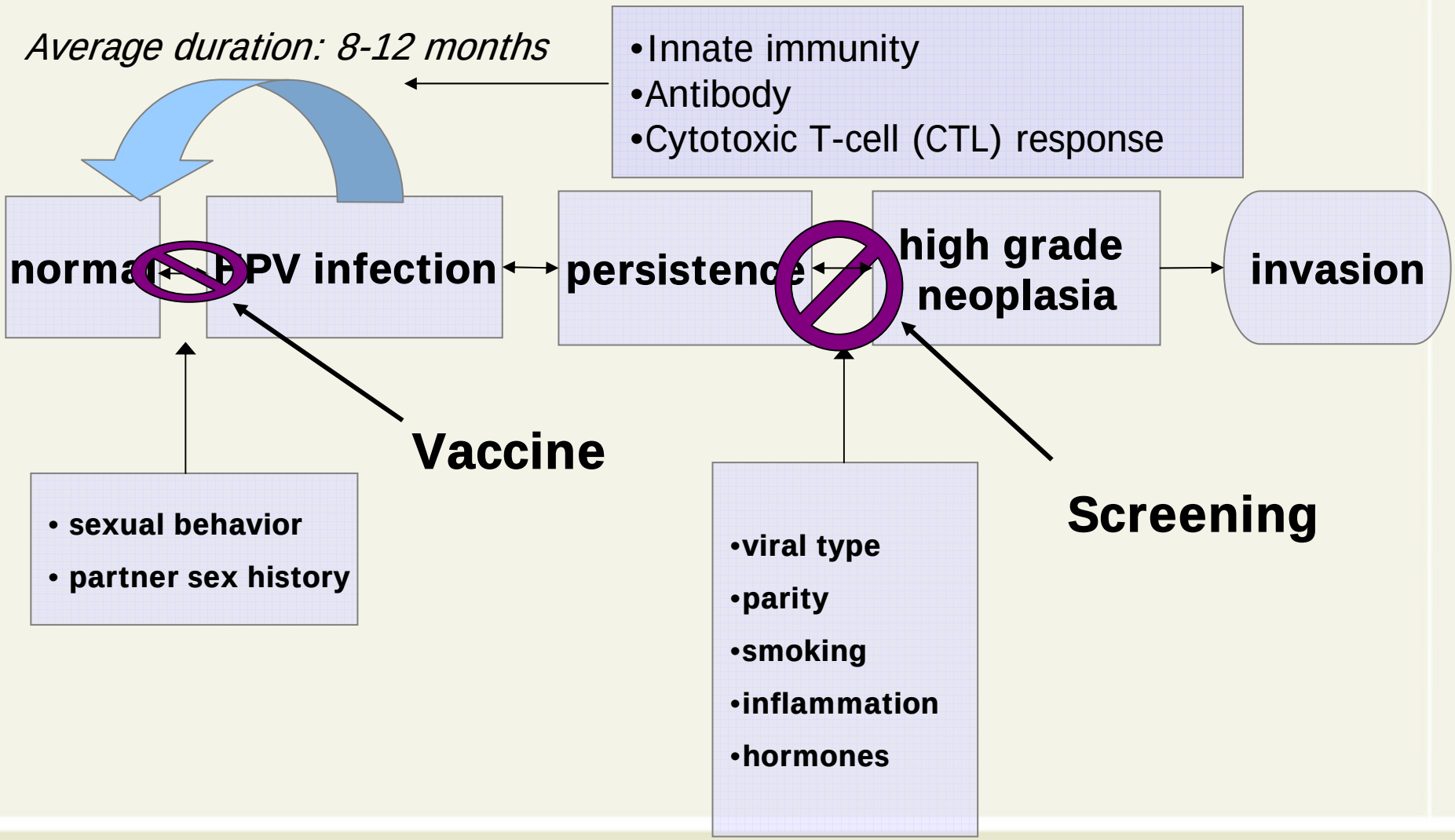
Figure 9 Age specific prevalence (%) of high rish (HR) human papillomavirus (HPV) DNA in 3700 women entering a screening programme and age specific incidence rate (x10^5) (ASIR) of cervical cancer in the Netherlands. Adapted from Jacobs *et al* and Parkin *et al*.[106 108]

Bosch FX et al. J Clin Path 2002;55:244

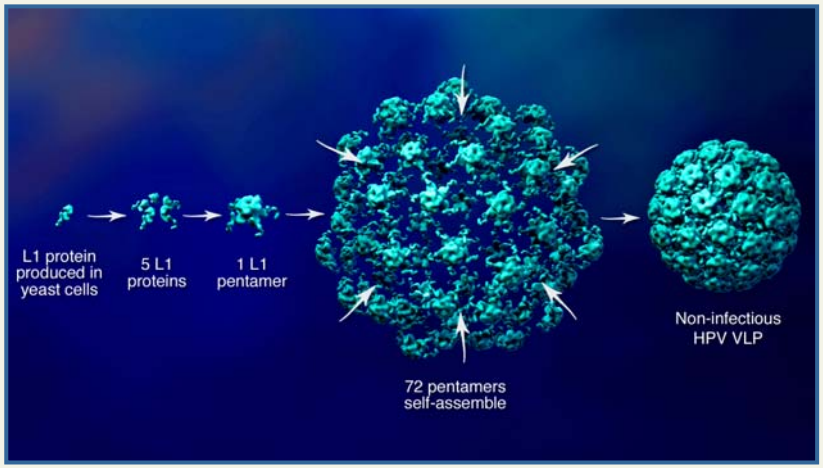
Slide 5

pp19 i think if you are thinking that the presentation is still too long, you can take this slide out and leave it as a reference)
proma paul , 4/20/2006

Natural history of cervical cancer



Virus-like Particle (VLP) vaccines



- HPV L1 expressed from a strong heterologous promoter will self-assemble into empty viral particles in yeast, insect, and bacterial cells
- Morphologically indistinguishable from native HPV virions; contains no DNA, therefore non-infectious; low risk
- Vaccine-induced antibodies specific to single HPV type
- Parenteral vaccination induces nearly 100% protection (up to 4.5 years so far).

HPV Phase III, Placebo-controlled Trials

	Merck (1)	Merck (2)	GSK (3)
Formulation	HPV 16 VLP	HPV 6/11/16/18 VLP	HPV 16/18 VLP
Adjuvant	alum	alum	AS04
Dose	40 μg	20/40/40/20 μg	20/20 μg
Schedule	0, 2, 6 months	0, 2, 6 months	0, 1, 6 months
Mean age	20 years	20 years	20.4 years
Follow-up	~17 mo.	~18 mo.	~30 mo.

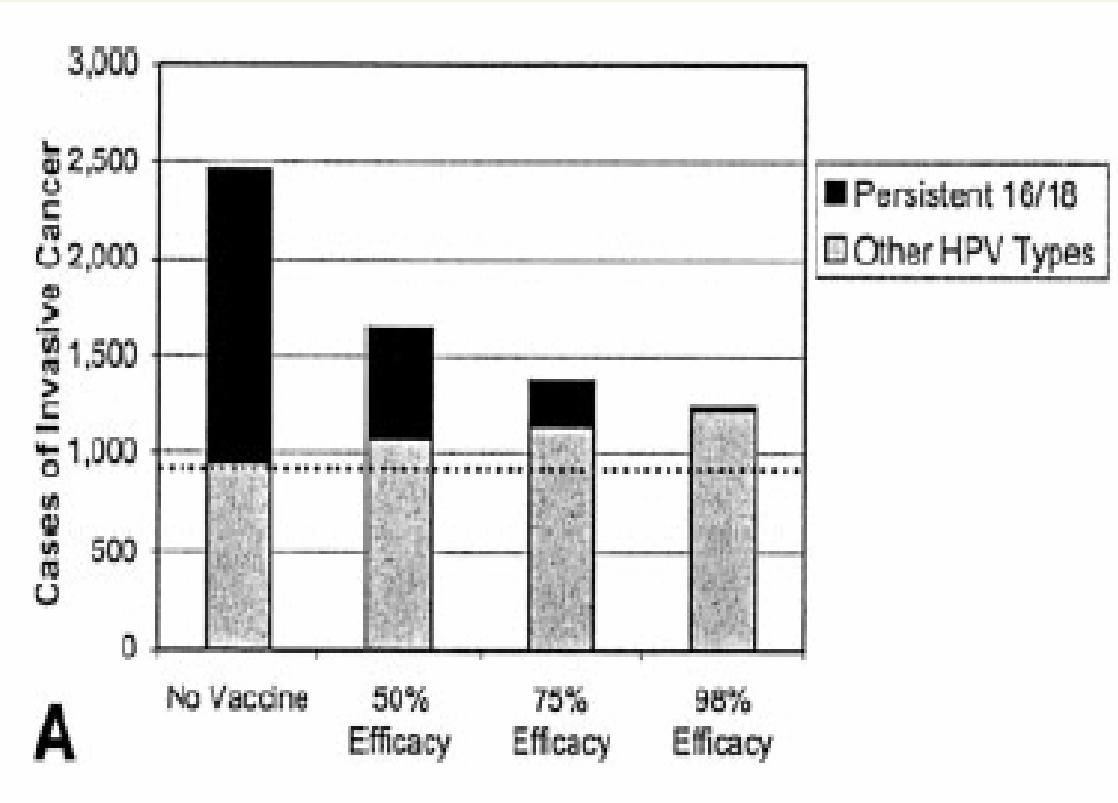
From (1) Koutsky LA *et al.* NEJM 2002;347:1645-51/(2) Villa LL, et al. Lancet Oncol 2005;6:271-78 /(3) Harper DM, et al. Lancet 2004;364:1757-65.

