

# HPV Vaccines: Facts and Controversies

Jim Bentley

Dalhousie University

# Conflict of interest

- \* I am involved in research with both GSK and Merck
- \* I have been on advisory boards and given talks for both GSK and Merck

FACT: This is a controversial  
issue!



# Health

- HEALTH
- WELLNESS AND PREVENTION
- WEIGHT LOSS
- EXERCISE
- NUTRITION
- DISEASES

## Spotlight on Health

brought to you by  
the  
COLOR of  
hope

Share Send Print Comments

### The HPV Vaccination Debate

By Dr. Jennifer Ashton

Doctors say it could prevent cervical cancer. So why are some women hesitating to vaccinate themselves and their daughters? Dr. Jennifer Ashton, an ob-gyn and CBS News medical correspondent, argues both sides so that you can make an educated decision.

**Jade Goody: celebrity's fatal illness changed cervical cancer attitudes**  
Jade Goody's well-publicised condition sparked renewed interest in screening and changed NHS policy

Sarah Boseley, health editor  
guardian.co.uk, Sunday 22 March 2009 10:28 GMT  
Article history



Jade Goody after learning she had cervical cancer, on Indian reality TV. Photograph: Rex Features/Rex Features

Jade Goody's illness and the shocking news that it was fatal had a major impact on the NHS cervical cancer screening programme. It caused an upsurge in women asking to be screened and – in response to a tabloid newspaper campaign – triggered a review of the evidence to establish whether screening women before the age of 25 would save lives.

MICHAEL BUBLE Singing sweet, talking dirty P.46

FESCHUK'S SUMMER OSCARS P.51

RADICALS AT THE DOOR How Pakistani extremism is taking hold in Canada P.24

INSIDE OTTAWA: The top chefs dish it P.7

MACLEAN'S

BARBARA ARTEL I'm home alone P.12

OUR GIRLS AREN'T GUINEA PIGS

A mass inoculation of Canadian girls against a sexually transmitted virus is under way. Experts say it's unnecessary—and potentially dangerous.

P.38

www.macleans.ca

THE WORLD'S MOST HEARTBREAKING WEDDING

OK! JADE GOODY MARRIES JACK TWEED

FIRST FOR CELEBRITY WEDDINGS

SPECIAL TRIBUTE ISSUE 'I'VE HAD THE HAPPIEST DAY OF MY LIFE, NOW I'M READY TO GO TO HEAVEN'

ONLY IN OK! WORLD EXCLUSIVE

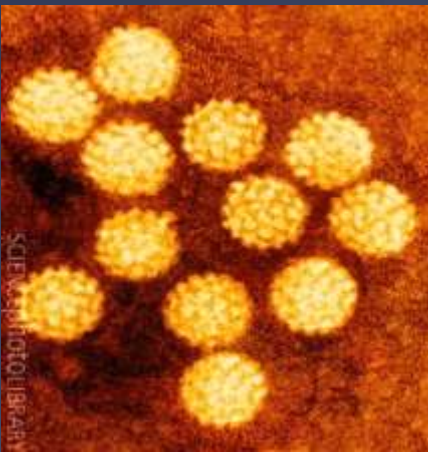
JADE CELEBRATES HER SHORT LIFE WITH HUSBAND JACK & HER BELOVED BOYS FREDDY & BOBBY

INSIDE THE ELIZABETHAN COUNTRY MANSION STUNNING MARIKI MOTA BRIDAL GOWN, THE EMOTIONAL CEREMONY, STAFFS, SPEECHES, CELEBRITY GUESTS, ONI BAND, RINGS, WHITE DOVES, FAIRY-TALE CARL, PINK CHAMPAGNE, HELICOPTER ARRIVALS & FENDI DONATED TO JADE'S CHILDREN

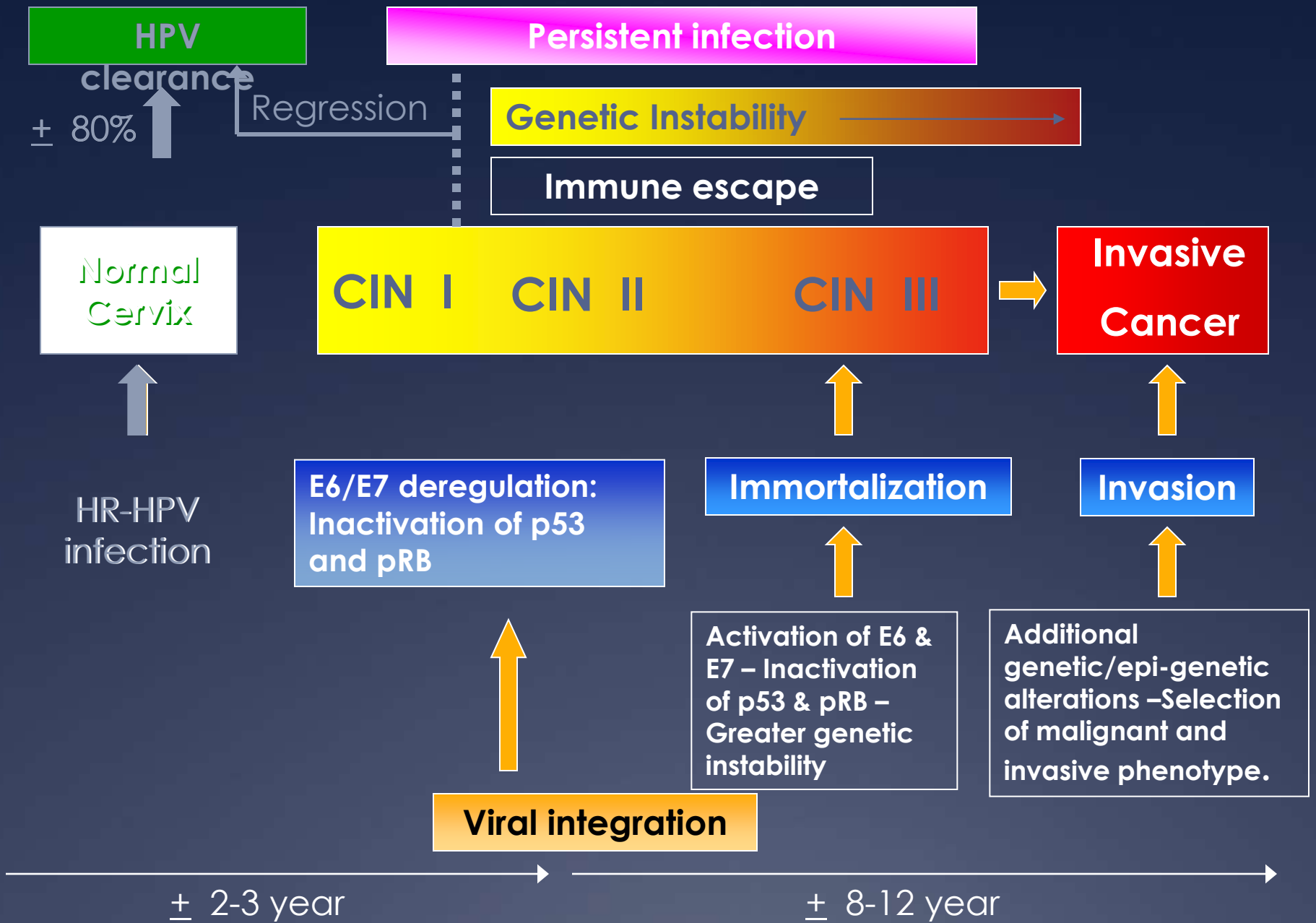
FACT: HPV is responsible for  
cervical Cancer

# Cervical Dysplasia and cancer

- \* Abnormal cells on the cervix, classified into CIN I, II and III
  - \* CIN: cervical intraepithelial neoplasia
- \* Etiological factor:
  - \* Human Papillomavirus 99.7%<sup>1</sup> of cancers

