Human Papillomavirus and vaccination

National Study Day

for

Irish Cervical Screening Programme

Limerick, 22nd March 2007

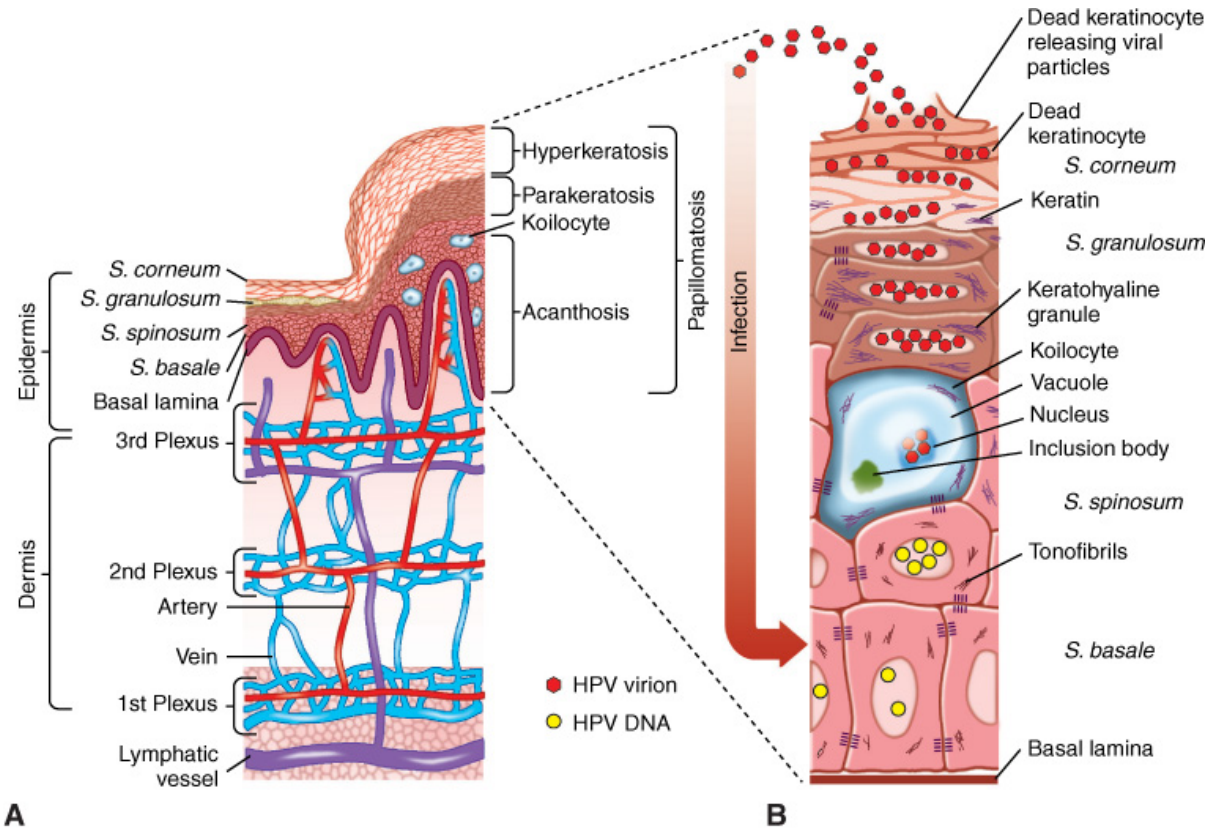
Dr. Aidan P. O'Hora

Objectives

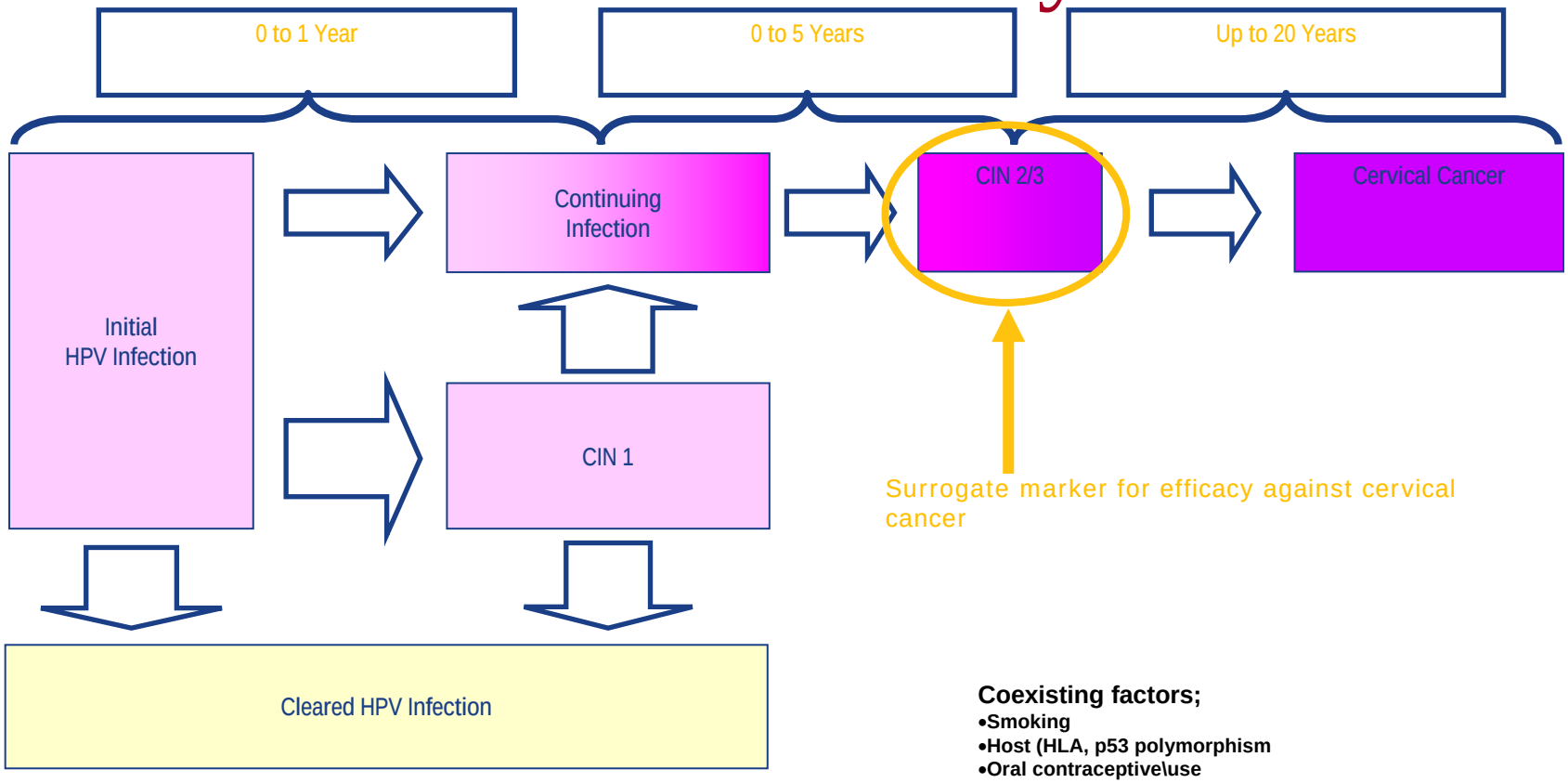
- Human Papillomaviruses
- Epidemiology of HPV
- HPV Vaccines
  - What we know
  - What we don't know
- Conclusions & Discussion