HPV Phase III, Placebo-controlled Trials Efficacy Data

	Merck (1)		Merck (2)		GSK	
	vaccine	placebo	vaccine	placebo	vaccine	placebo
Sample size	768	765	235	233	366	355
Persistent HPV 16	0	41	3	21	0	7
HPV 16 efficacy	100% (90-100%)		86% (54-97%)		100% (47-100%)	
Persistent HPV 18			1	9	0	0
HPV 18 efficacy			89% (21-100)		NC	
Persistent HPV 6			0	13		
HPV 6 efficacy			100% (68-100)			
Persistent HPV 11			0	3		
HPV 11 efficacy			NC			

From (1) Koutsky LA *et al.* NEJM 2002;347:1645-51/(2) Villa LL, et al. Lancet Oncol 2005;6:271-78 /(3) Harper DM, et al. Lancet 2004;364:1757-65.

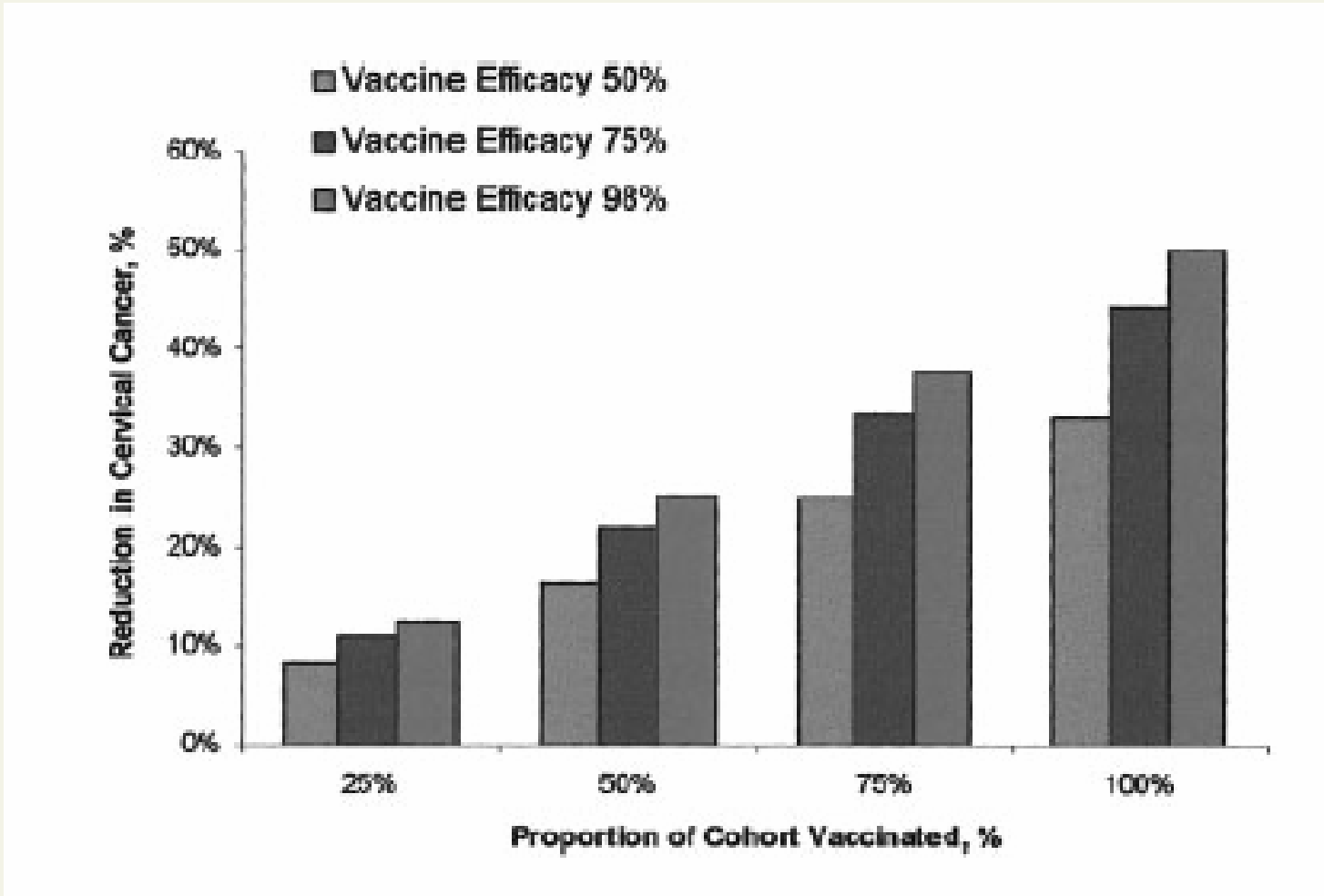
Projected Impact of Vaccine



- Vaccine preventing 98% of persistent HPV 16/18 vaccine
  - 98% reduction in HPV 16/18 assoc'd cancer
  - 51% reduction in total cervical cancer
- Even 50% efficacy can reduce substantial fraction of cervical cancers

Goldie SJ, et al. Int. J. Cancer 2003;106:896-904

Impact sensitive to coverage



Goldie SJ, et al. Int. J. Cancer 2003;106:896-904

Epidemiologic considerations for global impact of HPV vaccine

- Biology strong – demonstration of 80-100% efficacy at least 4 years out.
  - Longer term follow-up of trial participants needed to understand (a) duration of immunity and (b) minimal protective neutralizing Ab titer
- Population impact will be more sensitive to coverage (at least in the near term).
  - Type specificity
  - Age at vaccination
  - Compliance

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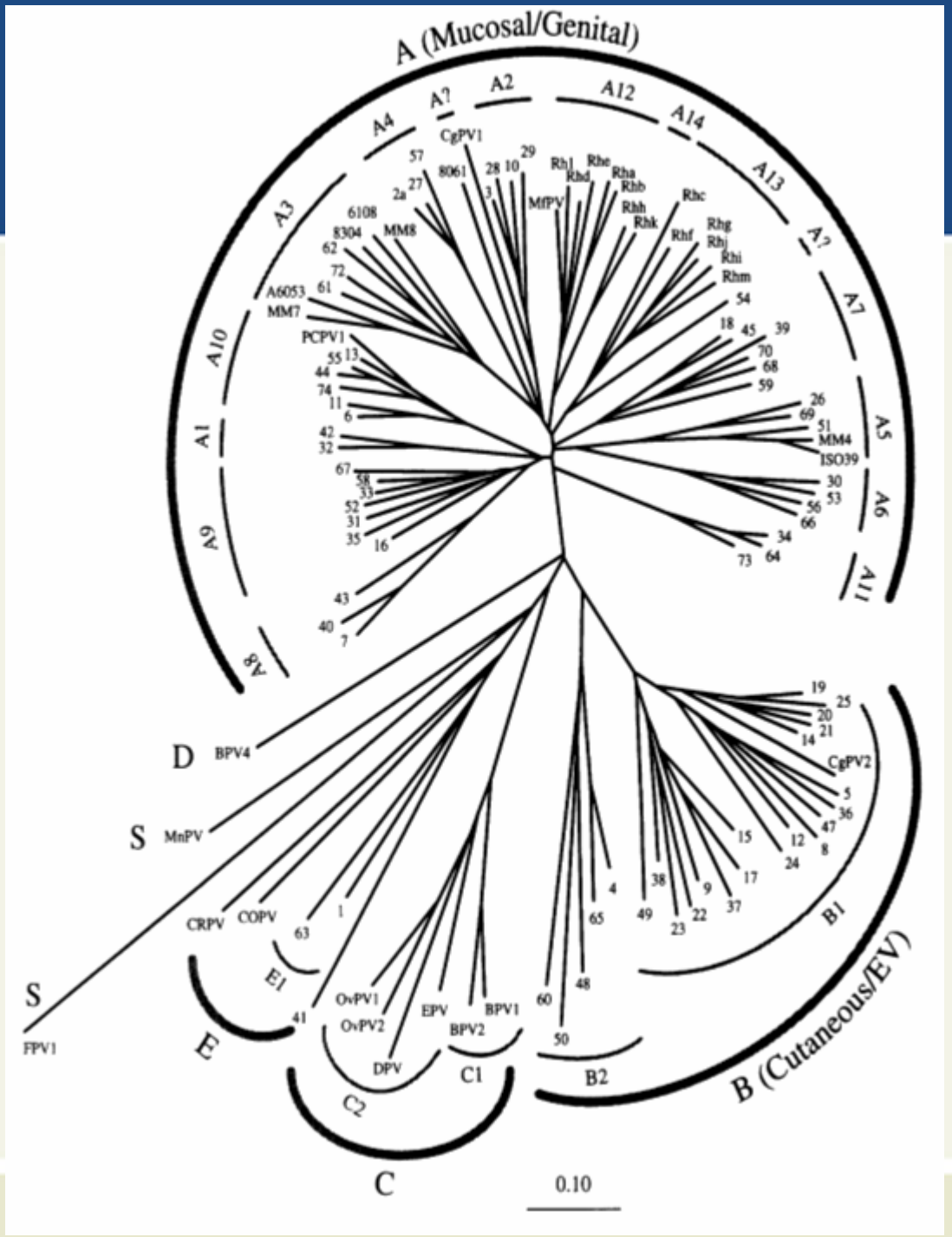
HPV Type Diversity