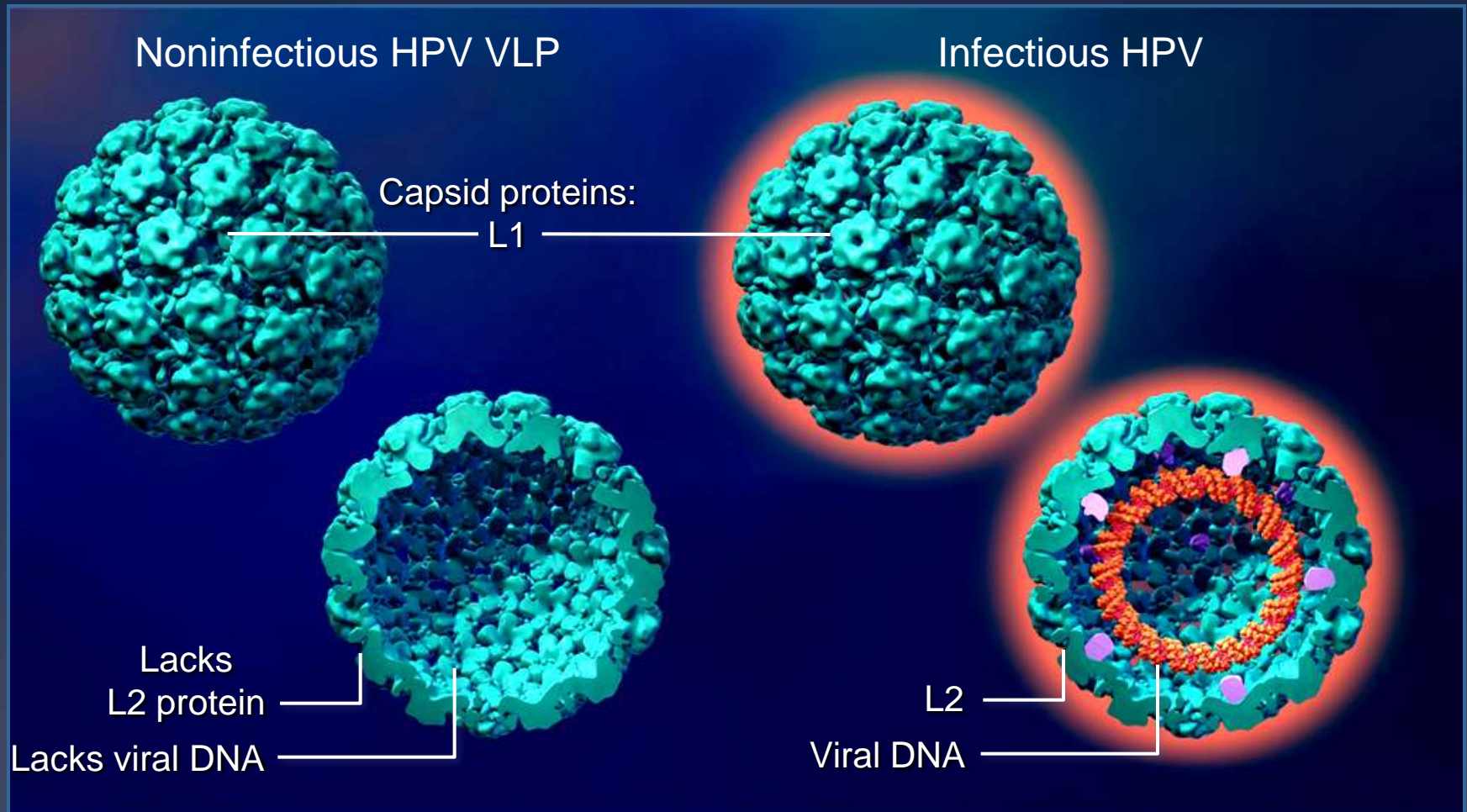


<sup>1</sup>Walboomers et al. J Pathol 1999;189:12-9



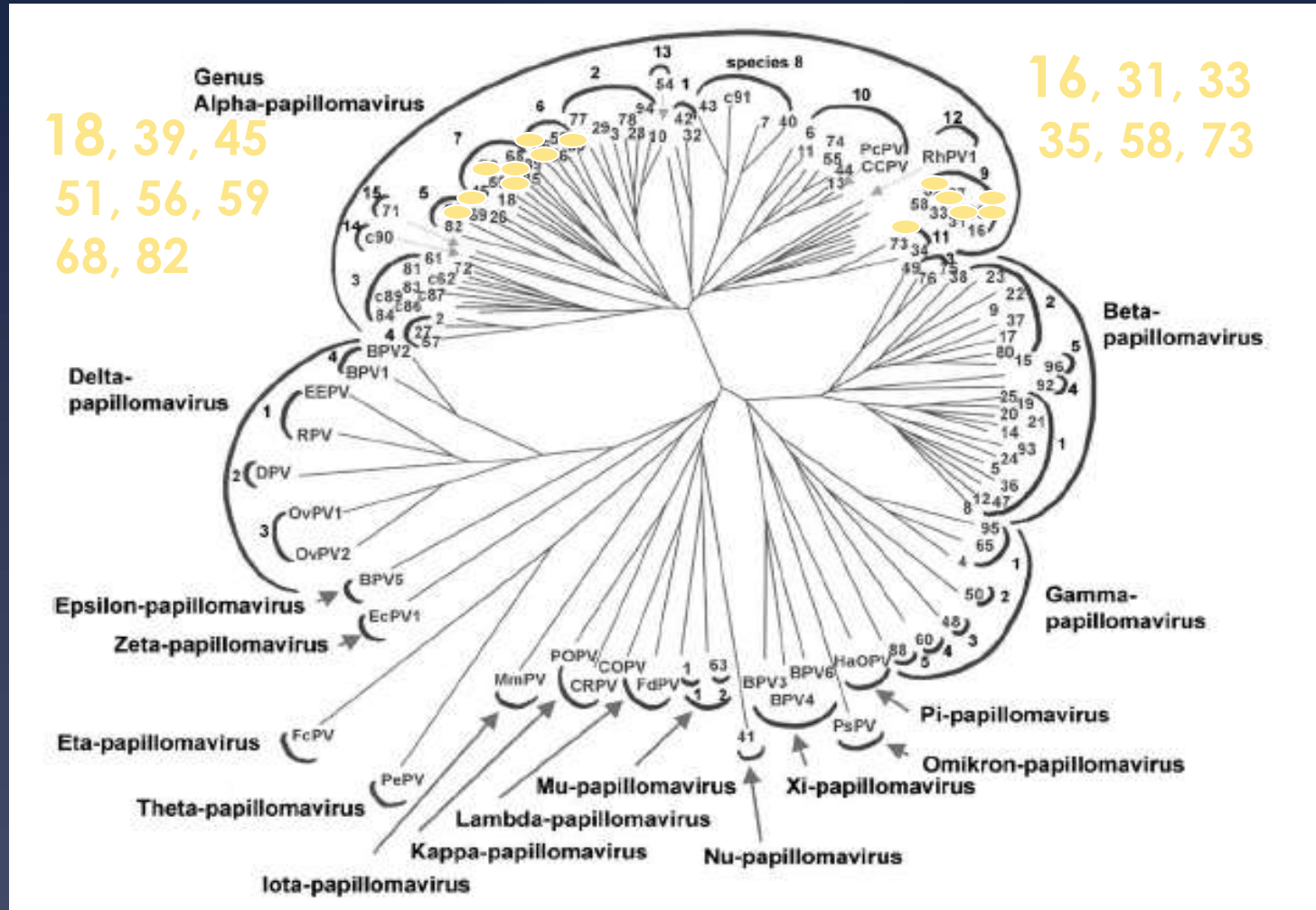
Adapted from Stenbergen R D M, et al. J Clin Virol. 2005; 32S: S25-S33.

# L1 VLPs Mimic the HPV Virion<sup>1-4</sup>

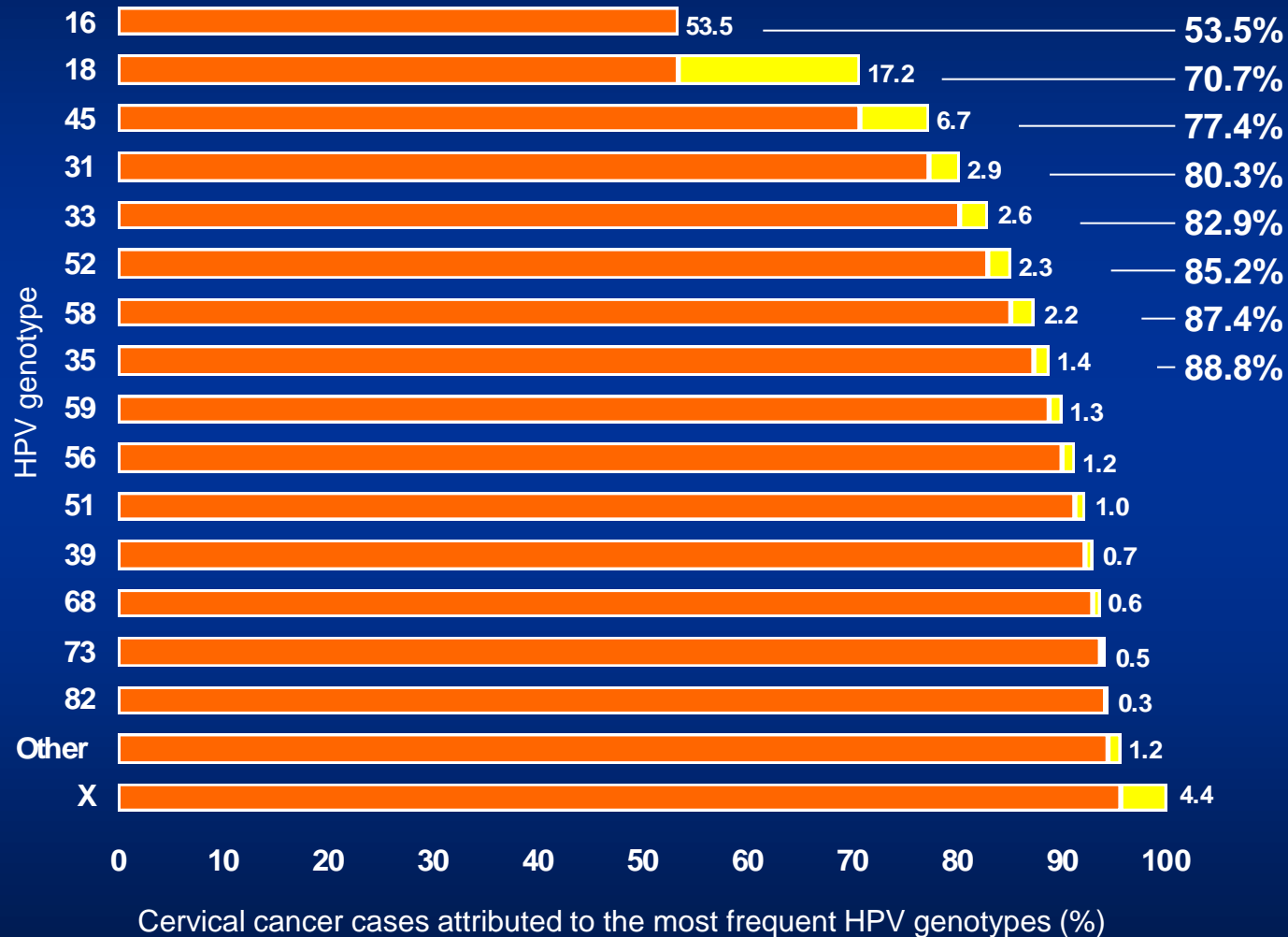


1. Stanley M. *Vaccine*. 2006;24(Suppl 1):S16–22.
2. Berzofsky JA, et al. *J Clin Invest*. 2004;114:450–462.
3. Baker TS, et al. *Biophys J*. 1991;60:1445–1456.
4. Chen XS, et al. *Mol Cell*. 2000;5:557–567.