Natural History

Human Papillomaviruses



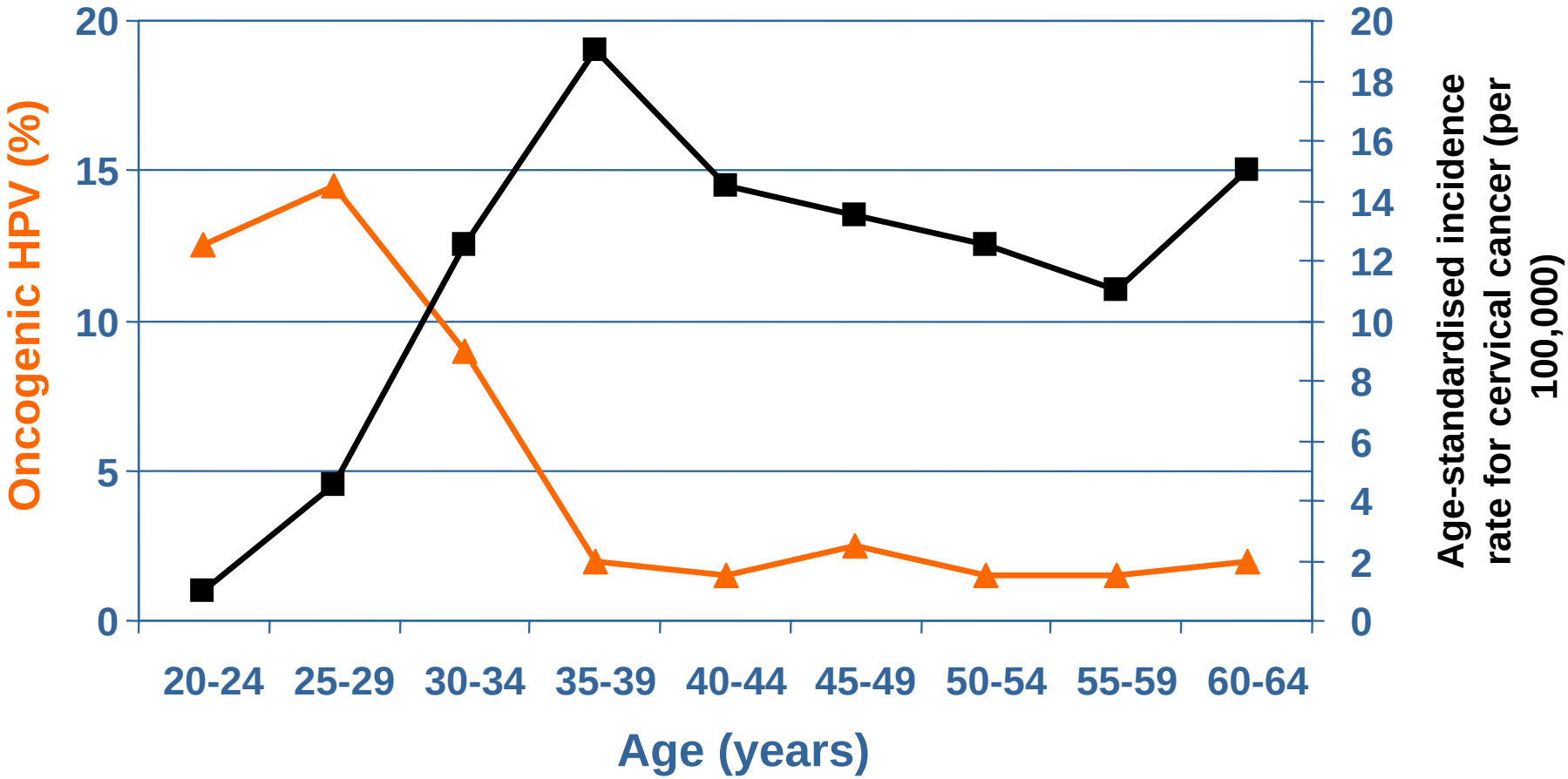
Natural History



Coexisting factors;

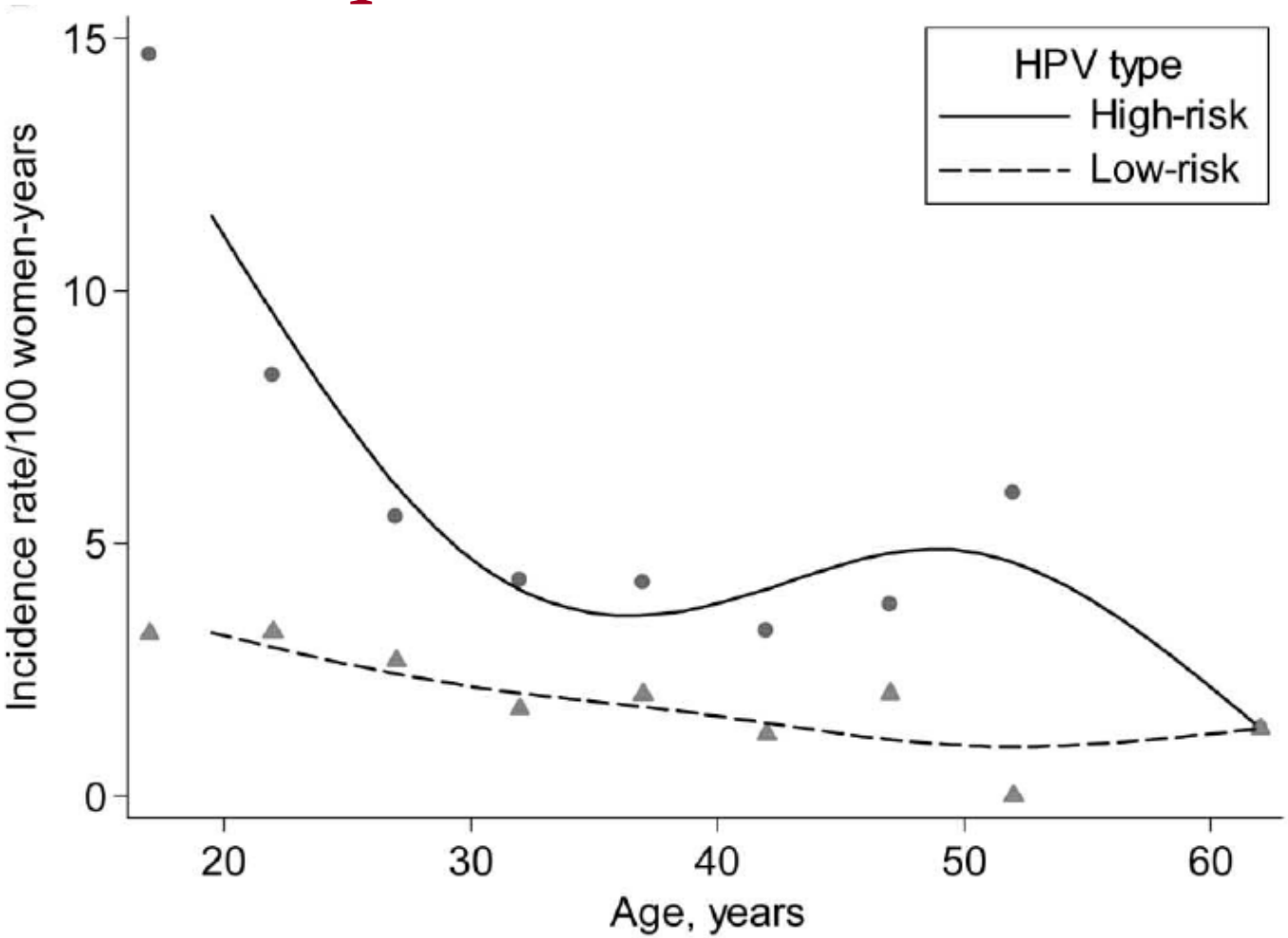
- **Smoking**
- **Host (HLA, p53 polymorphism**
- **Oral contraceptive\use**
- **Parity**
- **Other STDs**
- **Nutrition**