Focus on Asia

HPV Diversity

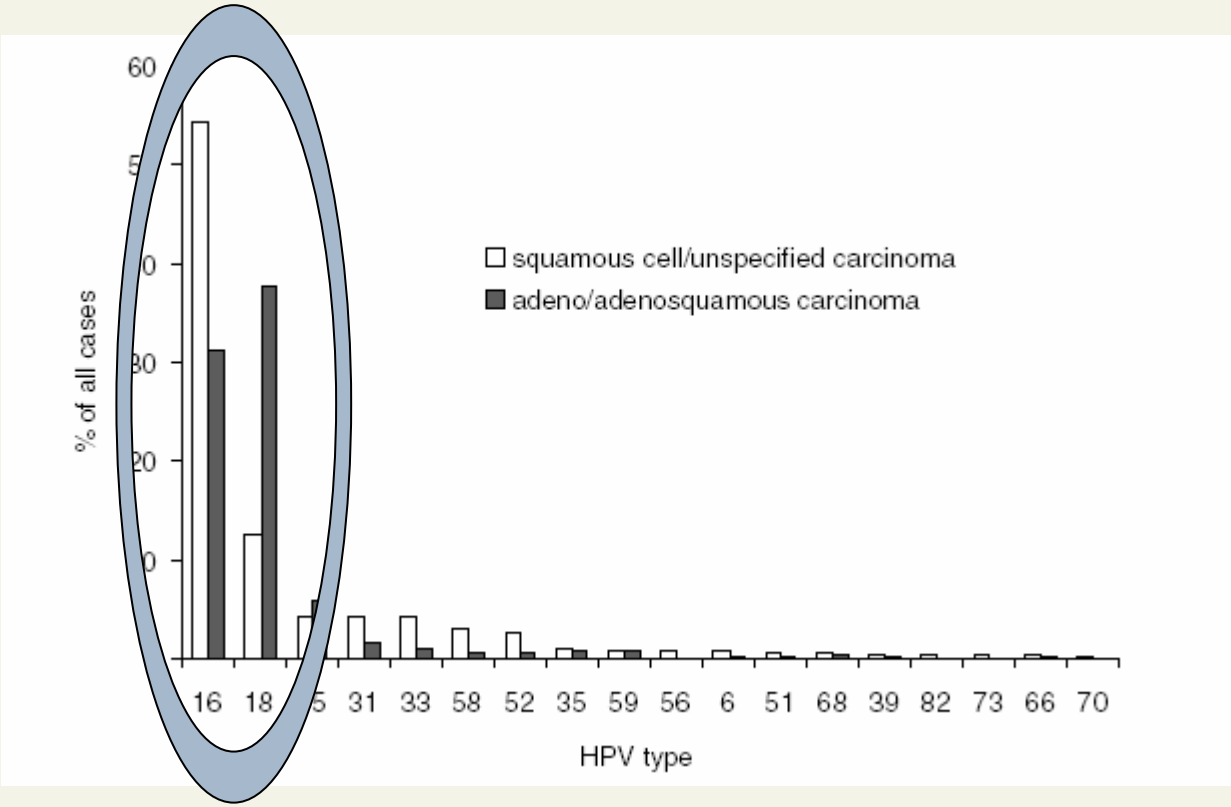
There are more than 50 types of HPV that infect the anogenital and oral tract of men and women