# Papillomavirus – phylogenetics

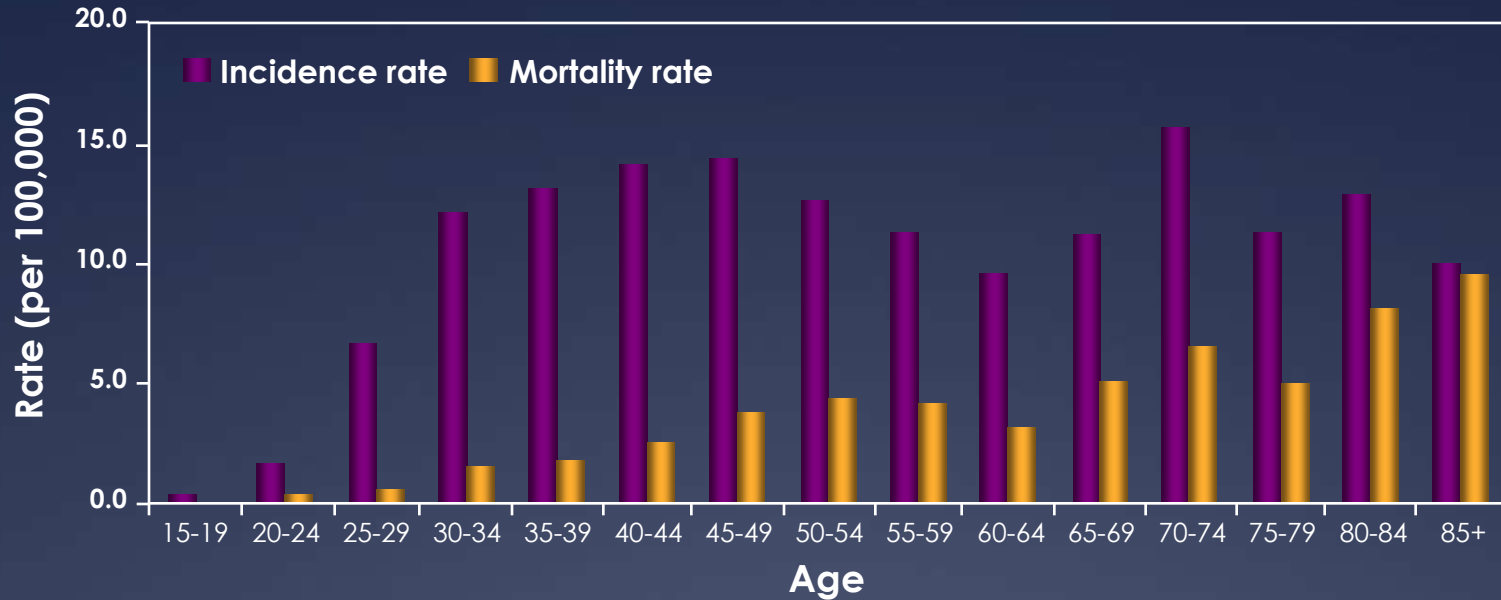


# HPV types in cervical cancer



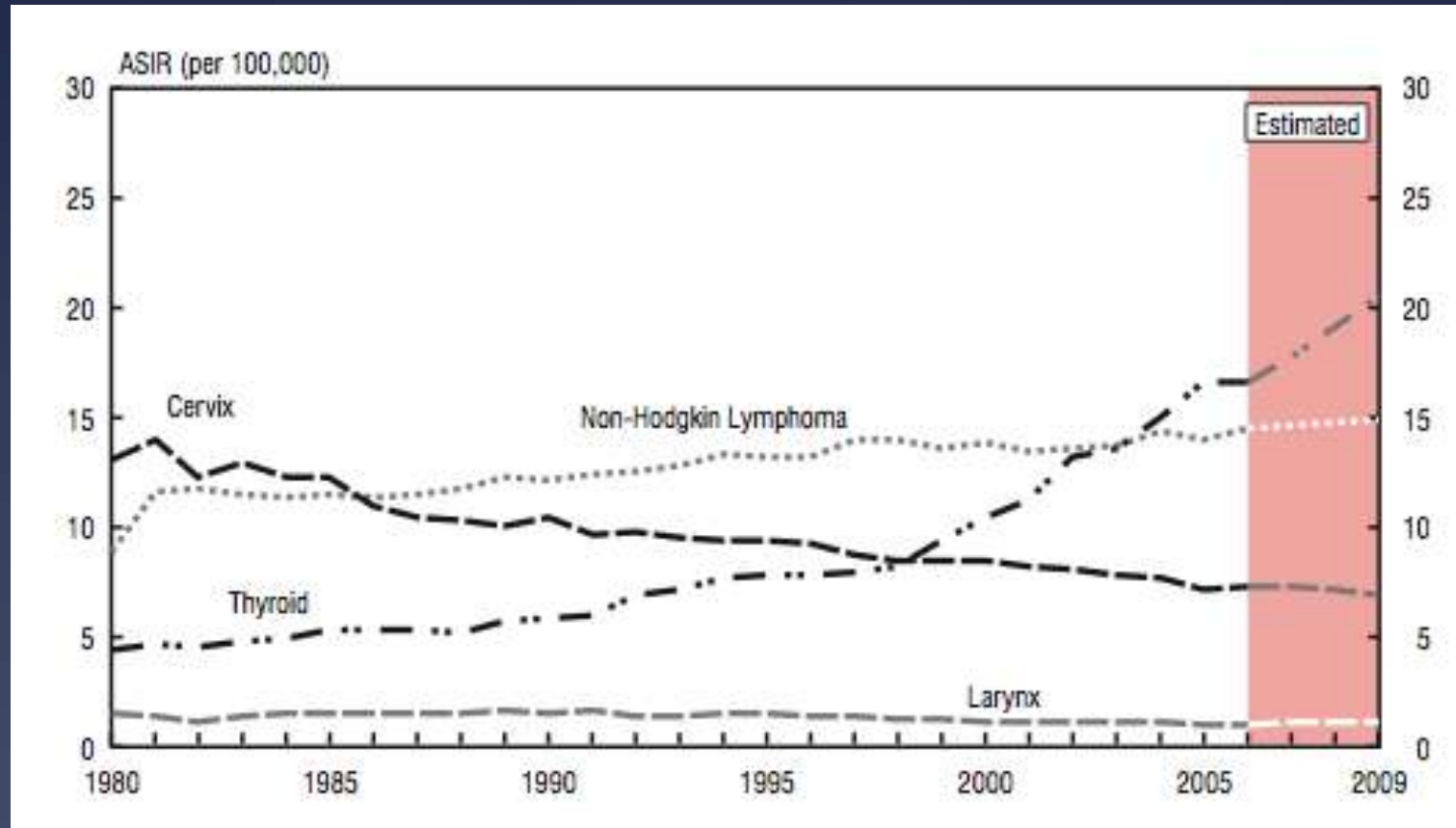
# Canadian epidemiology of cervical cancer

## Incidence and mortality rates of cervical cancer in Canada<sup>1</sup>



- Incidence of cervical cancer peaks among women in their 40s and among women  $\geq 70$  years of age<sup>1</sup>
- The median age at diagnosis of cervical cancer is 47; the median age at diagnosis for all types of cancer is between ages 60 and 69<sup>2</sup>

# Incidence 1980-2009



FACT: HPV vaccination is recommended by national authorities

# NACI Guidelines

- \* NACI Recommendations Feb 2007 for Gardasil
  - \* Females between 9 and 13 years
  - \* Females between 14 and 26 years even if they have been sexually active
  - \* Females >26 no recommendation
  - \* Females < 9 yrs not recommended
  - \* Males Not recommended
  - \* Immunocompromised not recommended
  - \* Pregnancy not recommended

# HPV Vaccination Current Status

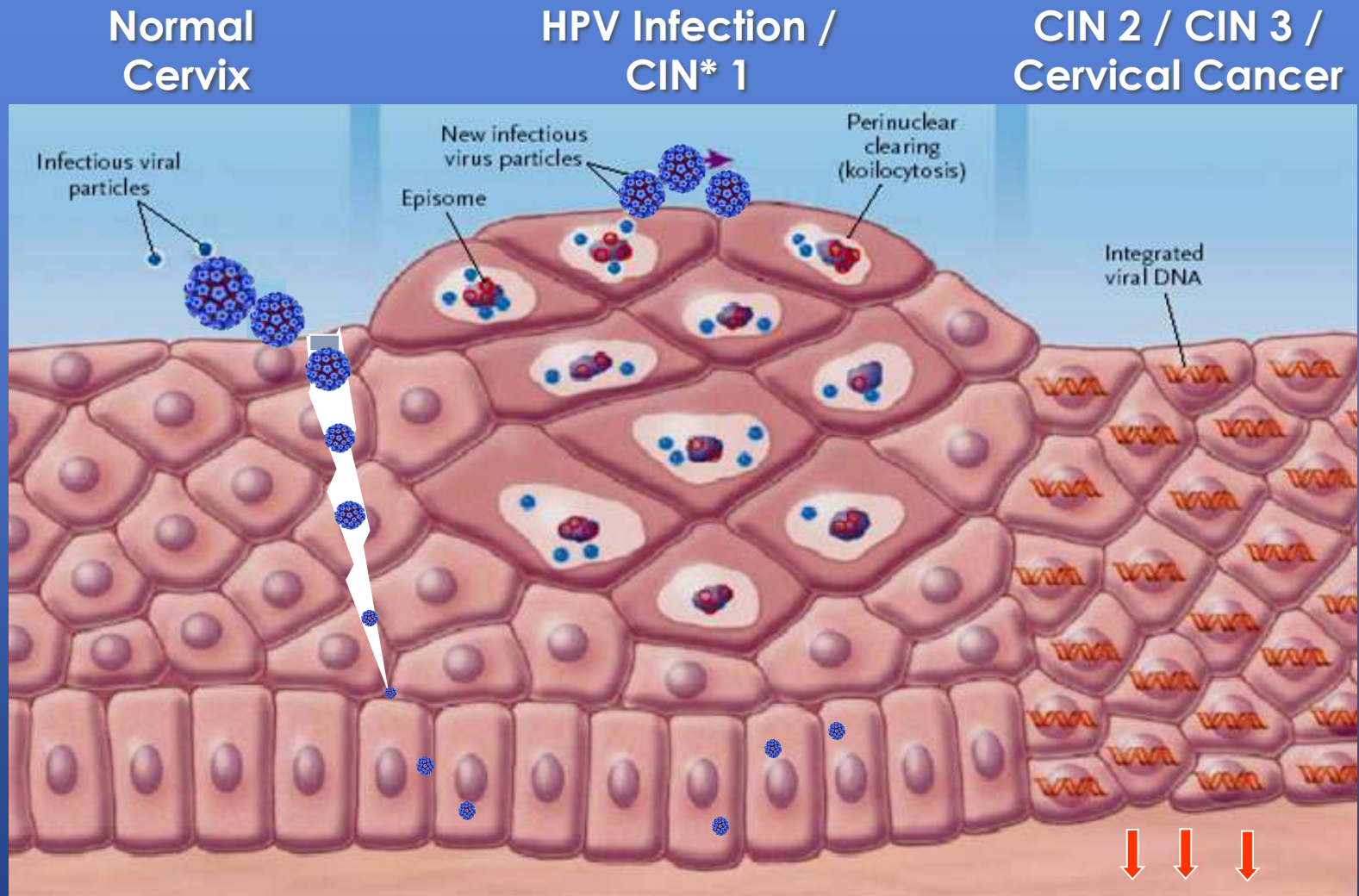
- \* Gardasil (Merck) available since July 2006
  - \* FDA Panel recommended approval for boys 9-26 yrs for indication of preventing EGW
    - \* Sought approval for penile and anal cancer but not given
- \* Cervarix (GSK) not yet available
  - \* Approved in > 100 countries but not Canada
  - \* FDA panel recommended approval for women 9-26 sept 11 2009

# Vaccination current status

- \* School based programs in all provinces
- \* NS, PEI, NL started in 2007
- \* This year grade 7 and 10 in NS
  - \* Grades 7-10 will have been vaccinated, i.e. girls up to 16 years old
- \* Vaccination rates vary from 85% in NS to 50% in Ontario
- \* Rates in USA 20-25%
  - \* No school based programs

Controversy: “my daughter  
will not be at risk”

# Spectrum of Changes in Cervical Squamous Epithelium Caused by HPV Infection<sup>1</sup>



\*CIN = cervical intraepithelial neoplasia

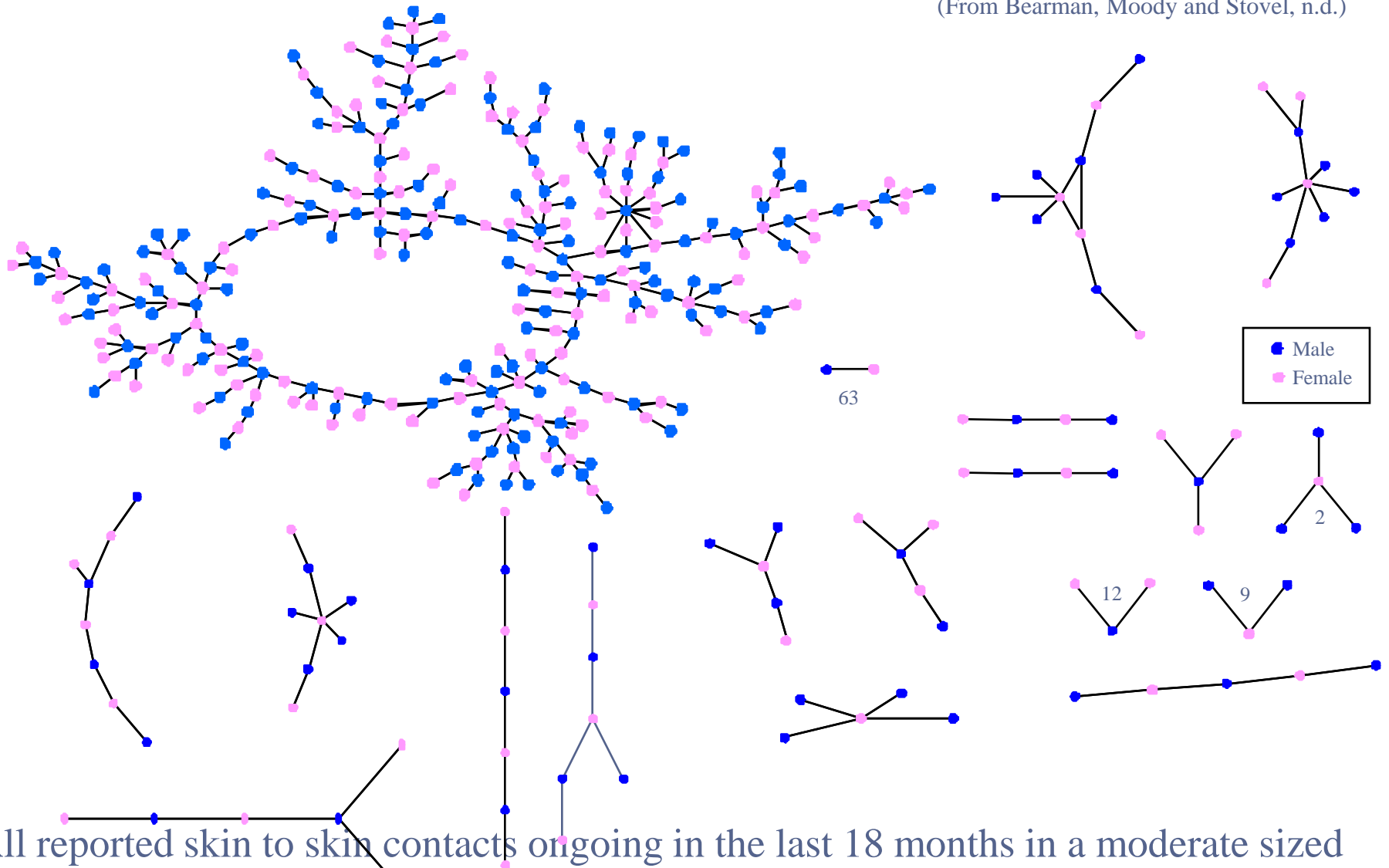
1. Adapted from Goodman A, Wilbur DC. *N Engl J Med*. 2003;349:1555–1564. Copyright © 2003 Massachusetts Medical Society. All rights reserved. Adapted with permission.