Age-specific Incidence

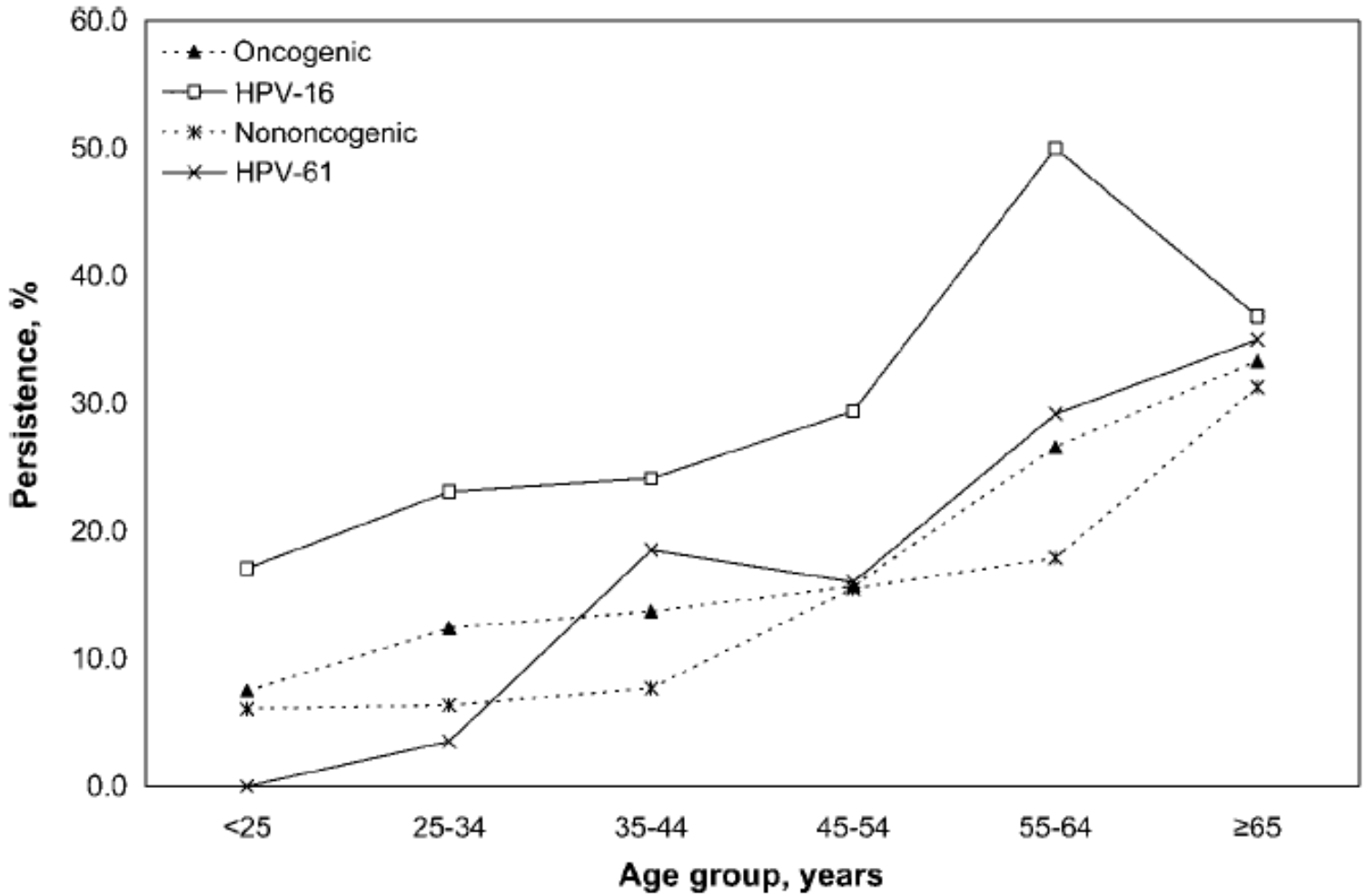


Bosch FX et *al*. *J Clin Pathol* 2002; 55: 244–65.