Approximately 18-20 are likely carcinogenic



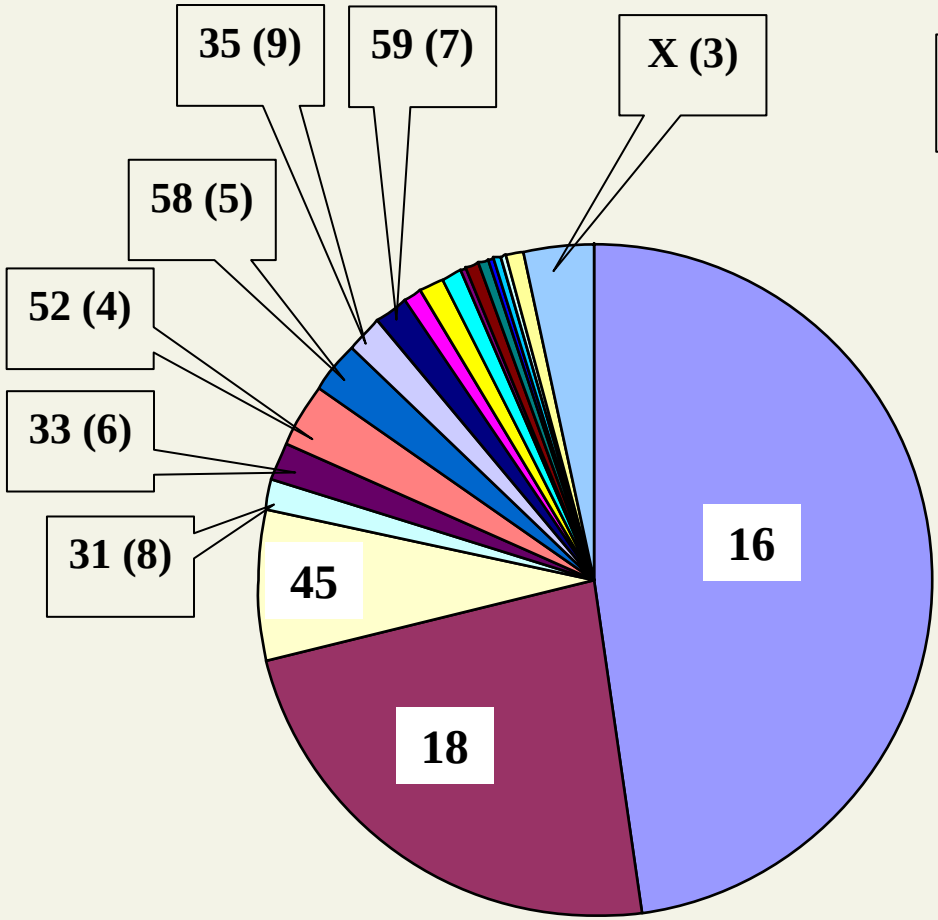
Reduction, not elimination

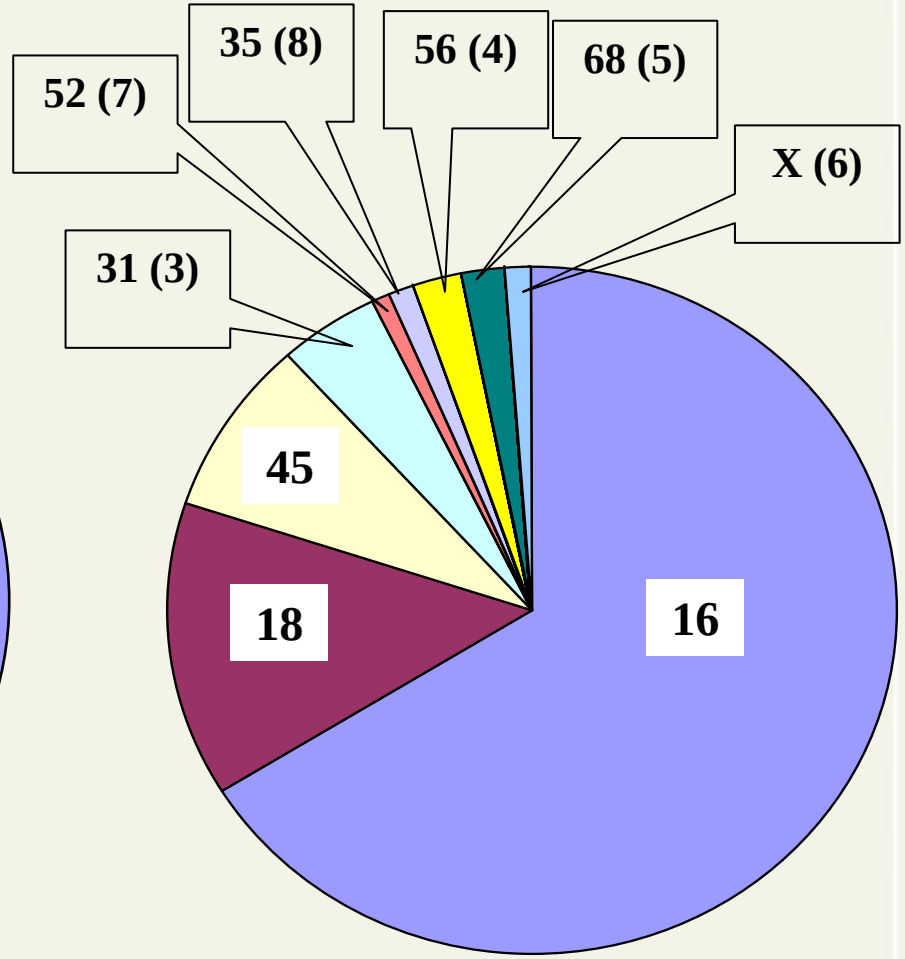
- Why does vaccine only reduce, but not eliminate cervical cancer risk?



Clifford G, et al. Br. J. Cancer 2003; 88:63-73.

South Asia vs. Europe/N. America

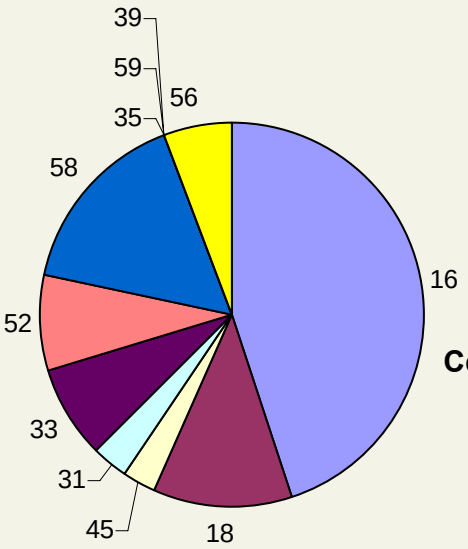




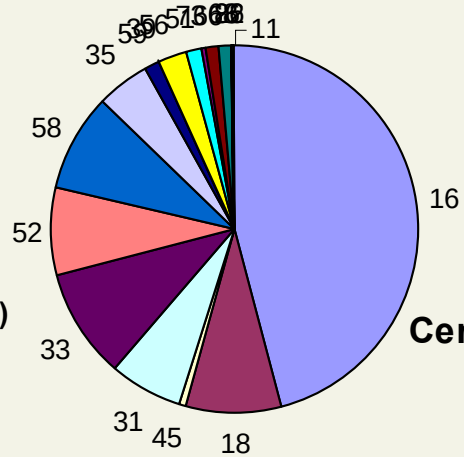
Adapted from Clifford G, et al. Br. J. Cancer 2003; 88:63-73.

Regional Variation in South Asia

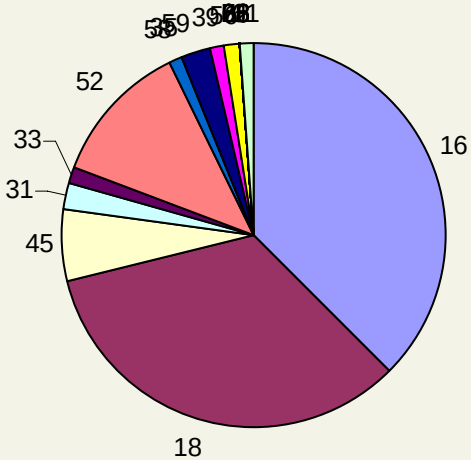
Kohn Kaen, Thailand
Cervical Cancer Cases (N=33)



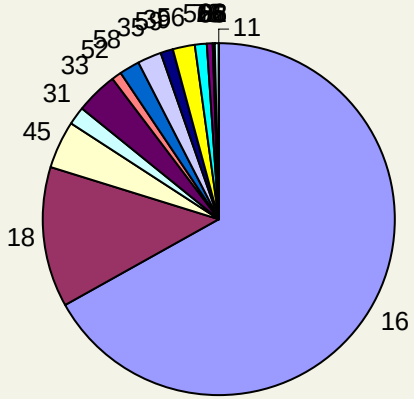
JAPAN Cervical Cancer Cases (N=311)



INDONESIA
Cervical Cancer Cases (N=74)



INDIA
Cervical Cancer Cases (N=397)



From Sriamporn S, et al. Int J Gynecol Cancer 2006;16:266 (Thailand); Asato T, et al. JID 2004;189:1829 (Japan); Schellekens MC, et al. Gynecol Oncology 2004;93:49 (Indonesia); Franceschi S, et al. Int J Cancer 2003;107:127, Sowjanya P, et al. BMC Infect Dis 2005;5:116, Peedicayil, et al. Int J Gynecol Oncol, *in press*, and Bhatla, et al. Int J. Pathol, *in press* (India)

Summary slide type variation

- HPV 16 and 18 are uniformly accountable for at least 50% of invasive cervical cancers worldwide.
- Increasing the vaccine valency by inclusion of additional type-specific VLPs will have variable impact across the world depending on the types chosen
  - Some reported evidence of cross-protection with GSK vaccine; L2 vaccine?
- HPV type-specific prevalence varies regionally
  - Overall HPV prevalence also may vary within country
    - 5-times higher in Ho Chi Minh City relative to Hanoi, Vietnam
      - Anh PTH, et al. Int J Cancer 2003;104:213.

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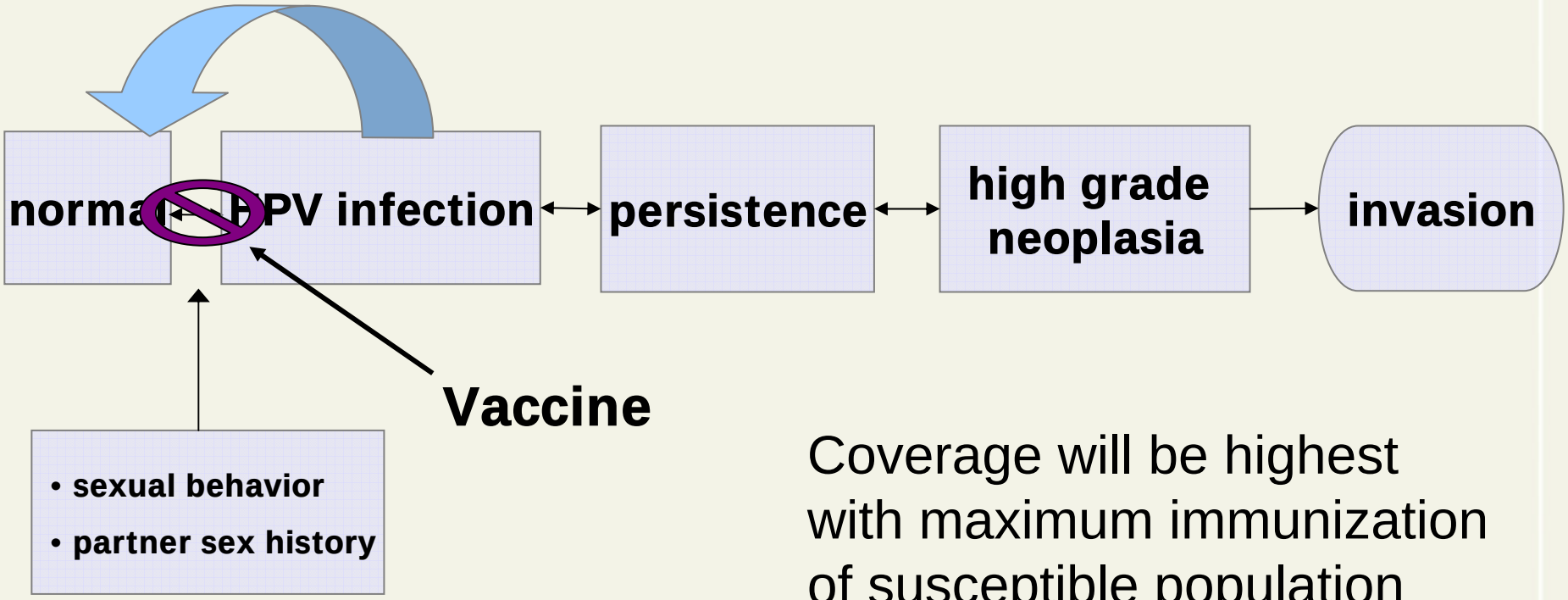
Recommended age at vaccination