# Transmission of HPV

- \* Prevalence in asymptomatic women is 2-40 % mean 10.41%
  - \* Highest in young women
- \* Sexual contact primary route of transit, important factors
  - \* Earlier age at sexual debut
  - \* Increased number of partners
- \* Estimated risk of getting HPV per coital act 5-100% median 40%
- \* More transmissible than any virus but less than bacterial infections

# HPV - What goes around...

(From Bearman, Moody and Stovel, n.d.)



■ Male  
● Female

63

2

12

9

All reported skin to skin contacts ongoing in the last 18 months in a moderate sized high school ( Special romantic +/- intercourse , or nonromantic sexual relationship)

FACT: HPV vaccination is  
effective

# HPV Vaccines: Published data

	Gardasil (Merck)	Cervarix (GSK)
	FUTURE I FUTURE II	PATRICIA
Study type	RCT Phase III	RCT Phase III
Vaccine	Quadrivalent HPV 6/11/16/18 VLP, L1 capsid component	Bivalent HPV 16/18 VLP capsid component
Manufacturing	Yeast	Insect cells
Adjuvant	Aluminum hydroxyphosphate Sulphate	Proprietary ASO4

FUTURE I/II NEJM 2007;356:1915-53

PATRICIA Lancet 2009;

# HPV Vaccines: Published data

	Gardasil(Merck)	Cervarix (GSK)
Dose and administration	0.5 ml IM	0.5 ml IM
Schedule	0,2,6 months	0,1,6 months
Trial size	17622	18644
comparator	Placebo with alum	Hepatitis A
Site	Up to 16 countries	14 countries
Age range	16-24; 15-26	15-25
eligibility	≤ 4 sexual partners ( median 2)	≤ 6 sexual partners
exclusion	Hx of abnormal pap smears; pregnancy	Hx of colposcopy, immunocompromised or pregnant
duration	48 month study, 3 year data	Mean 34.9 months

**Intention to treat population  
Or Total Vaccinated cohort  
(ITT/TVC)**

**Per protocol susceptible  
population (PPS/ ATP-E)**

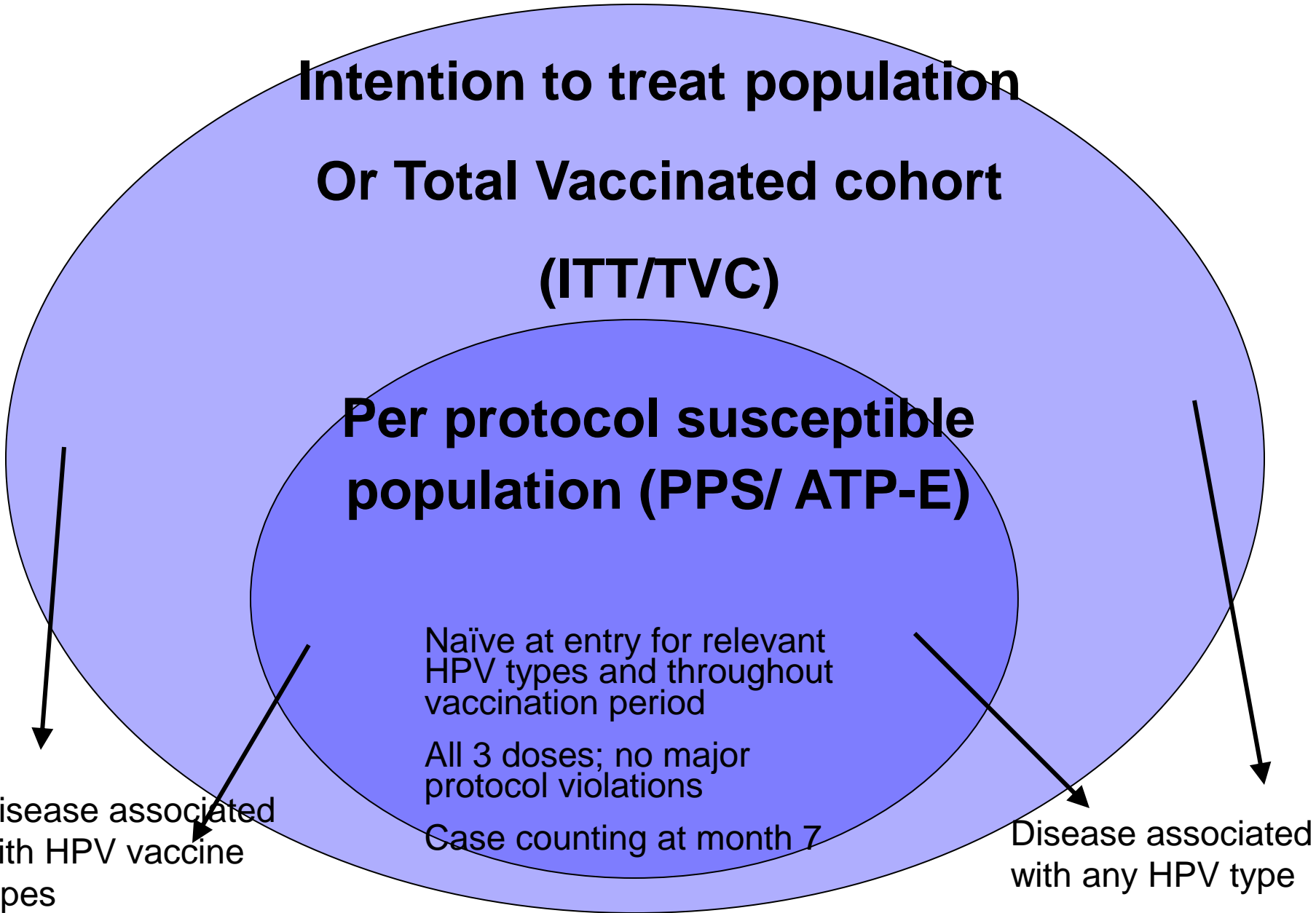
Naïve at entry for relevant  
HPV types and throughout  
vaccination period

All 3 doses; no major  
protocol violations

Case counting at month 7

Disease associated  
with HPV vaccine  
types

Disease associated  
with any HPV type



# FUTURE I: CIN 1, 2, 3, AIS

Quadravalent, Gardasil

Efficacy against disease associated with HPV

6,11,16 or 18:

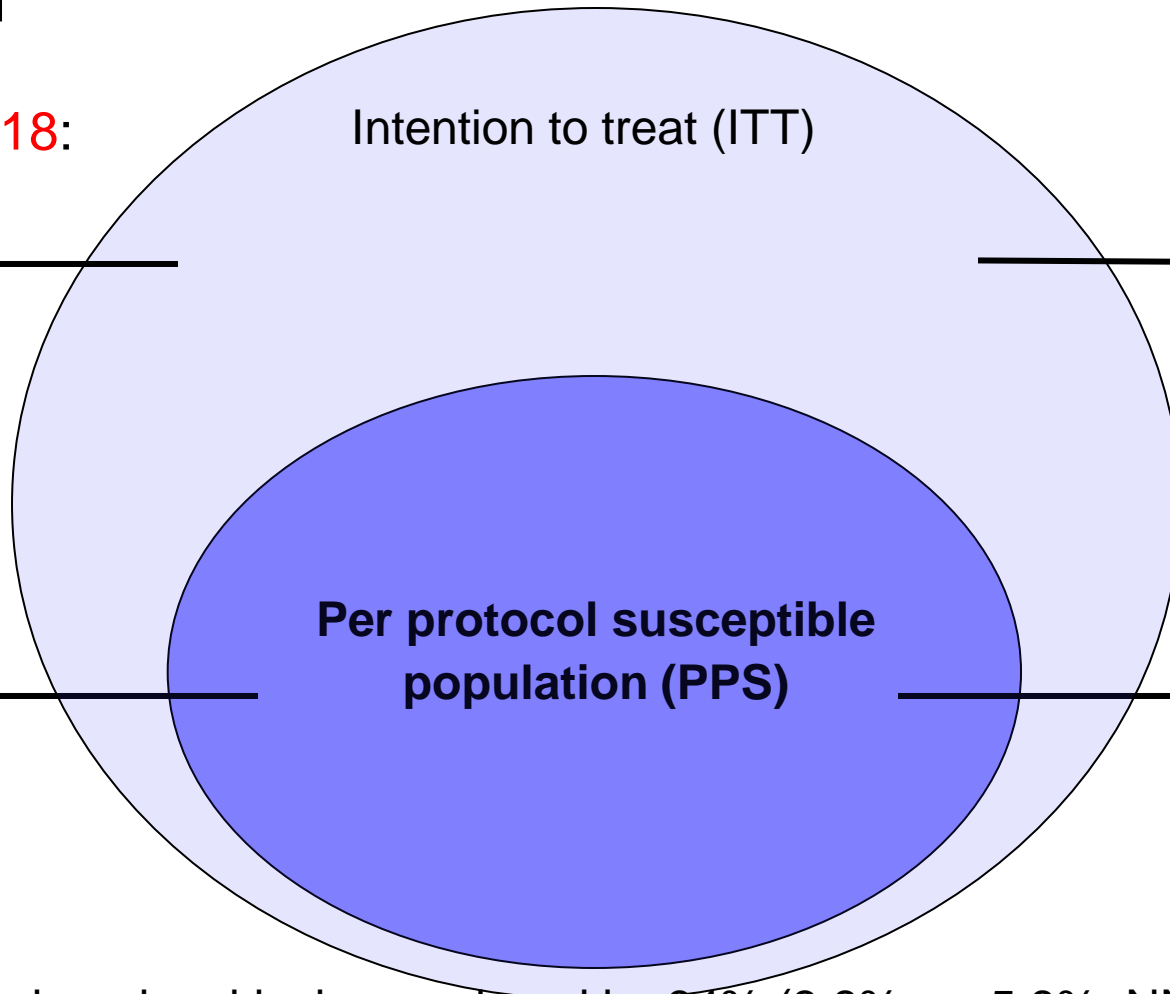
55%  
(2.6, 5.7%;  
32)

100% (0,  
2.6%, 38)

Efficacy against disease regardless of HPV type:

20%  
(12, 15.4%, 29)

Not reported



Vulvar, vaginal, perianal lesions reduced by 34% (3.8% vs. 5.8%; NNT=50).