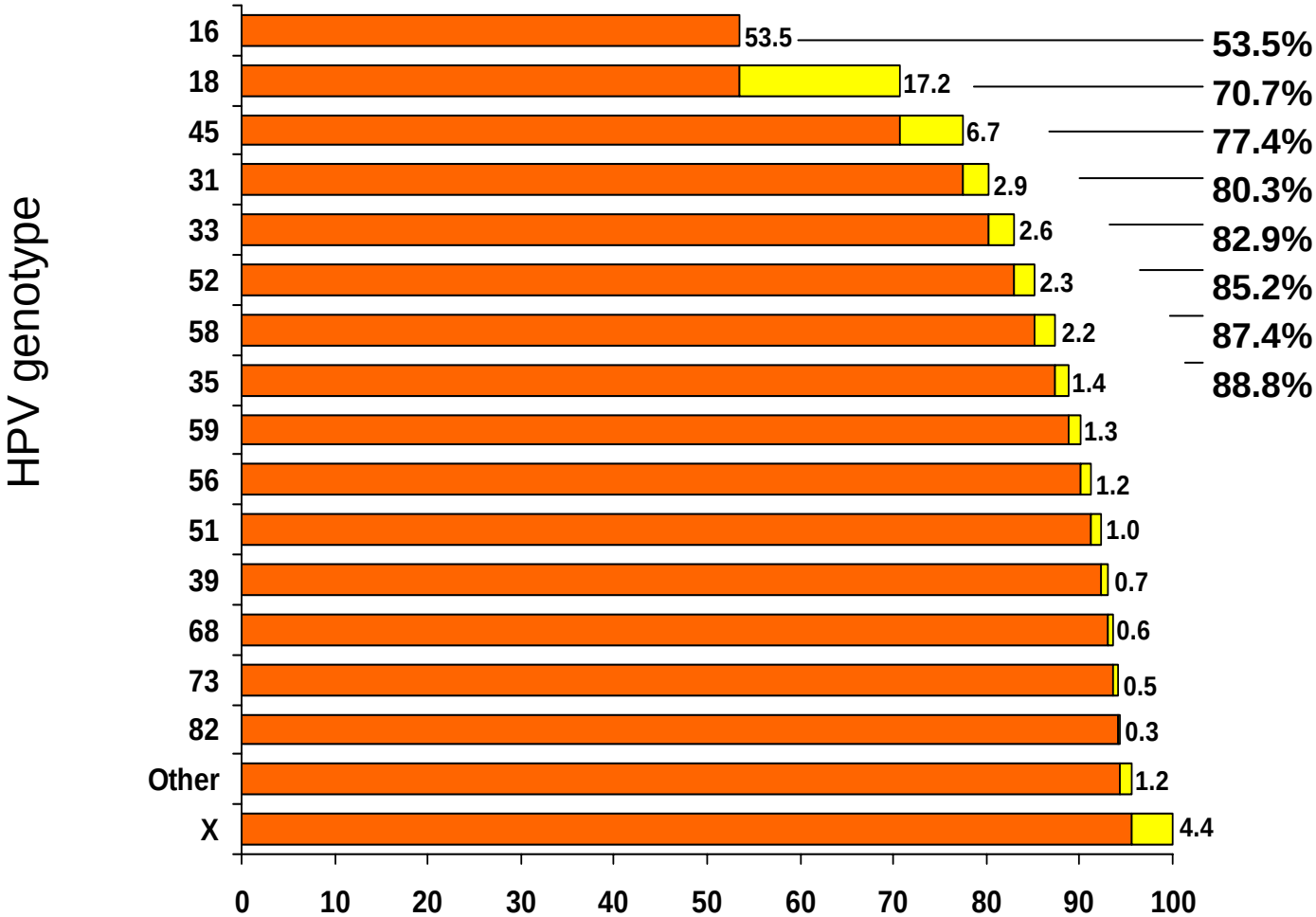
HPV acquisition



HPV Persistence

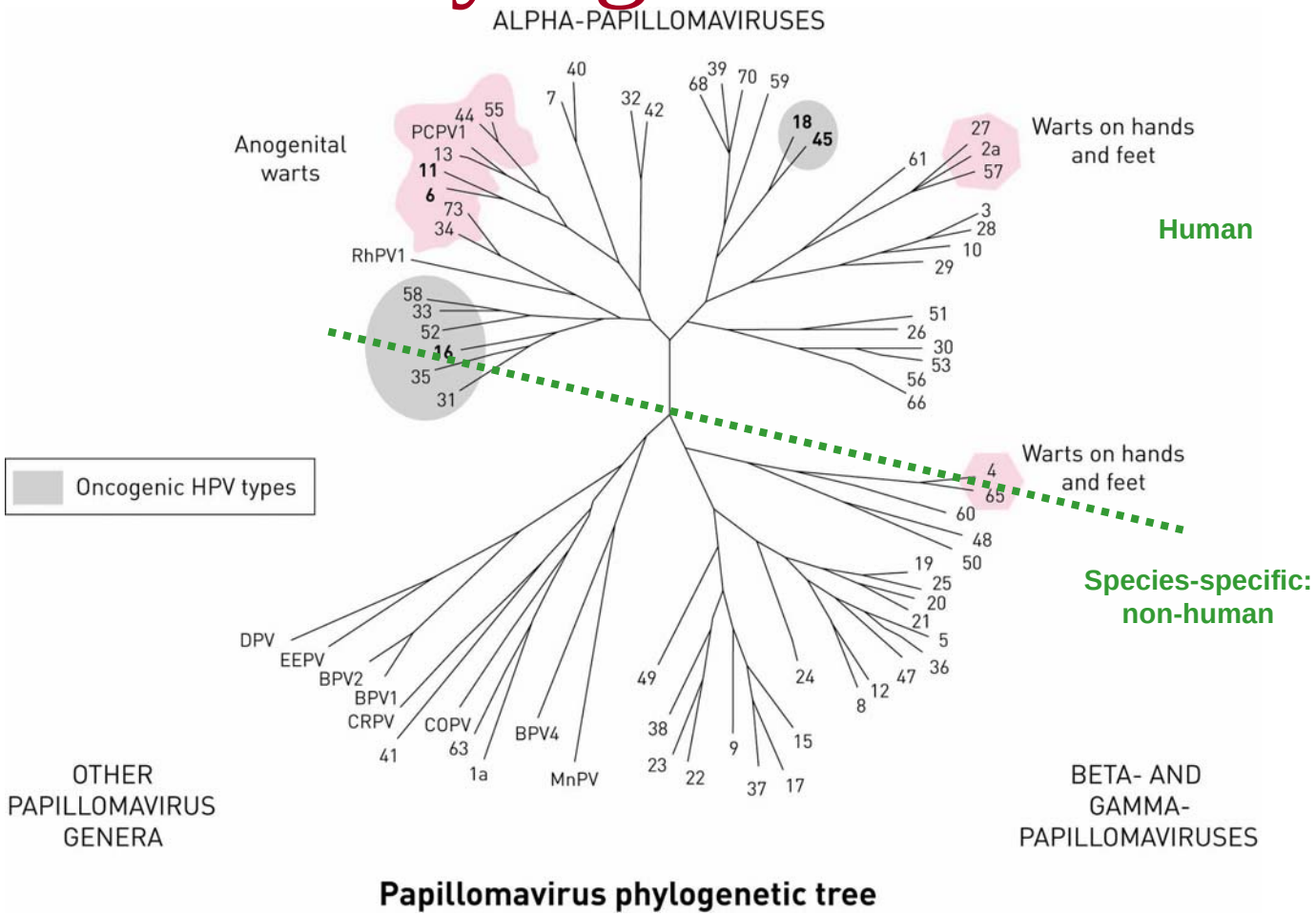


Cervical cancer cases attributed to the most frequent HPV genotypes (%)



Source: Muñoz N et al. Int J Cancer 2004; 111: 278–85

Phylogenetic Tree



Papillomavirus phylogenetic tree

de Villiers EM *et al. Virology* 2004; 324: 17–27.

Human Papillomaviruses

Classification	**HPV Types**
High Risk or carcinogenic	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Probably carcinogenic	26, 53, 66, 68, 73, 82
Low-risk	6,11, 40, 42, 43, 44, 54, 61, 70, 72, 81, 89

Type of Cancer	Papillomavirus types involved	Percentage of cases HPV-positive
Cervical	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 (26, 68, 73, 82)	>95
Vulval: Basaloid Warty Keratinizing	16, 18 16, 18 16	>50 >50 <10
Penile: Basaloid Warty Keratinizing	16, 18 16, 18 16	>50 >50 <10
Vaginal	16,18	>50
Anal	16, 18	>70
Oral cavity and tonsils	16, 18, 33	~25
Nail bed	16	~75

Global Distribution

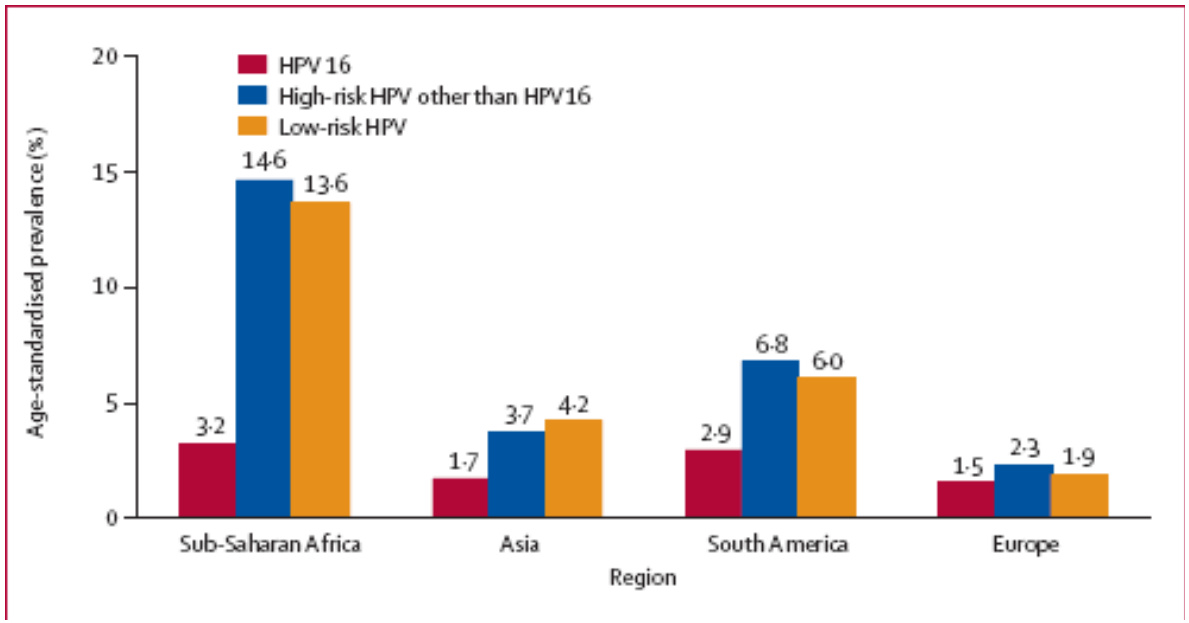
HPV DNA

- 9.2% of all women HPV +ive
  - 6.1% HR HPV
  - 2.5% LR HPV
  - 0.5% HPV X
- HPV + women
  - 66.8% HR HPV
  - 27.7% LR HPV
  - 5.5 % HPV X

	HPV 16 (%)	HR HPV (other than HPV16) (%)	LR HPV (%)
Sub-saharan Africa	3.2	14.6	13.6
Asia	1.7	3.7	4.2
South America	2.9	6.8	6.0
Europe	1.5	2.3	1.9

Source: Parkin et al. Int J Cancer 2006.

HPV DNA


HPV 16
High-risk HPV other than HPV16
Low-risk HPV
Age-standardised prevalence (%)
20
15
10
5
0
14·6
13·6
3·2
1·7
3·7
4·2
2·9
6·8
6·0
1·5
2·3
1·9
Sub-Saharan Africa
Asia
South America
Europe
Region

Global Burden of HR HPV Disease

Site	AF (%)	Attributable cancers	% all cancers
Cervix	100	492,800	4.5
Penis	40	10,500	0.1
Vulva, vagina	40	16,000	0.2
Anus	90	27,400	0.2
Mouth	3	8,200	0.1
Oro pharynx	12	6,300	0.1
All sites		561,200	5.2

Source: Parkin et al. Int. J Cancer 2006.