Focus on Asia

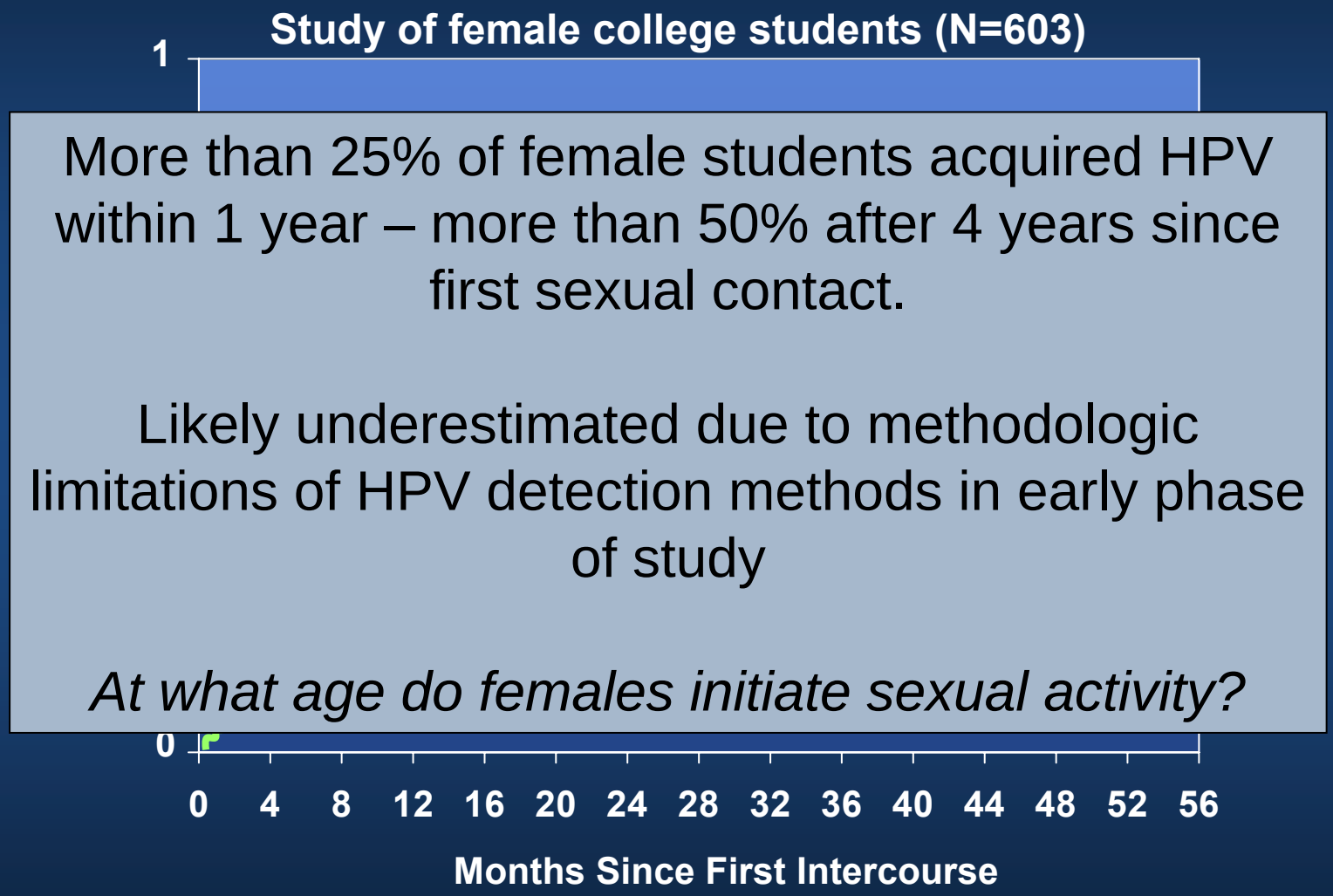
Working model of cervical carcinogenesis



Coverage will be highest with maximum immunization of susceptible population

How soon after sexual debut does woman acquire HPV?

Infection From Time of First Sexual Intercourse



More than 25% of female students acquired HPV within 1 year – more than 50% after 4 years since first sexual contact.

Likely underestimated due to methodologic limitations of HPV detection methods in early phase of study

At what age do females initiate sexual activity?

From Winer RL, Lee S-K, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. *Am J Epidemiol.* 2003;157:218–226. Reprinted with the permission of Oxford University Press.

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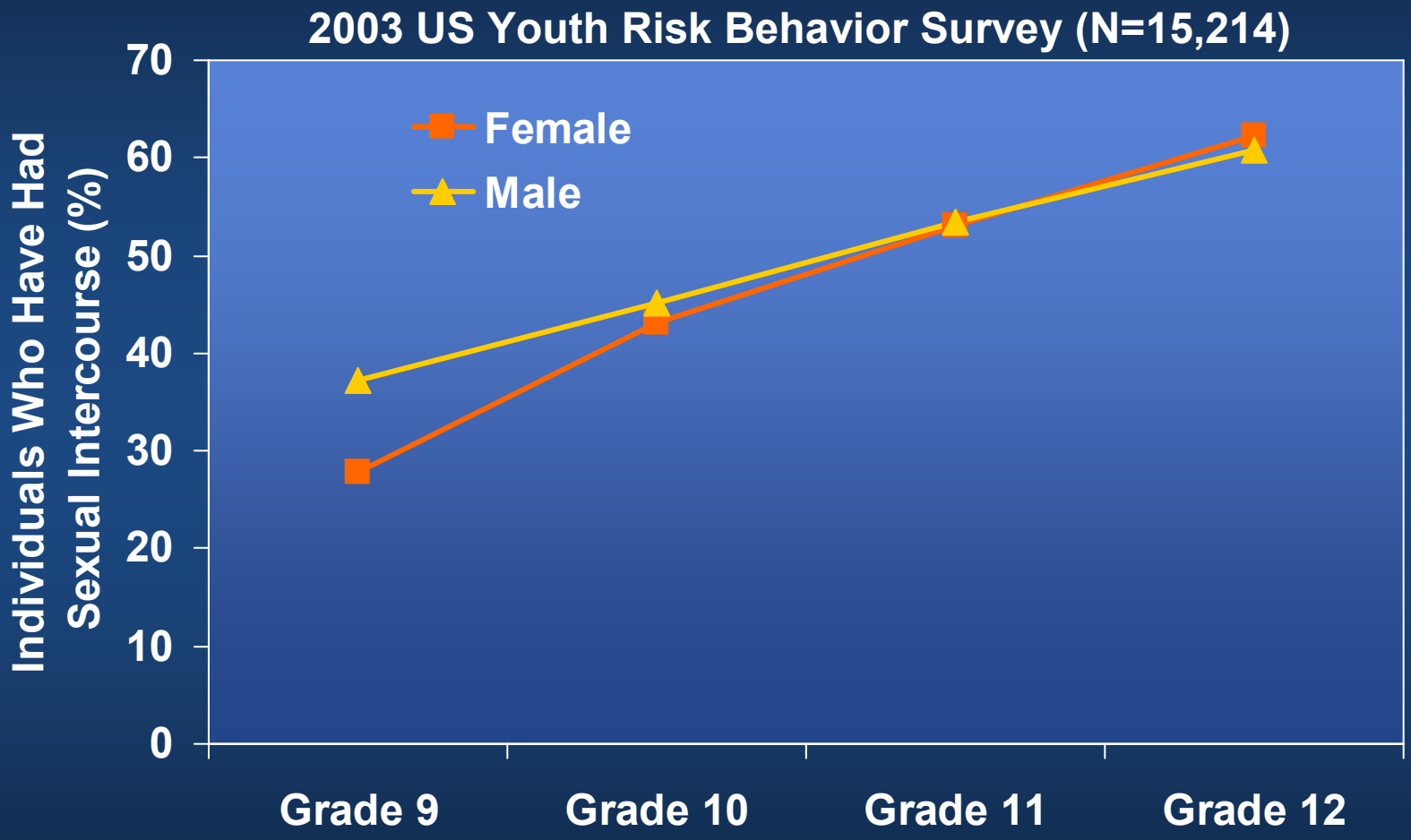
Percentage of US High School Students Who Have Had Sexual Intercourse[1]



In addition, 7.4% of US adolescents reported sexual debut before 13 years of age. By Grade 12, 20.3% of US adolescents reported ≥4 lifetime sexual partners.