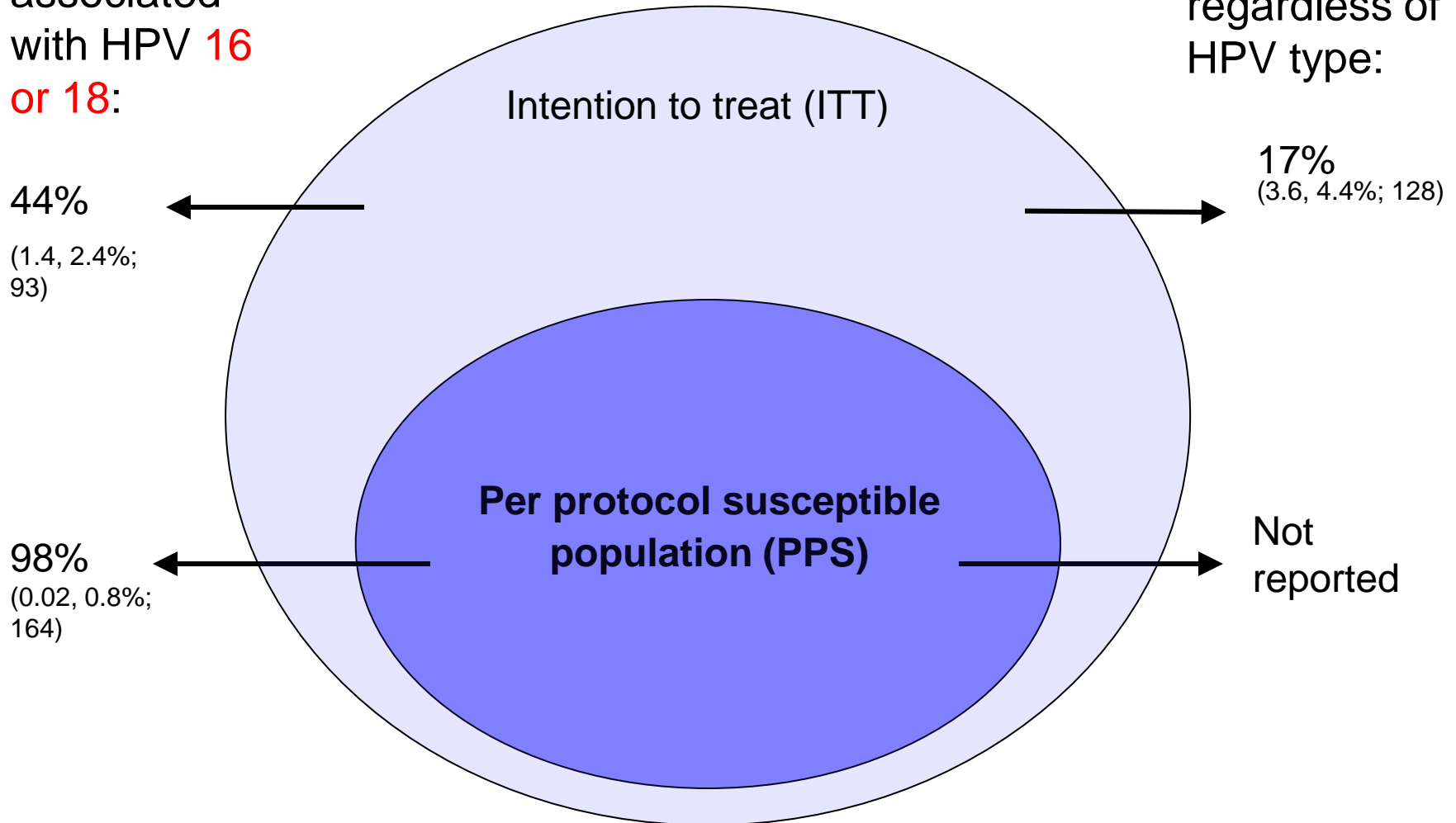
Numbers on parentheses are absolute risks over ~3 years, vaccine vs placebo, with NNT for benefit.

# FUTURE II: CIN 2,3,AIS

Quadravalent, Gardasil

Efficacy against disease associated with HPV 16 or 18:

Efficacy against disease regardless of HPV type:



Numbers on parentheses are absolute risks over ~3 years, vaccine vs placebo, with NNT for benefit.

# PARTICIA: CIN 2,3,AIS

Bivalent, Cervarix

Efficacy against disease associated with HPV 16 or 18:

Efficacy against disease regardless of HPV type:

52.8%  
(37.5-64.7)

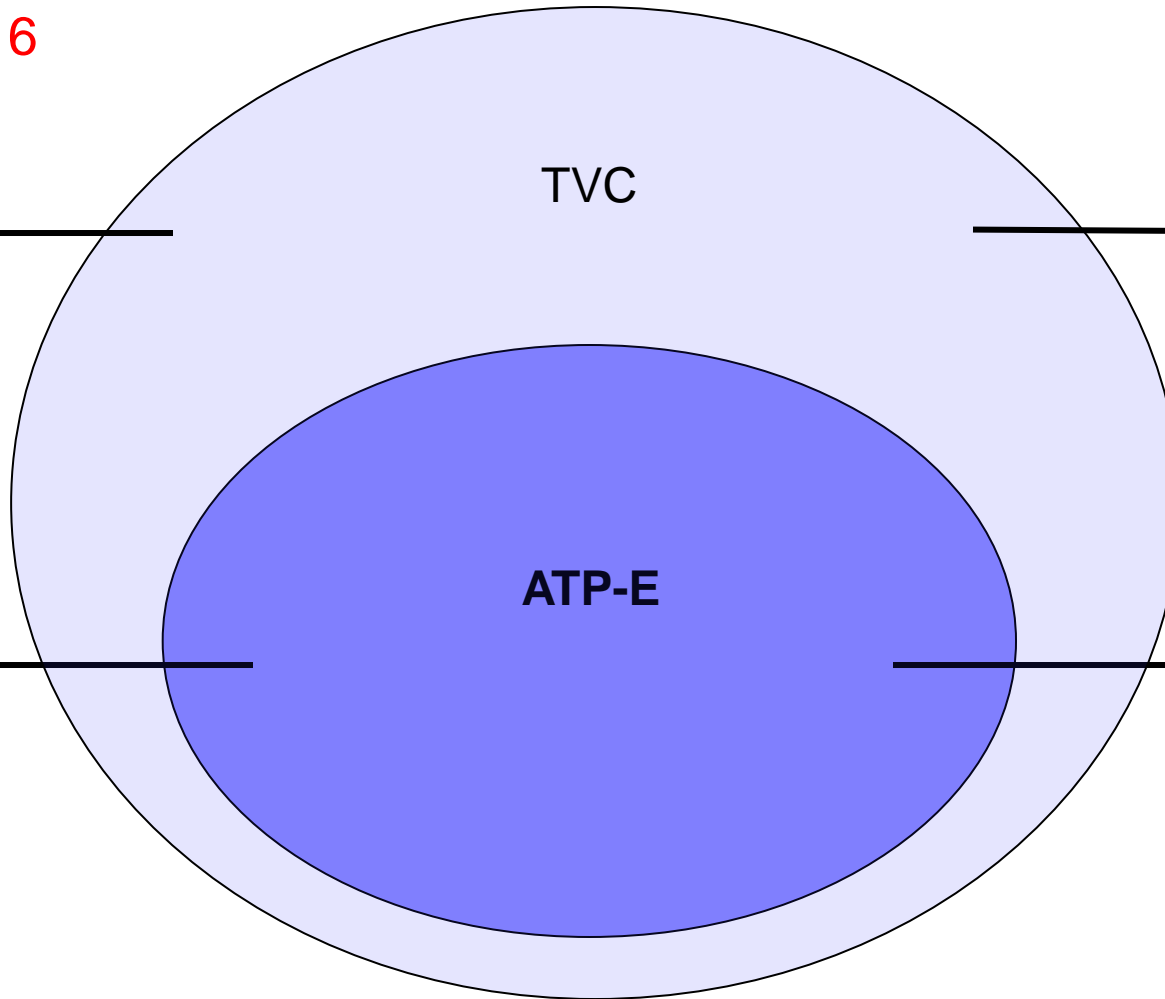
30.4%  
(16.4-42.1)

TVC

92.8%  
(79.9-98.3)

61.9  
(46.7-73.2)