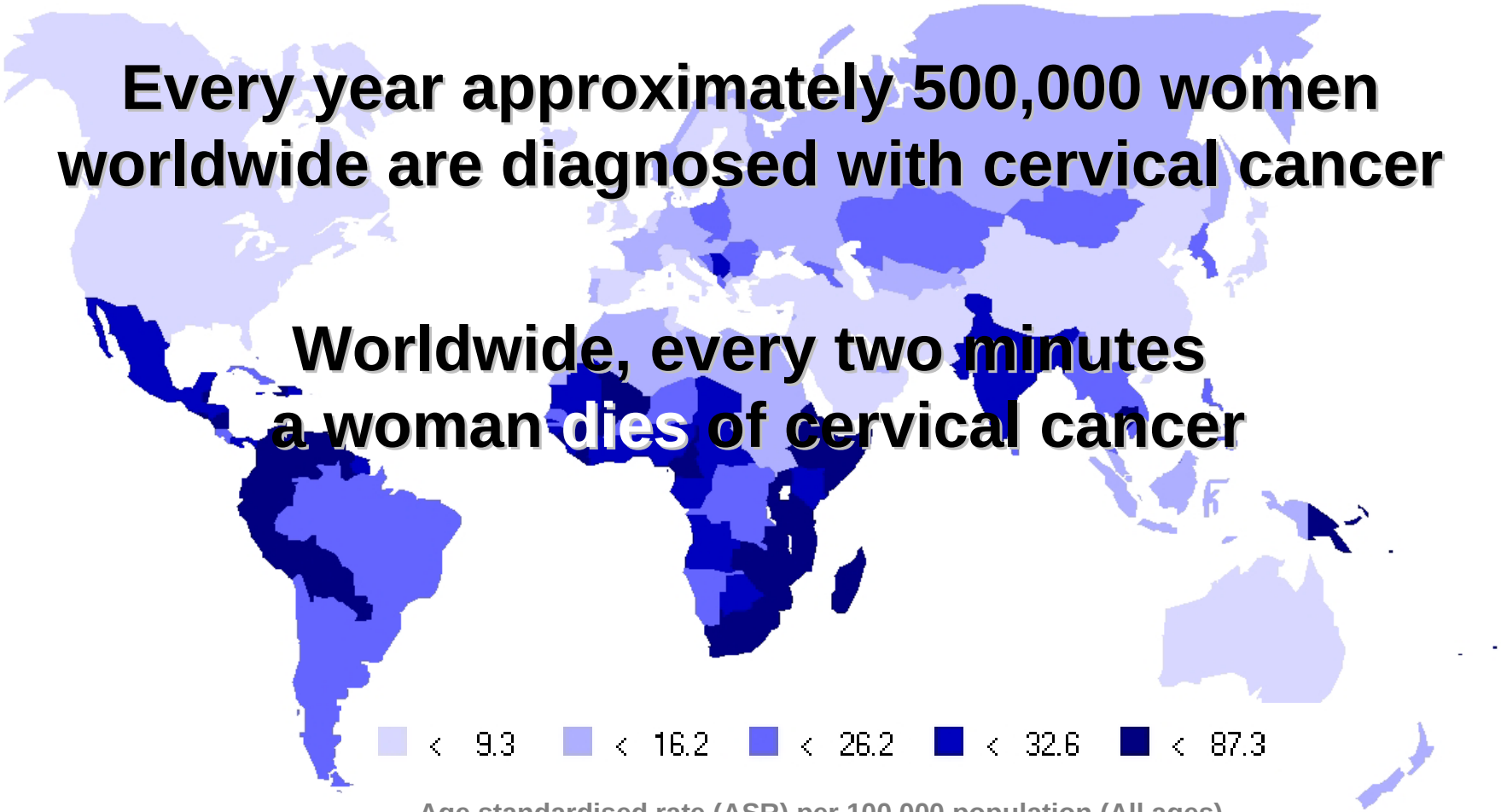
Burden of HR HPV Disease in Developed Countries

Site	AF (%)	Attributable cancers	% all cancers
Cervix	100	83,400	1.7 **7.0**
Penis	40	2,100	0.04 **0.14**
Vulva, vagina	40	7,300	0.2 **0.2**
Anus	90	13,100	0.3 **0.2**
Mouth	3	2,700	0.1 **0.1**
Oro pharynx	12	2,900	0.1 **0.1**
All sites		111,500	2.2 **7.7**

Source: Parkin et al. Int. J Cancer 2006.

Every year approximately 500,000 women worldwide are diagnosed with cervical cancer

Worldwide, every two minutes a woman dies of cervical cancer



Age standardised rate (ASR) per 100,000 population (All ages)

Source: Ferlay J et al. GLOBOCAN 2002. IARC 2004.

Cervical Cancer

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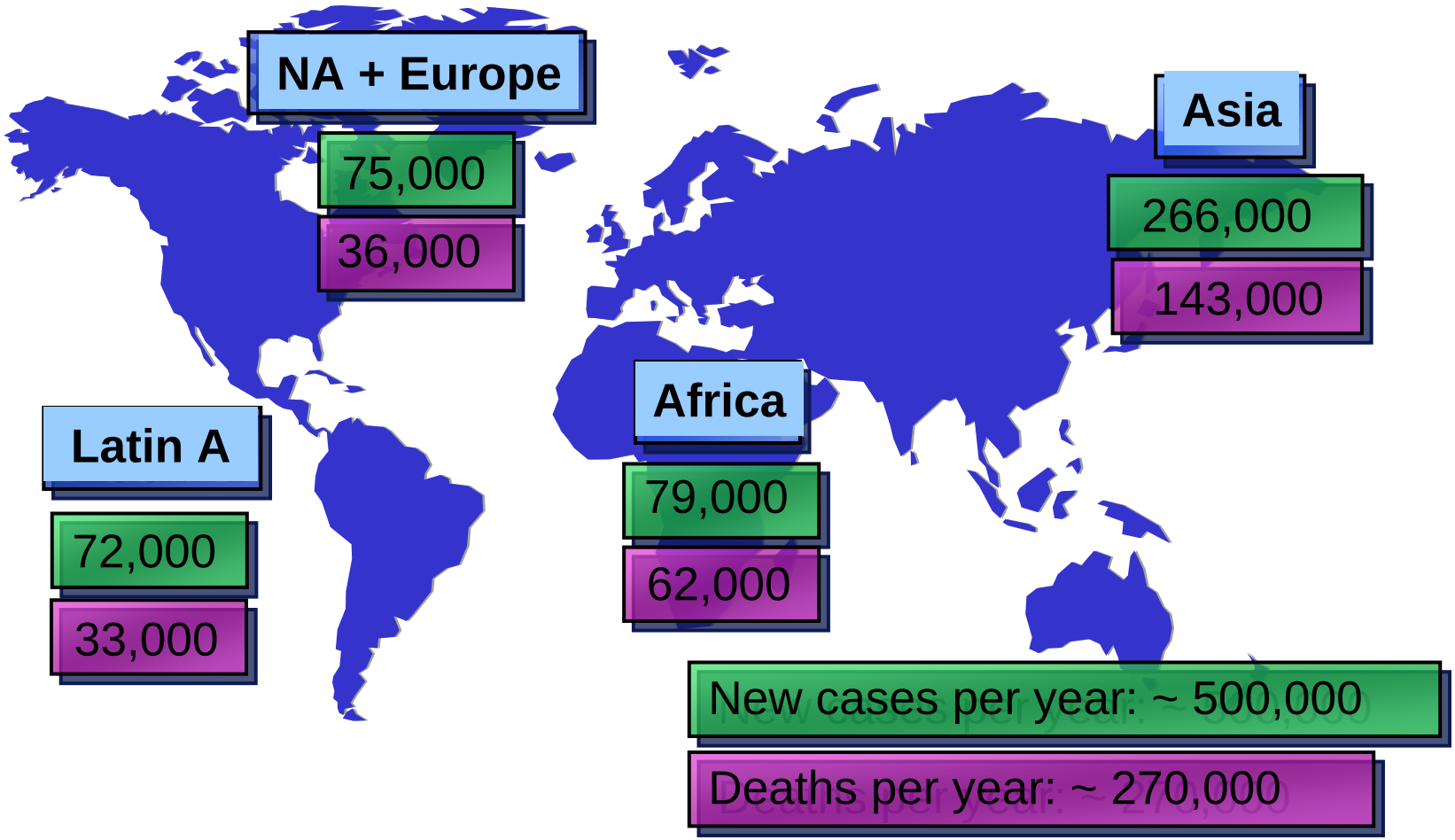
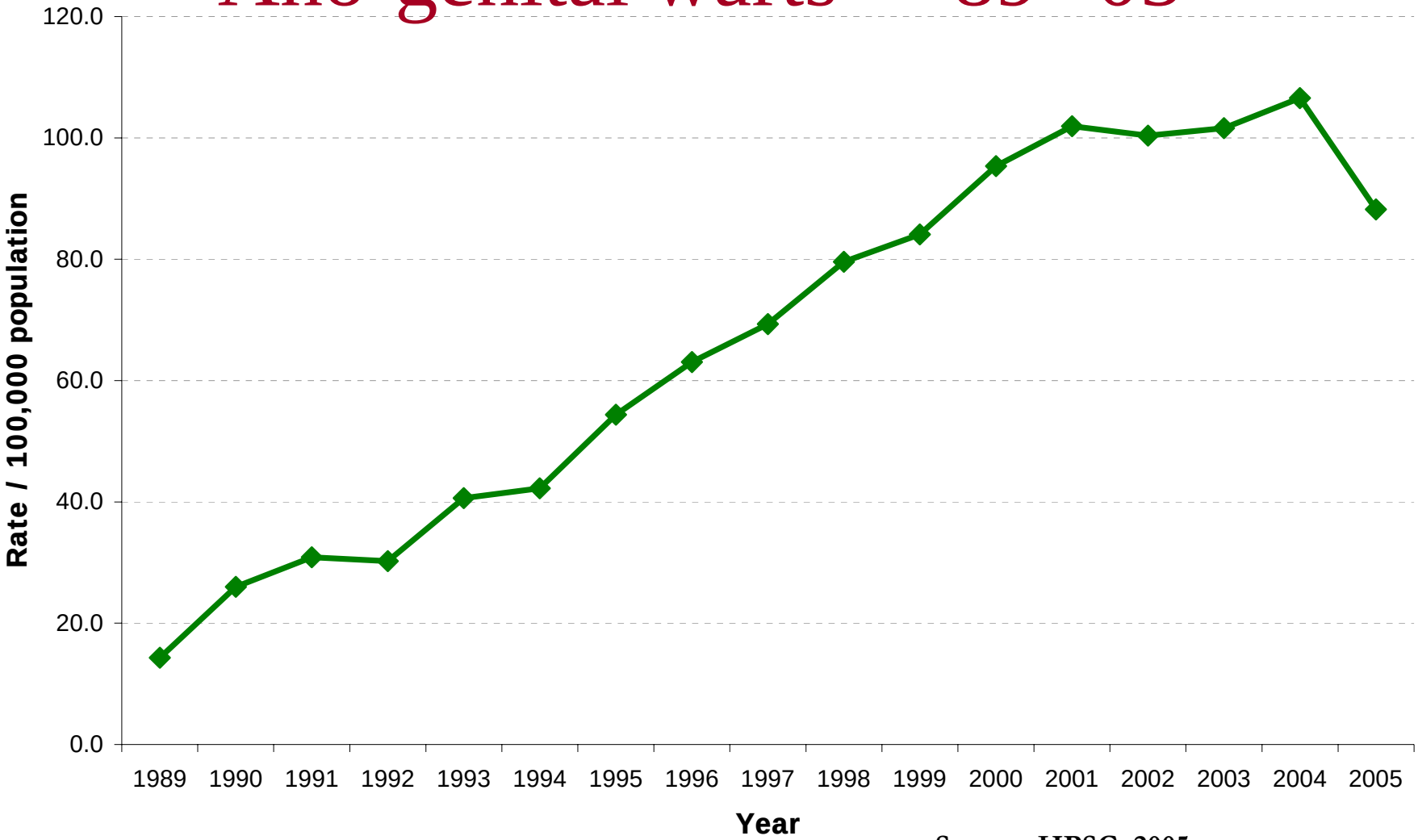