1. Grunbaum JA, Kann L, Kinchen S, et al. *MMWR*. 2004;53(SS-2):1–96.

slide courtesy of Merck & Co., Inc.

Indications and Usage for GARDASIL®

US Recommendations

- GARDASIL is a vaccine indicated in girls and women 9 to 26 years of age for the prevention of the following diseases caused by HPV types 6, 11, 16, and 18:
  - Cervical cancer
  - Genital warts (condyloma acuminata)

  and the following precancerous or dysplastic lesions:
  - Cervical AIS
  - CIN grades 2 and 3
  - VIN grades 2 and 3
  - VaIN grades 2 and 3
  - CIN grade 1

Age at vaccination in Asia

- Few data on pre-marital sexual behaviors in some countries (e.g., India), particularly in rural areas
- The greatest population impact will be realized if immunization occurs prior to sexual debut
  - Transmission can occur from non-penetrative sexual exposures
  - Condoms offer some protection, but limited unless used absolutely consistently and correctly
- Vaccination at the time of marriage is unlikely to yield the optimum pre-exposure coverage.

example in India

Age specific HPV prevalence among married women in Dindigul, India

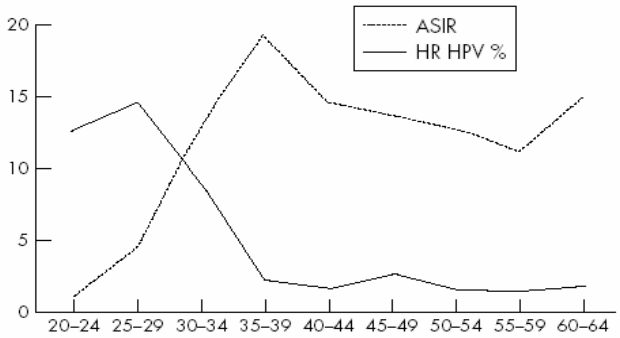


Figure 9 Age specific prevalence (%) of high risk (HR) human papillomavirus (HPV) DNA in 3700 women entering a screening programme and age specific incidence rate (x10^5) (ASIR) of cervical cancer in the Netherlands. Adapted from Jacobs *et al* and Parkin *et al*.[106 108]

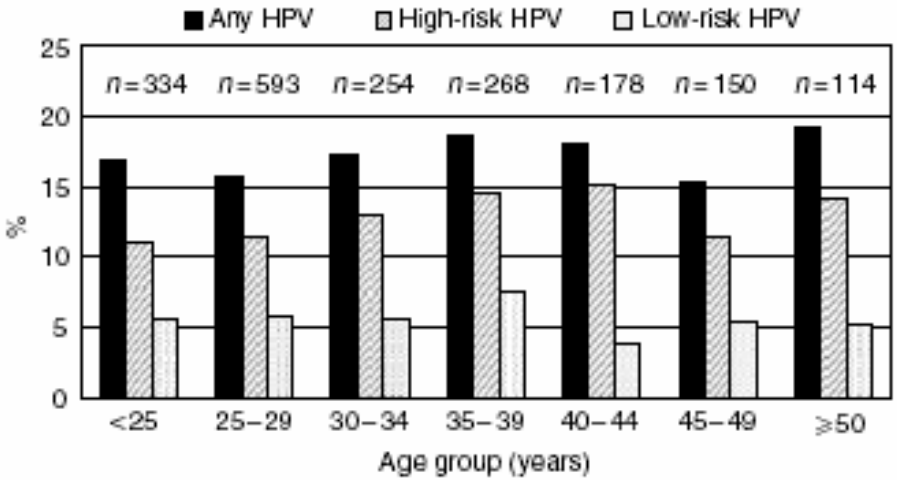
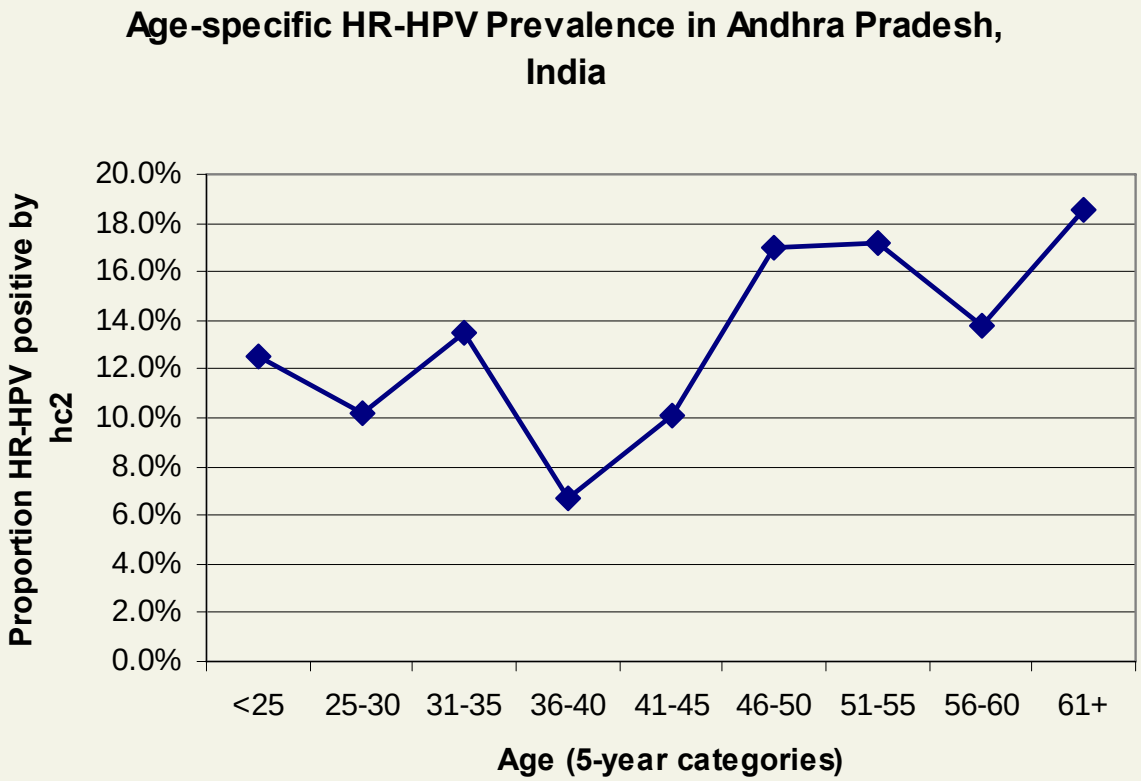


Figure 2 Age-specific prevalence of cervical human papillomavirus (HPV) DNA. (Dindigul, India).