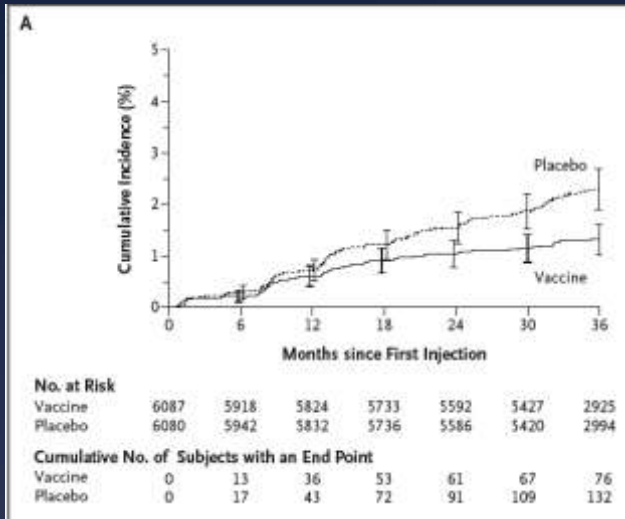
ATP-E



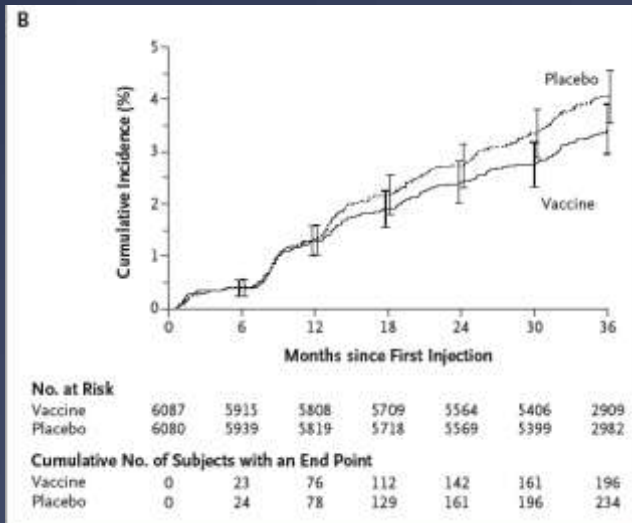
# Cumulative incidence of CIN 2+

## Quadravalent

## Bivalent



Associated with HPV 16/18



Associated with any HPV type

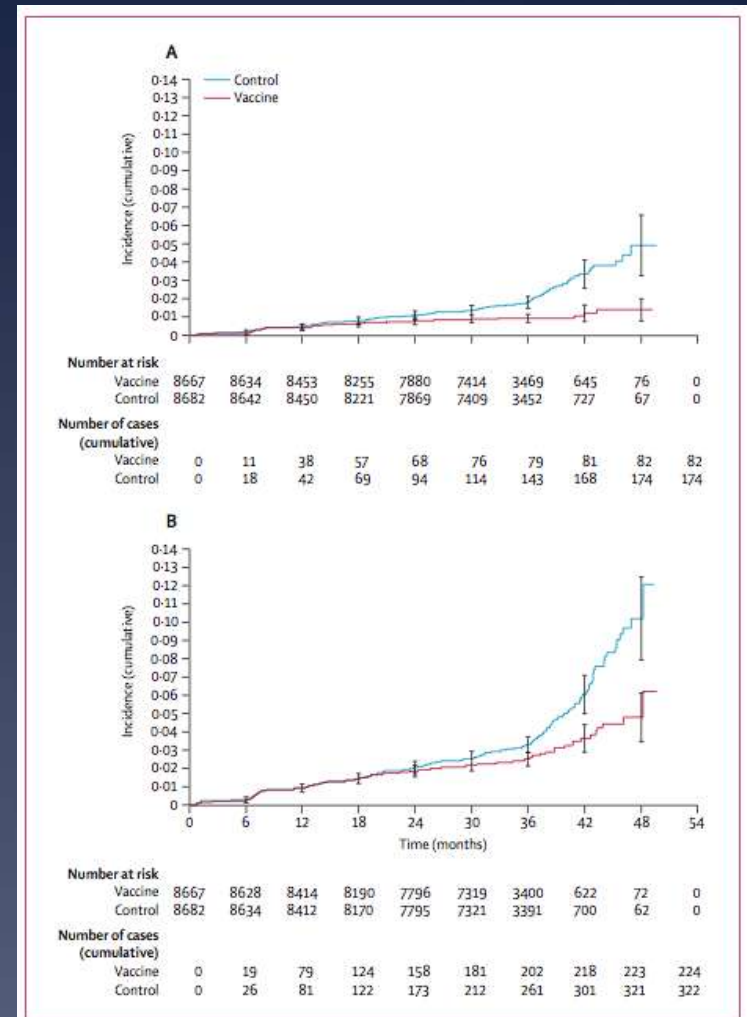


Figure 4: Cumulative incidence of cervical intraepithelial neoplasia grade 2 or more (CIN2+) regardless of human papillomavirus (HPV) DNA status or serostatus at baseline (total vaccinated cohort) (A) associated with HPV-16/18 and (B) irrespective of HPV DNA in the lesion

# Cervarix: Reduction in colposcopy

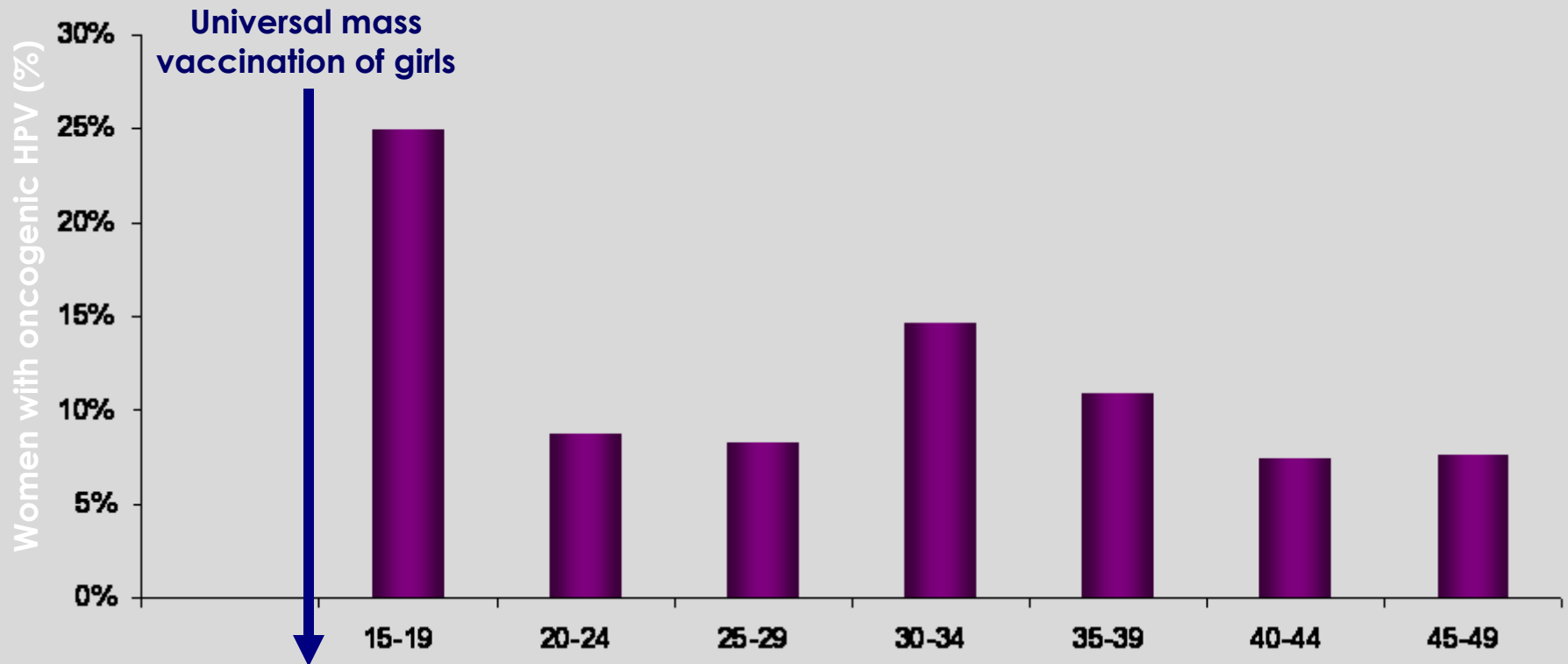
- \* Total Vaccinated cohort:
- \* Reduction in colposcopy referrals: 10.4% (2.3-17.8)
- \* Reduction in number of LEEPs: 24.7% (7.4%-38.9%)

Controversy: is the older woman  
at risk?

What about in the colposcopy  
clinic?

# Women remain at risk during each phase of life

## Incidence of new oncogenic HPV over 14 months in Canadian women previously negative



Efficacy against outcomes associated with HPV 6, 11, 16 or 18:

3,819 sexually experienced women ages 24-35, interim results: **infection  $\geq$  6 months' duration, CIN 1+, external genital lesion**

Efficacy against outcomes regardless of HPV type:

31%



Intention to treat (ITT)



Not reported

91%



Per protocol susceptible population (PPS)



Not reported

Gardasil (Merck)

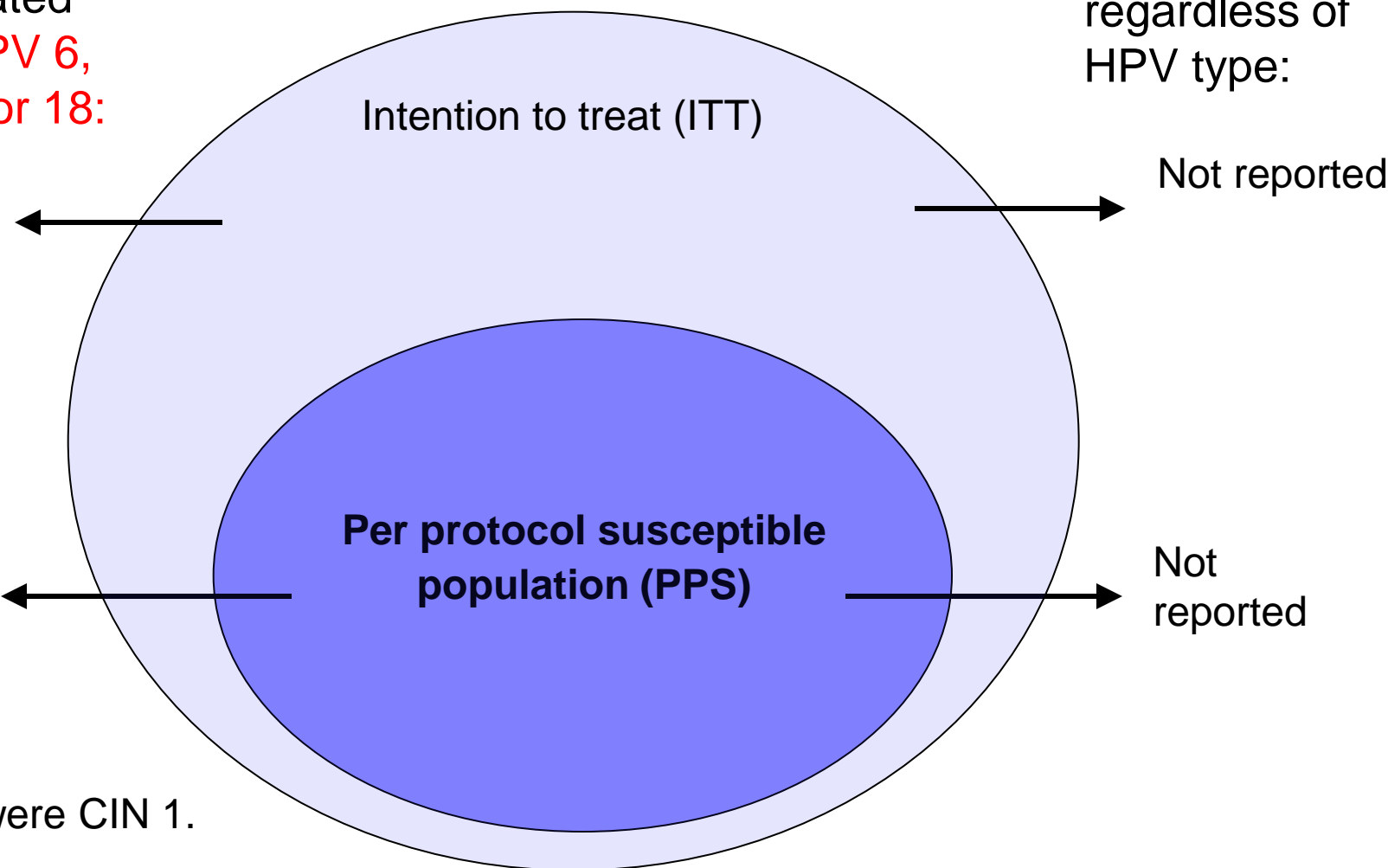
*Munoz et al. Lancet June 6, 2009*

Efficacy against outcomes associated with HPV 6, 11, 16 or 18:

**3,819 women 24-35, interim results:**  
**CIN 1+\*, external genital lesion only**

Efficacy against outcomes regardless of HPV type:

30% (NS)



92%

\*Most were CIN 1.