Source: Ferlay J et al. GLOBOCAN 2002. IARC 2004.

Burden of Disease

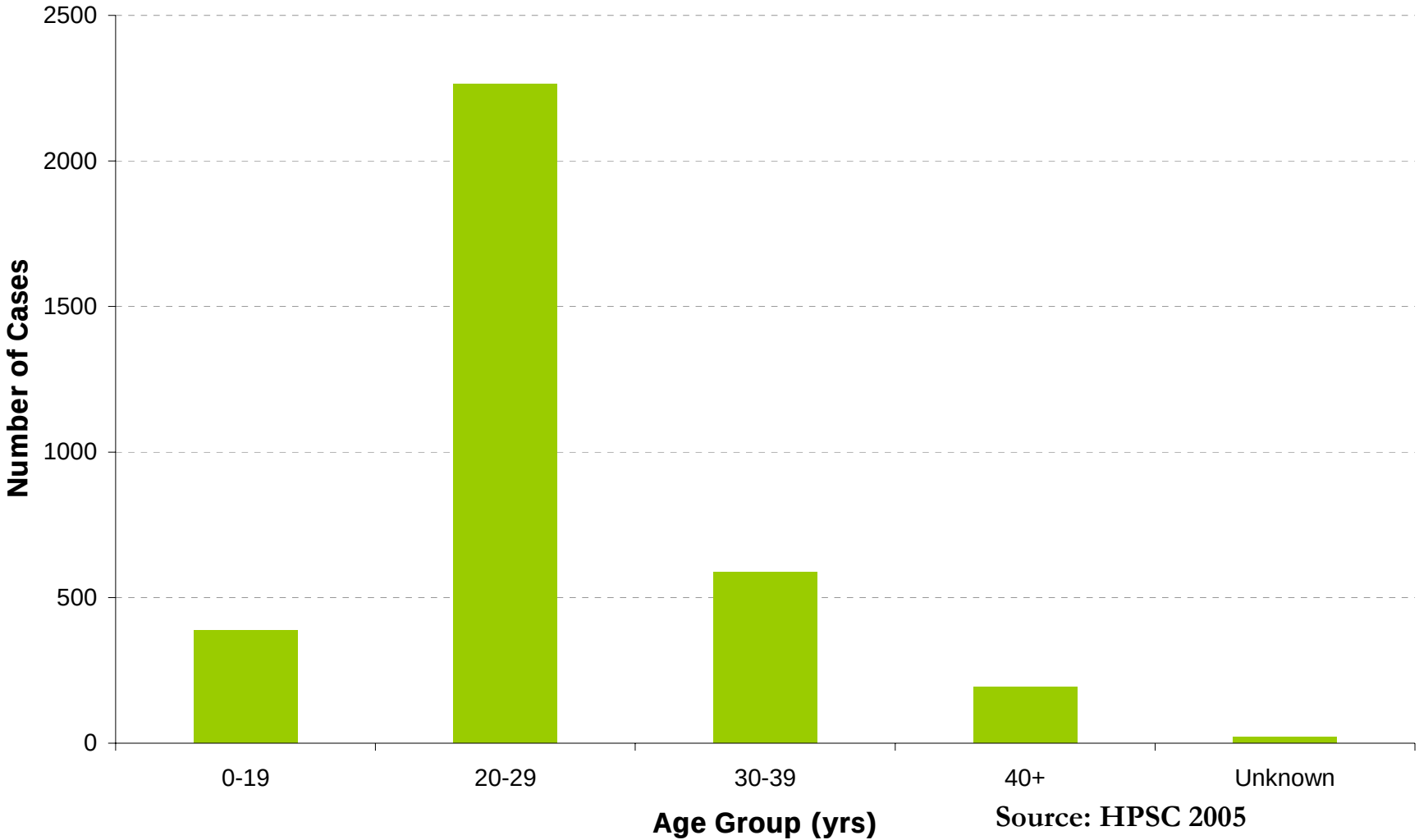
In Ireland

Ano-genital warts – ’89-’05



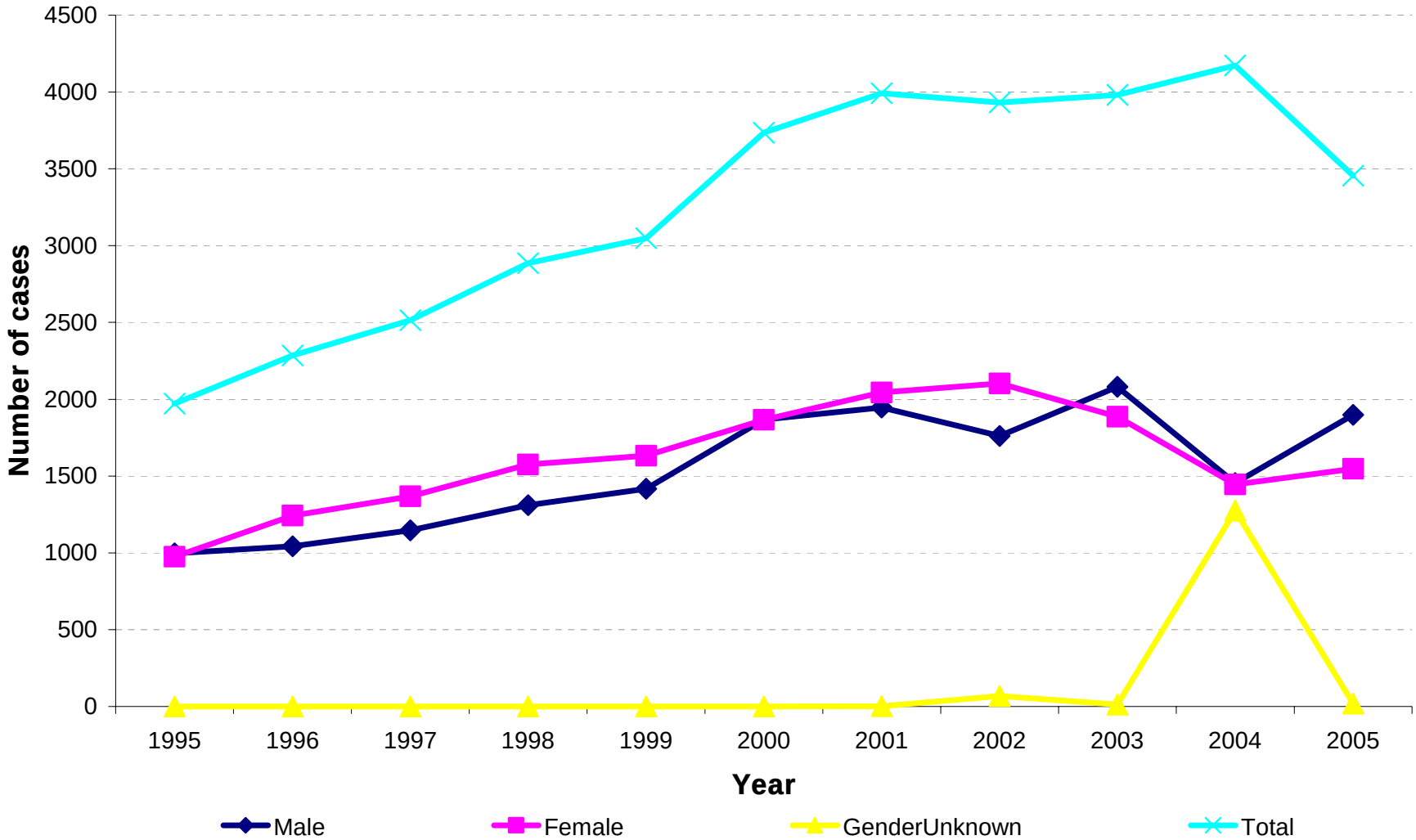
Source: HPSC, 2005

Ano –genital warts by age group



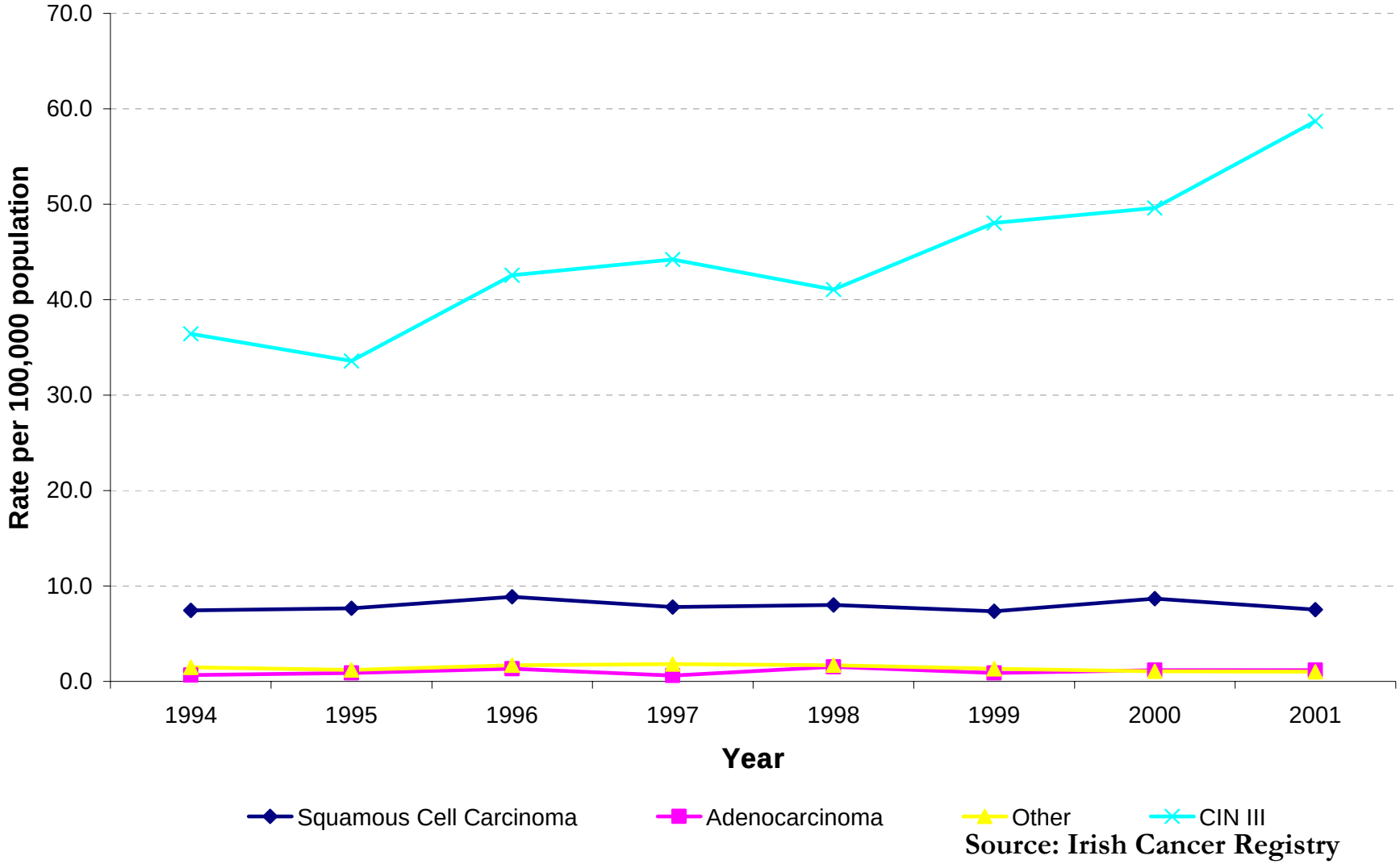
Source: HPSC 2005