From Franceschi S, et al. BJC 2005;92:601 and Bosch FX et al. J Clin Path 2002;55:244

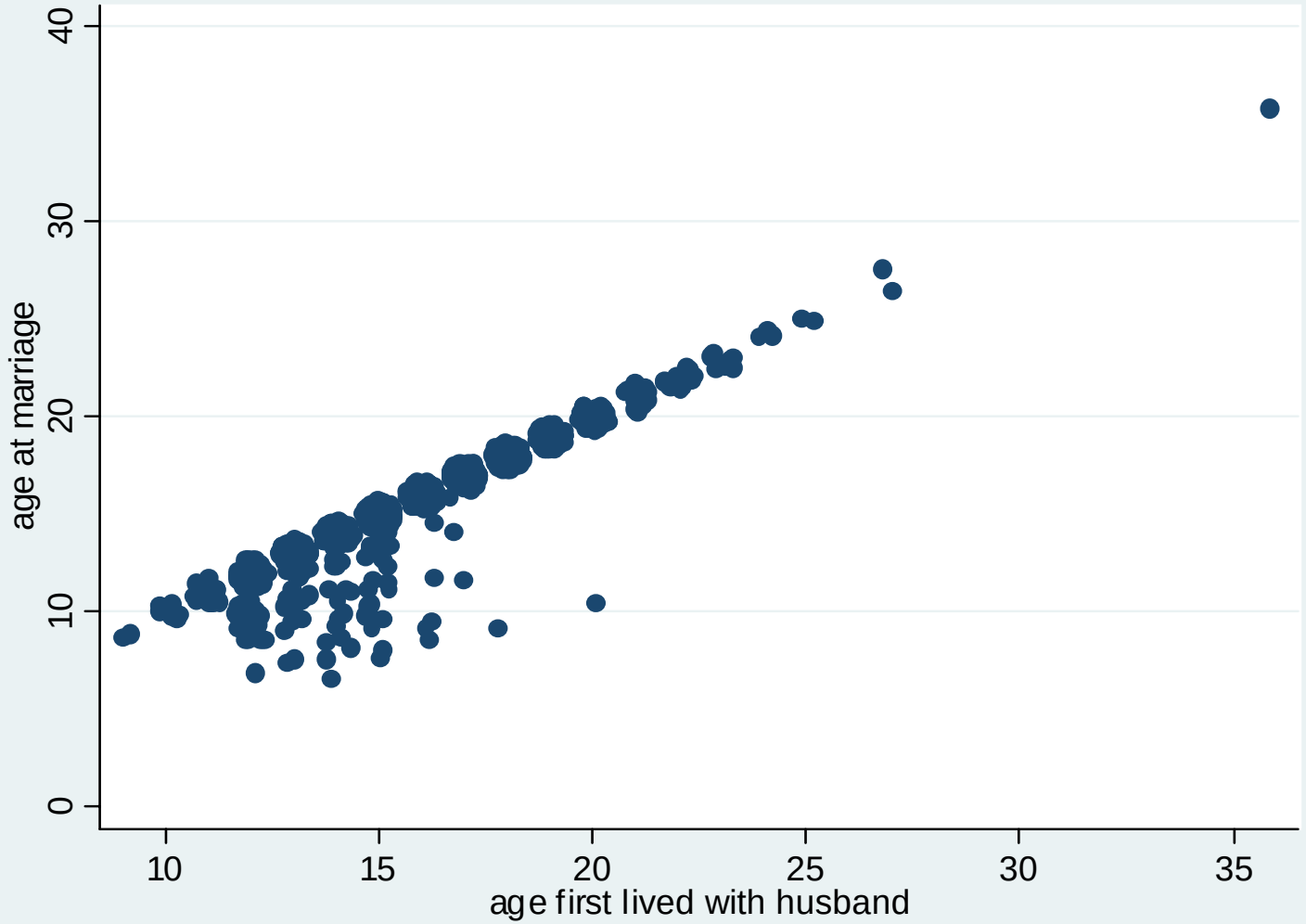
Age-specific prevalence in community-based population of married women in Andhra Pradesh, India

	N
<25	40
25-30	226
31-35	163
36-40	134
41-45	79
46-50	53
51-55	35
56-60	29
61+	27



Unpublished data: The CATCH Project; INDO-US Cooperative Grant (DBT, NIH), Cervical Cancer SPORE (NCI)

Age at marriage and shobodum in rural Indian population



Unpublished data: The CATCH Project; INDO-US Cooperative Grant (DBT, NIH), Cervical Cancer SPORE (NCI)

Age at vaccination: Summary

- HPV is easily transmitted and acquired by a majority of women within 1-5 years after onset of sexual activity
  - Recent simulation models estimate a median per act transmission rate of 40% (95% CI 5 – 100%)
    - *Burchell AN, et al AJE 2006;163:534*
- Waiting until marriage may insufficient for maximum population impact of HPV vaccine
  - Correlation with male sexual behaviors
- Surrogate markers for age at sexual debut are needed to estimate the appropriate age where cultural taboos prevent assessing sexual history
  - HSV-2 serology

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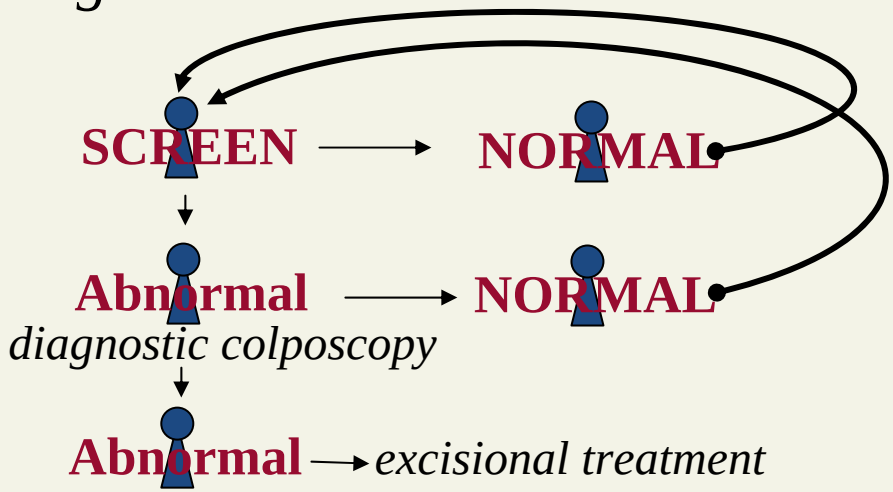
Compliance with immunization and dose schedule

Focus on Asia

Why has Pap smear screening failed in some places?

A single Pap is not sensitive – lifetime repeat screens compensate by increasing cumulative sensitivity

If lesion is present – it will take a minimum of 3 clinic visits to diagnose and treat.

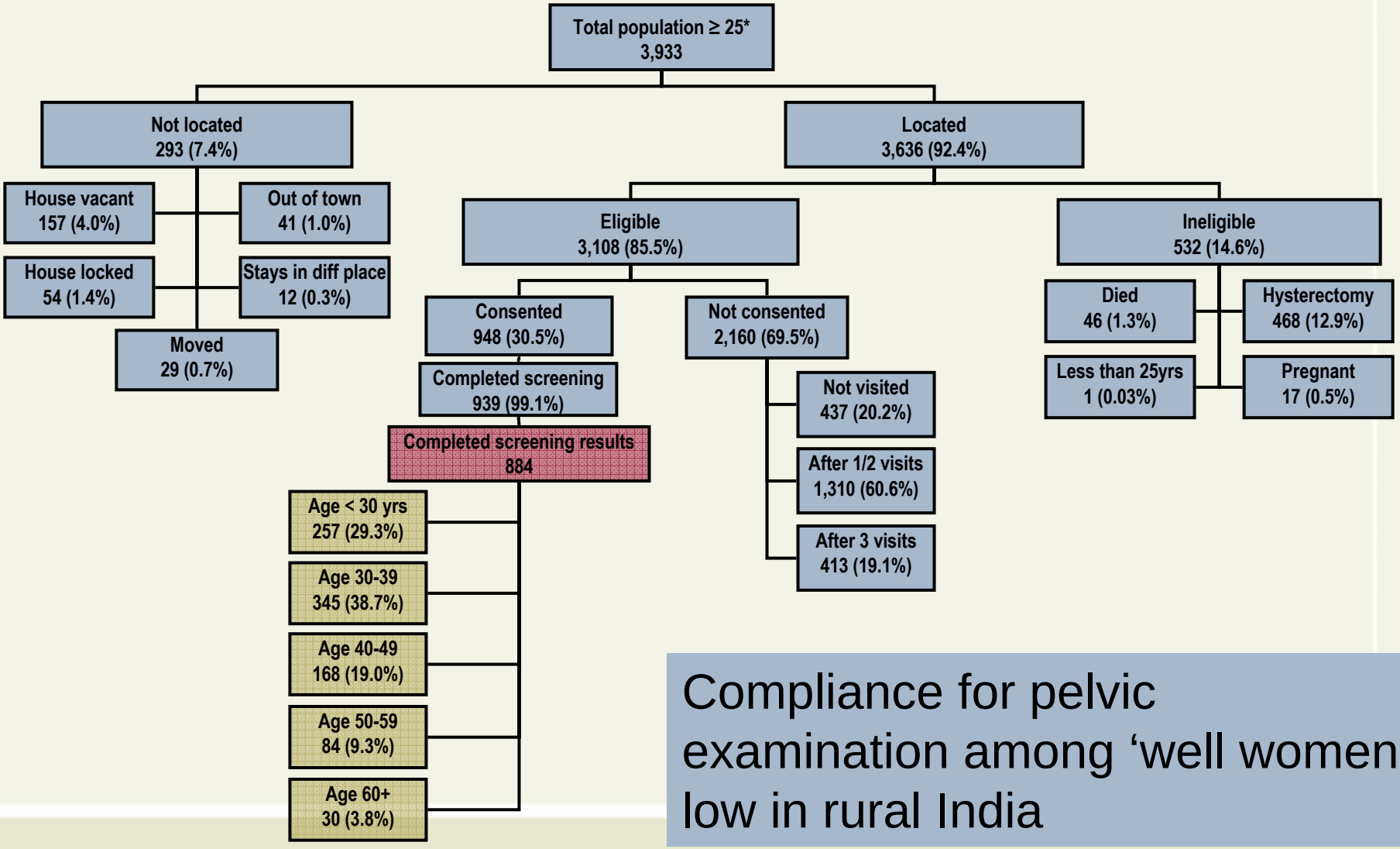


- **Infrastructural requirements high**
- **Patient compliance over entire reproductive and post-reproductive life**