**Gardasil (Merck)**

*Munoz et al. Lancet June 6, 2009*

# Vaccination in the exposed woman

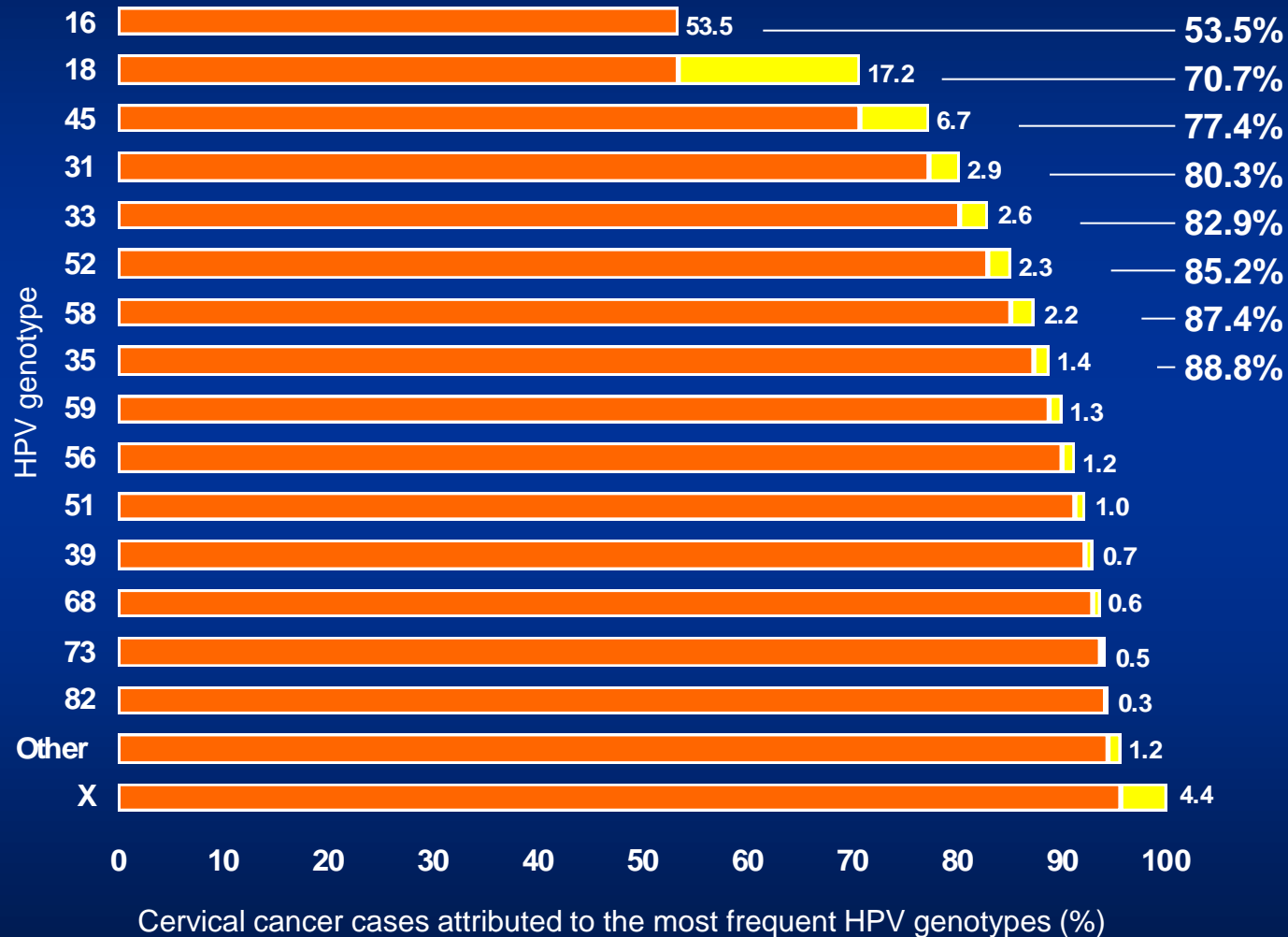
- \* Effective against infection
  - \* Generates an immune response
- \* In trials to date minimal CIN2+
- \* NNV to prevent CIN or EGW 159 women

# Cervarix: Vaccine efficacy in previously exposed women

	DNA +ve	DNA-ve
Seropositive	-13.3%	68.8%
Seronegative	35.2%	94.6%
	5.8%	92.4%

Fact: Cross Protection exists

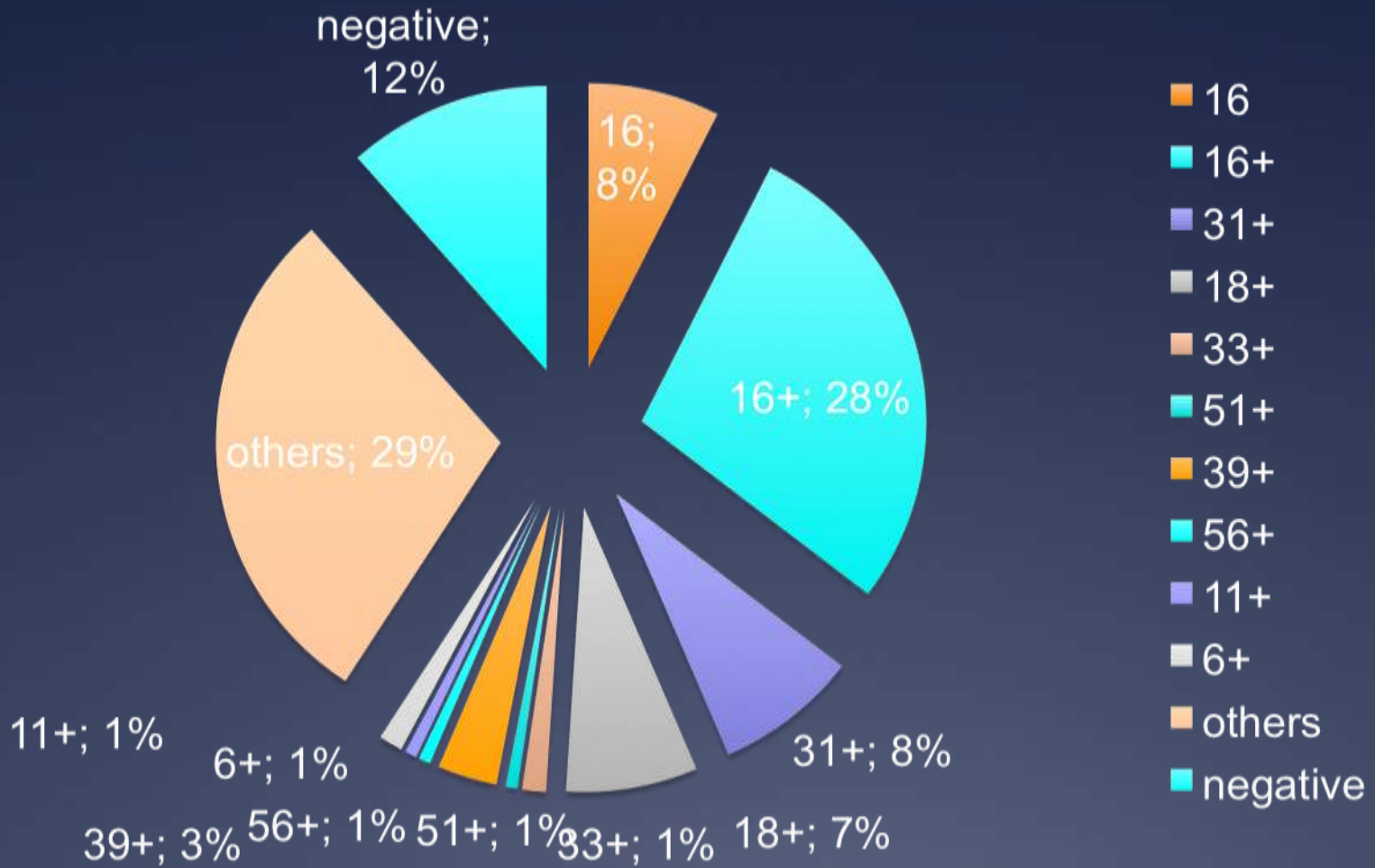
# HPV types in cervical cancer



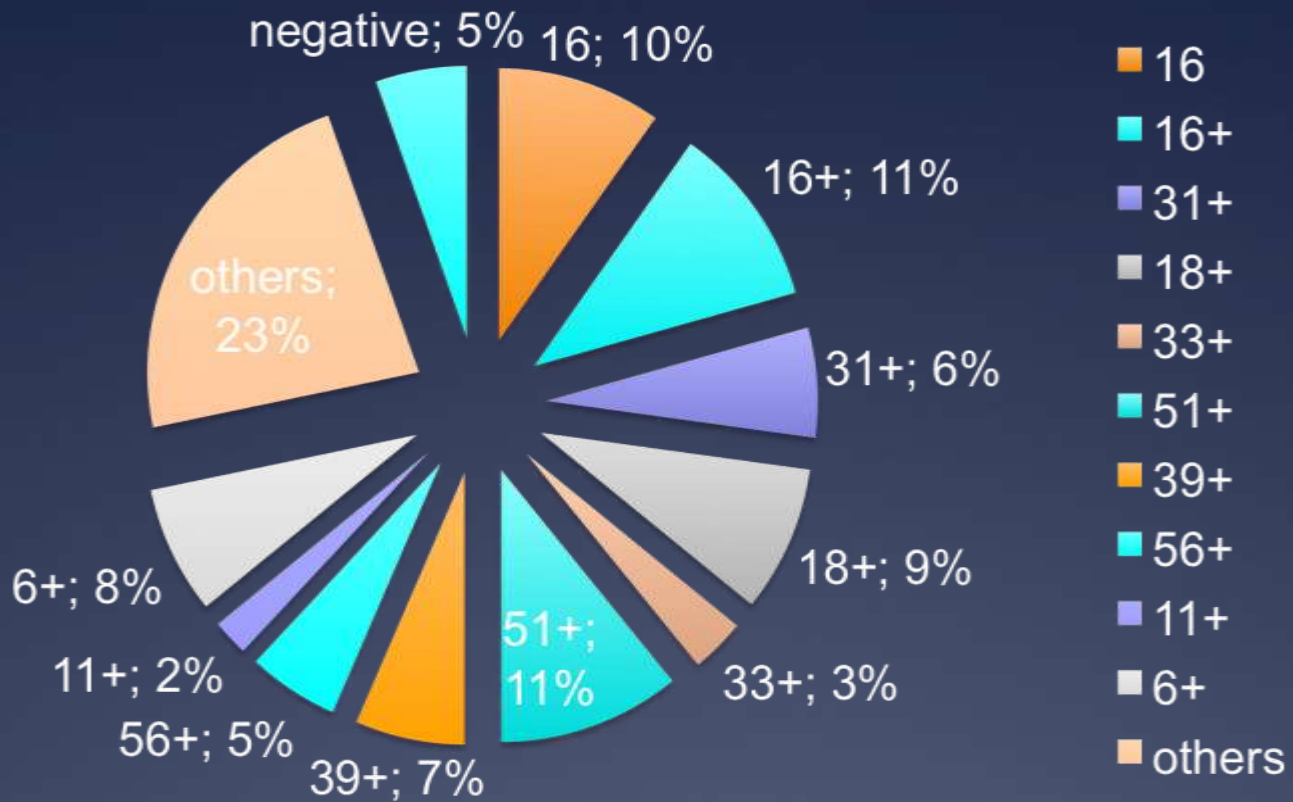
# HPV Vaccines: Cross Protection against lesions

	Gardasil(Merck) Quadrivalent	Cervarix (GSK) Bivalent
HPV 31 (related to 16)	V/P 5/21 Reduction 76%	V/P 2/25 Reduction 92%
HPV 33	V/P 7/13	V/P 12/25 Reduction 51%
HPV 45 (related to 18)	V/P 3/2	V/P 0/4 Reduction 100%(NS)
HPV 52	V/P 12/16	V/P 12/14 Reduction 14%
HPV 58	V/P 9/13	V/P 6/17 Reduction 64%
Any oncogenic except 16/18	V/P 38/62 Reduction 38%	V/P 50/109 Reduction 54%