Ano-genital warts by gender



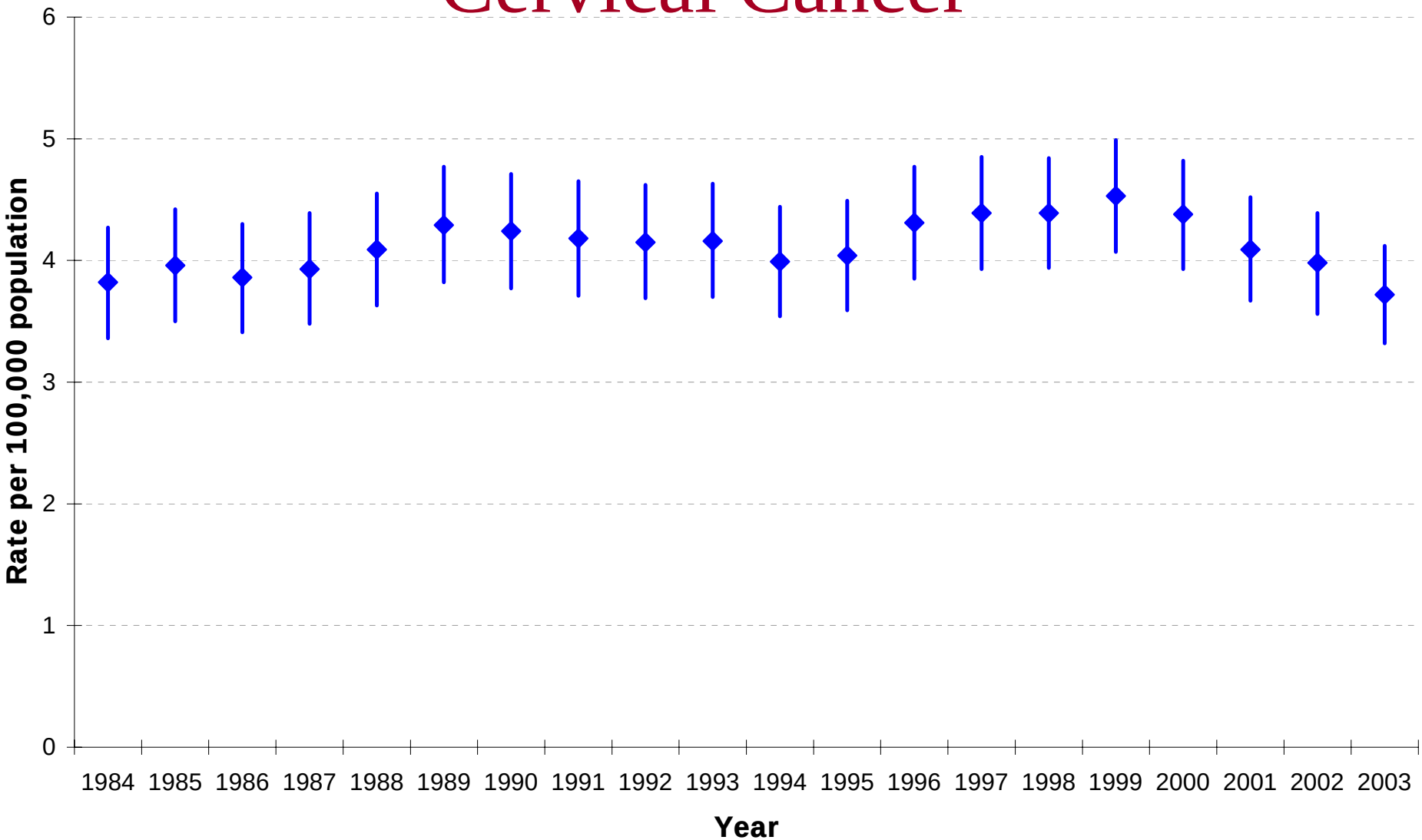
Source: HPSC, 2005

Cervical Neoplasia



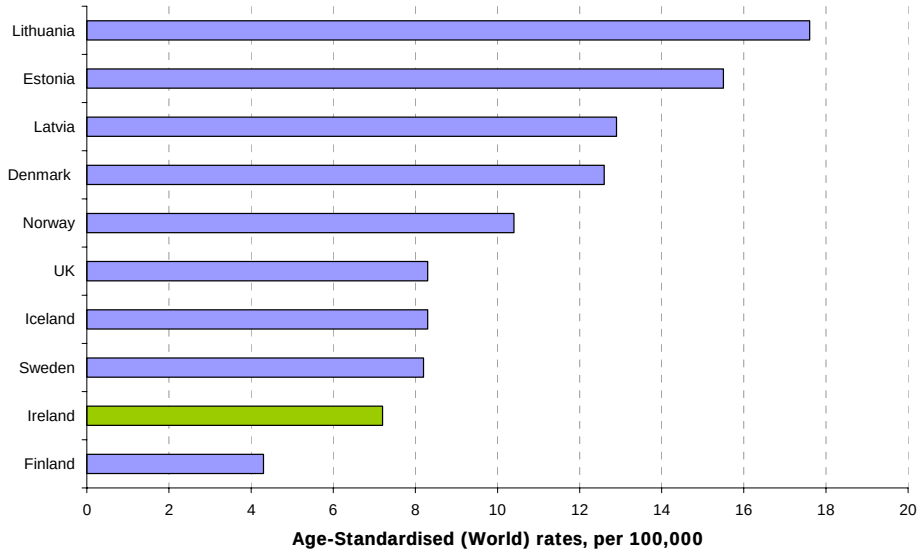
Source: Irish Cancer Registry

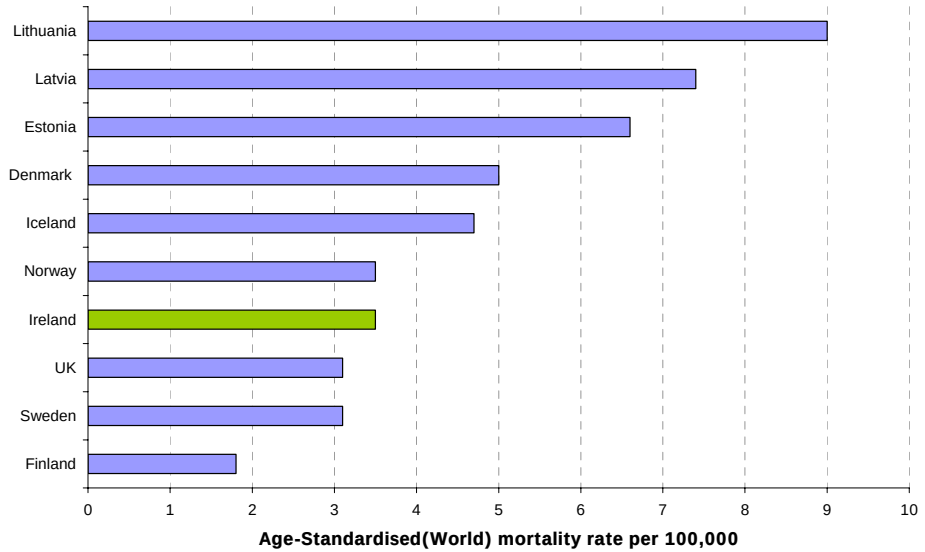
Cervical Cancer



Source: Irish Cancer Registry

Morbidity and Mortality





Source: GLOBOCAN 2002