Barriers to cervical cancer prevention

- Cultural, technological, financial ,and political
- Will primary prevention efforts via immunization face similar challenges?
- How diverse are the challenges
  - Regional differences, urban vs. rural
- Examination of barriers to current screening methods vs. immunization
  - *Is screening feasible everywhere? Will immunization programs offer a more feasible means of cervical cancer prevention?*

CATCH study participation



Compliance for pelvic examination among ‘well women’ low in rural India

Compliance with follow-up of abnormal result

- All positively screened women asked to return for colposcopy
- Results:
  - 249/884 women had 1+ positive screen
    - referral rate to colpo = 33.3%
  - 123/249 (49.4%) women returned for colposcopy
    - 47.1% = normal colposcopy
    - 44.7% = biopsy taken (N=55)
    - 1.0% = refused biopsy

Compliance for recommended follow-up and treatment <50%

Focus group assessment of barriers to cervical cancer screening

- Lack of perceived need (i.e., no symptoms)
  - *"...but we don't feel to go [to the doctor] without any problem. It is a waste of money."*
- Stigma of a cancer diagnosis
  - *"...some people will say even if we just go that we went because we have cancer, so we are scared."*
- Suspicion of free service
  - *"...what is the necessity to do this, what gain are they getting from this, what are they taking...they [our community] have all these doubts"*
- Lack of health education/common misconceptions
  - *"...they [other doctors] say that it will be cured if she uses these tablets and if not, it will be the same"*

Barriers to HPV vaccination

- Largely unknown – several hypothetical concerns
  - STD vs. cancer vaccine, vaccination of unmarried girls, assurance of reduced risk (vs. complete protection), perceived need (cost-benefit), ability to deliver 3 dose schedule in low-resource populations, reaching target age (adolescent girls), vaccination of men
- Fundamental barrier to screening appears to be resistance to repeated pelvic exam – this will not be an issue with immunization
- HBV vaccine introduction experience as a model?

Vaccine summary

- First demonstrated success for near complete prevention of genital tract STI and second vaccine to prevent cancer.
- Some questions remain regarding the logistics of vaccine delivery, accessibility, target population, duration of immunity, effect of malnutrition and HIV on vaccine effectiveness, etc., *HOWEVER...*
- Remarkable promise for reducing up to 50% of the world's cervical cancer

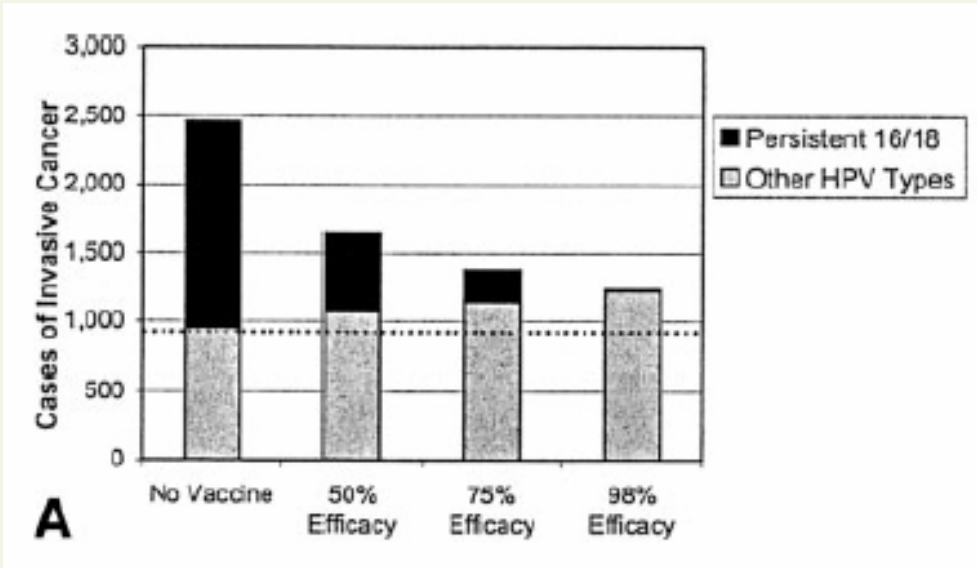
Concluding remarks

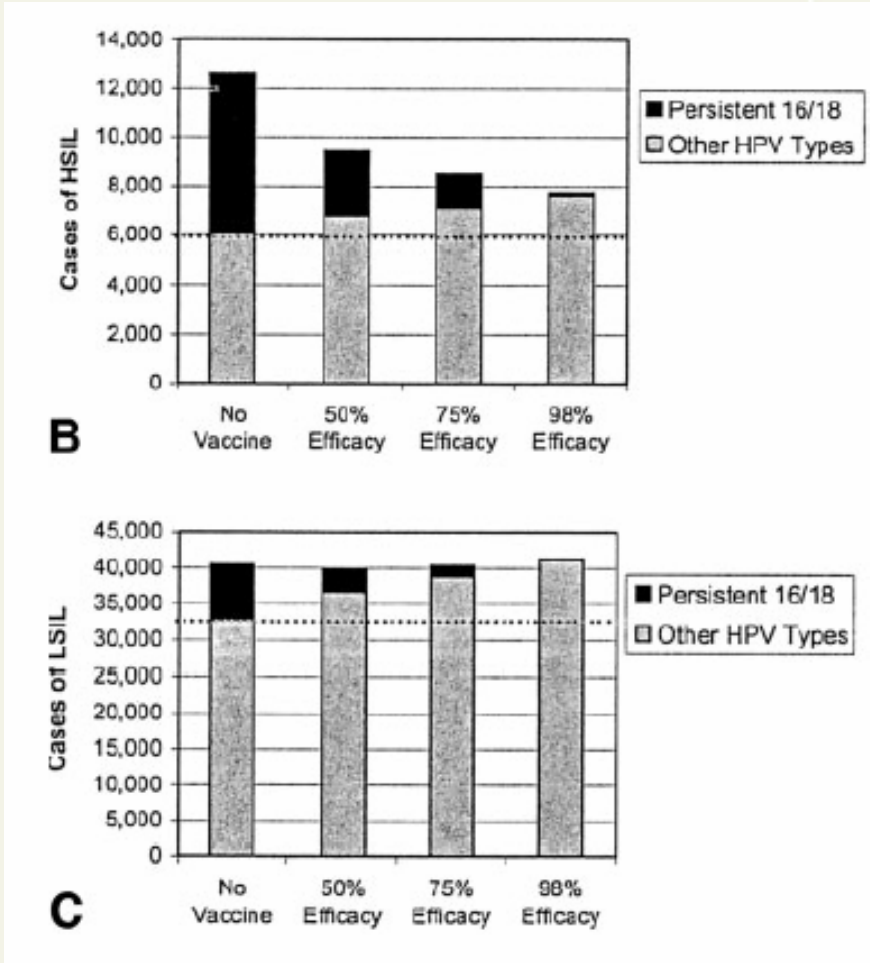
The scientific and medical community has made remarkable advances toward the prevention of cervical cancer worldwide in just 20 years.

The consequence of rapid advancement is a lag in dissemination of information to the general medical community and to the public.

Successful implementation of these advances into public health practice will ensure maximum impact on reduction of cervical cancer incidence and mortality. ***This will require substantial educational campaigns to providers and the general public.***

Etiologic fraction of ICC, HSIL, and LSIL





Goldie SJ, et al. Int. J. Cancer 2003;106:896-904