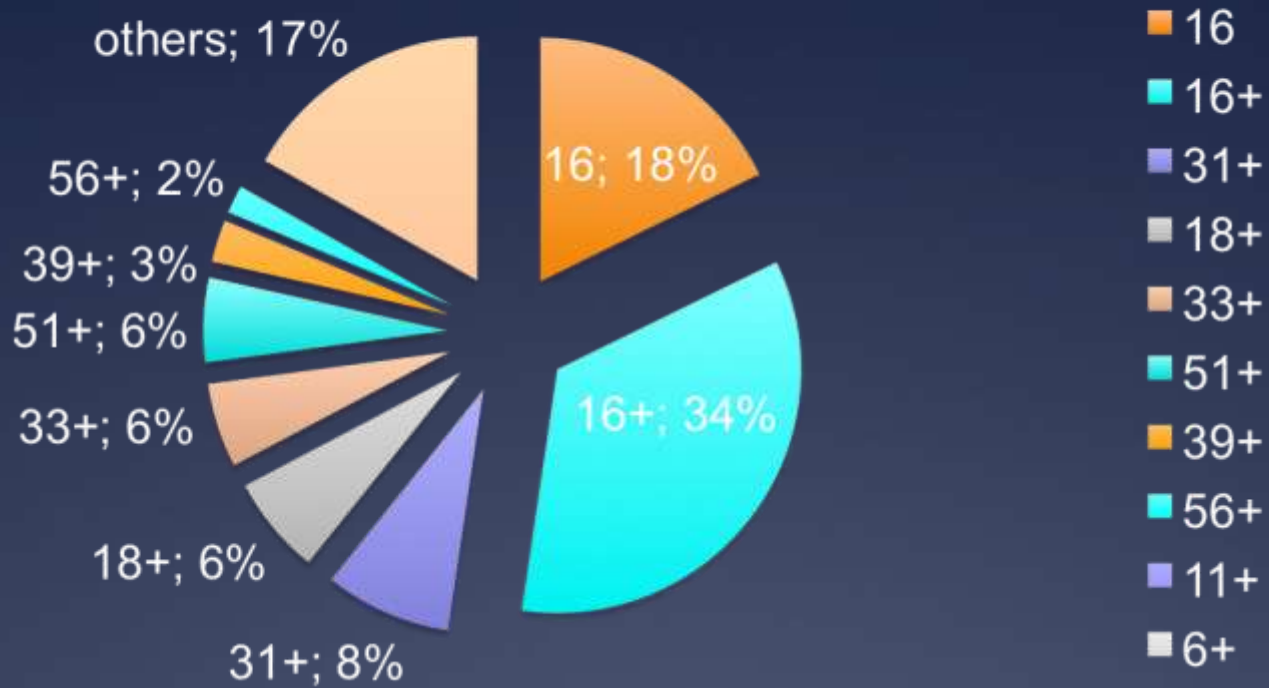
# Negative



# CIN1



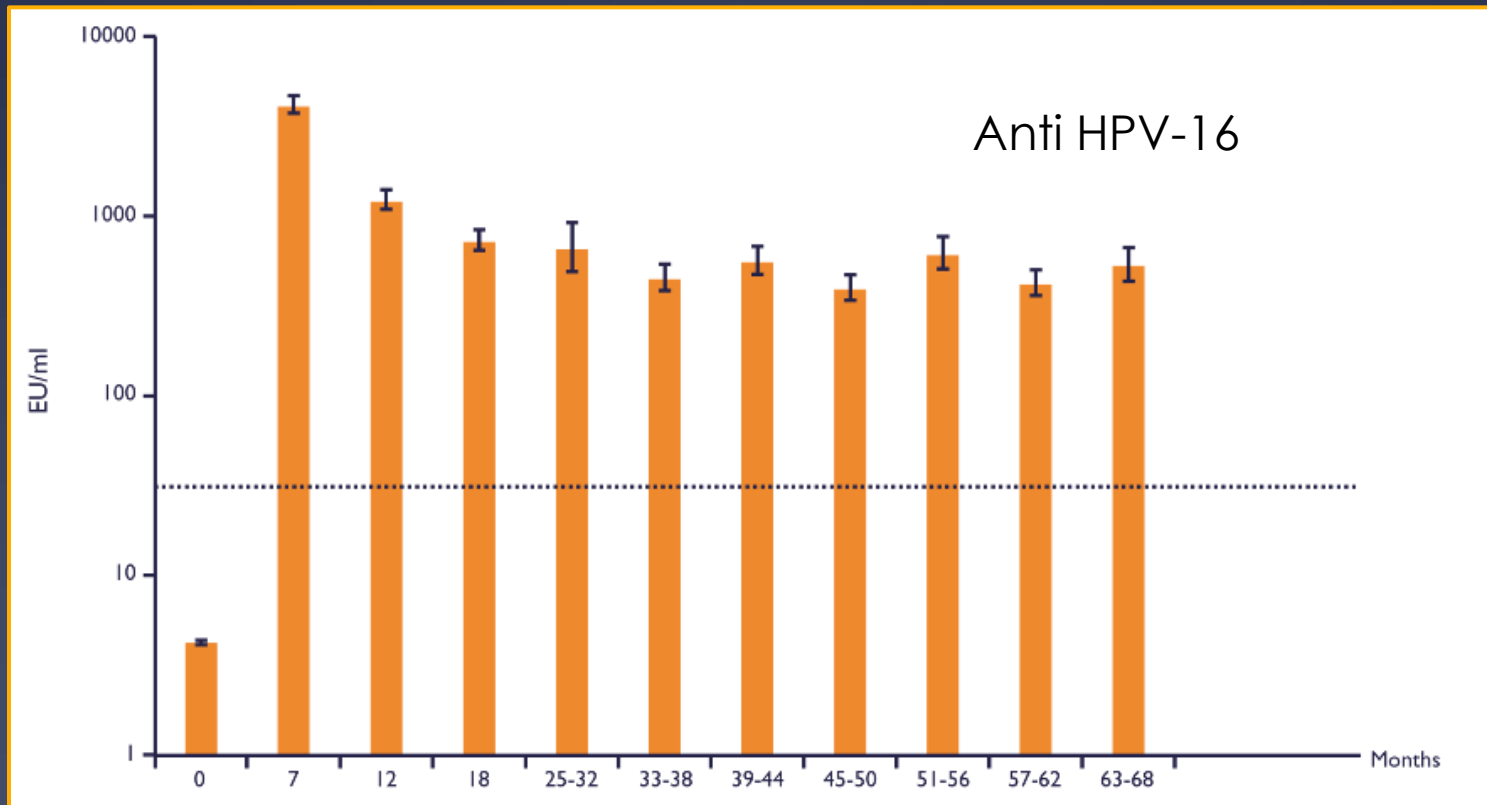
# CIN2 +



Controversy: will a booster shot  
be needed?

# HPV Vaccination: Duration of action

- \* Current data supports 6.5 years with signs of break through cases



Controversy: male vaccination

# HPV Vaccination: Men

- \* Shown to be equally immunogenic in boys < 15 years of age
- \* Prevention of HPV related disease in women
- \* Prevention of HPV related disease in men
  - \* Warts
  - \* Anal cancer
  - \* Penile cancer
  - \* Oral Cancers

## Palefsky et al. Efficacy of the Quadrivalent HPV vaccine against 6/11/16/18- related genital infection in young men

- \* RCT 4065 men 16-26 (MSM and heterosexual)
- \* 36 months of follow-up looking for HPV DNA and lesions
- \* Per protocol evaluation done on those seronegative at day 1 and month 7
- \* Analysis done on 1390 vaccine subjects and 1400 controls, looking for effect on persistent infection
  - \* HPV all 4 types persistent infection 85.6% effective
  - \* HPV-6 88%, HPV-11 93.4%, HPV-16 78.7%, HPV-18 96^
- \* Quadrivalent vaccine is effective at preventing persistent infection

# HPV Vaccination: Men

- \* Cost efficacy to prevent Ca Cervix
  - \* Not if >75% of women are vaccinated
- \* No estimations looking at the benefit in males for male cancers
- \* May benefit individual....

Controversy: safety of the  
vaccine.....

# Safety/Adverse Events

	GARDASIL Quadravalent			CERVARIX Bivalent		
14 days after injection	<b>Gardasil (14 days after injection) (n=5088)%</b>	Alum Placebo (n=3470)%	Saline Placebo (n=320)%	<b>Cervarix (7 days after injection) (n=22806)%</b>	Alum Placebo (n=4485)%	HAV 720 (n=8750)%
Injection site						
Pain	<b>83.9</b>	75.4	48.6	<b>78</b>	52.5	58.9
Swelling	<b>25.4</b>	15.8	7.3	<b>25.8</b>	8.2	10.1
Erythema	<b>24.6</b>	18.4	12.1	<b>29.6</b>	10.6	16.1
Puritis	<b>3.1</b>	2.8	0.6	<b>Not noted</b>	Not noted	Not noted
Systemic						
Fever(>37.8°C )	<b>10.3</b>	8.6		<b>5.1</b>	5.2	4.6
Nausea	<b>4.2</b>	4.1		<b>12.9</b>	11.6	14.0
Diarrhea	<b>1.2</b>	1.5				
Dizziness	<b>2.8</b>	2.6				

Data taken from product monograph Canada and Australia

# Serious Adverse Events

	Gardasil: Quadravalent Future I/II	Cervarix: Bivalent ( Paavonen 2007)
SAE's related to vaccination	48/2673 in vaccine vs. 45/2672 placebo <sup>1</sup> 1 vaccine related event 2 deaths in each group	9/9319 SAE's in vaccine vs. 6/9325 placebo <sup>2</sup>
New onset chronic disease		143 vaccine vs. 154 placebo <sup>2</sup>
New onset autimmune disease	27/13091 vaccine vs 20/11792 placebo <sup>1</sup>	31 vaccine vs. 26 placebo <sup>2</sup>

**NO SIGNIFICANT DIFFERENCE BETWEEN VACCINE  
AND PLACEBO**

- Fainting has also been reported

<sup>1</sup>Garland et al. NEJM 2007: 356;1928-43

<sup>2</sup> Paavonen et al. Lancet 2007: 369; 2161-2170

# Allergic Reactions

- \* Australia <sup>1</sup>:
  - \* 2.2 million doses given
  - \* 10 cases of anaphylaxis; 48 cases of urticaria
  - \* Rate of 5.1 per million doses (1.7 per million internationally)
  - \* Compares to 0 to 3.5 per million doses for other vaccines

## Guillain-Barre Syndrome

- USA <sup>2</sup>:
  - More than 7 million doses given
  - 13 cases concerning GBS, 2 met the case definition
  - 6 occurred with concurrent Menactra vaccine; being investigated
  - 13 reports of GBS is within the expected range
    - GBS occurs at a rate of 1-2/100000 person years

<sup>1</sup> <http://www.tga.gov.au/alerts/medicines/gardasil.htm> Nov 2007 accessed Jan 20 2008

<sup>2</sup> <http://www.cdc.gov/vaccines/vpd-vac/hpv/downloads/hpv-gardasil-gbs.pdf> Aug 2007 accessed Jan 20 2008

# Conclusion

- \* HPV Vaccination is safe
- \* Vaccination before exposure is effective
- \* Men may benefit to reduce warts (+ cancers)
- \* Older women may benefit but...
  - \* Lesser impact
- \* No evidence for use in the colposcopy clinic
  - \* Individual may benefit but need to vaccinate many women to benefit one

# Conclusion

- \* Pap always vaccinate ideally