Screening for Cervical Cancer

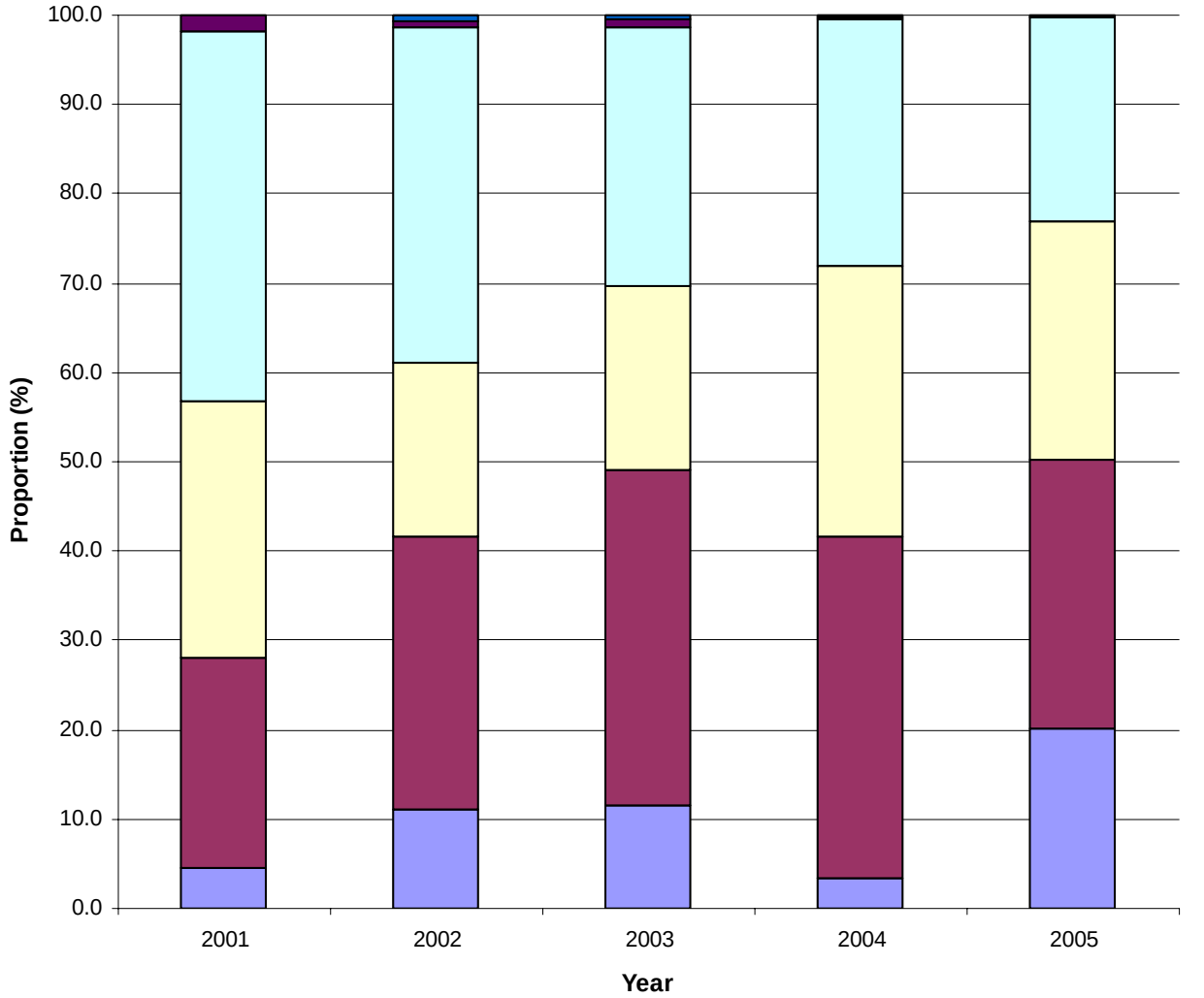
In Ireland

On average, 72 women die as a result of cervical cancer each year in Ireland.

The mean age of these women is;
56 years at time of death.

The mean age at the time of diagnosis is;
44 years

Histology findings 2001- 2005

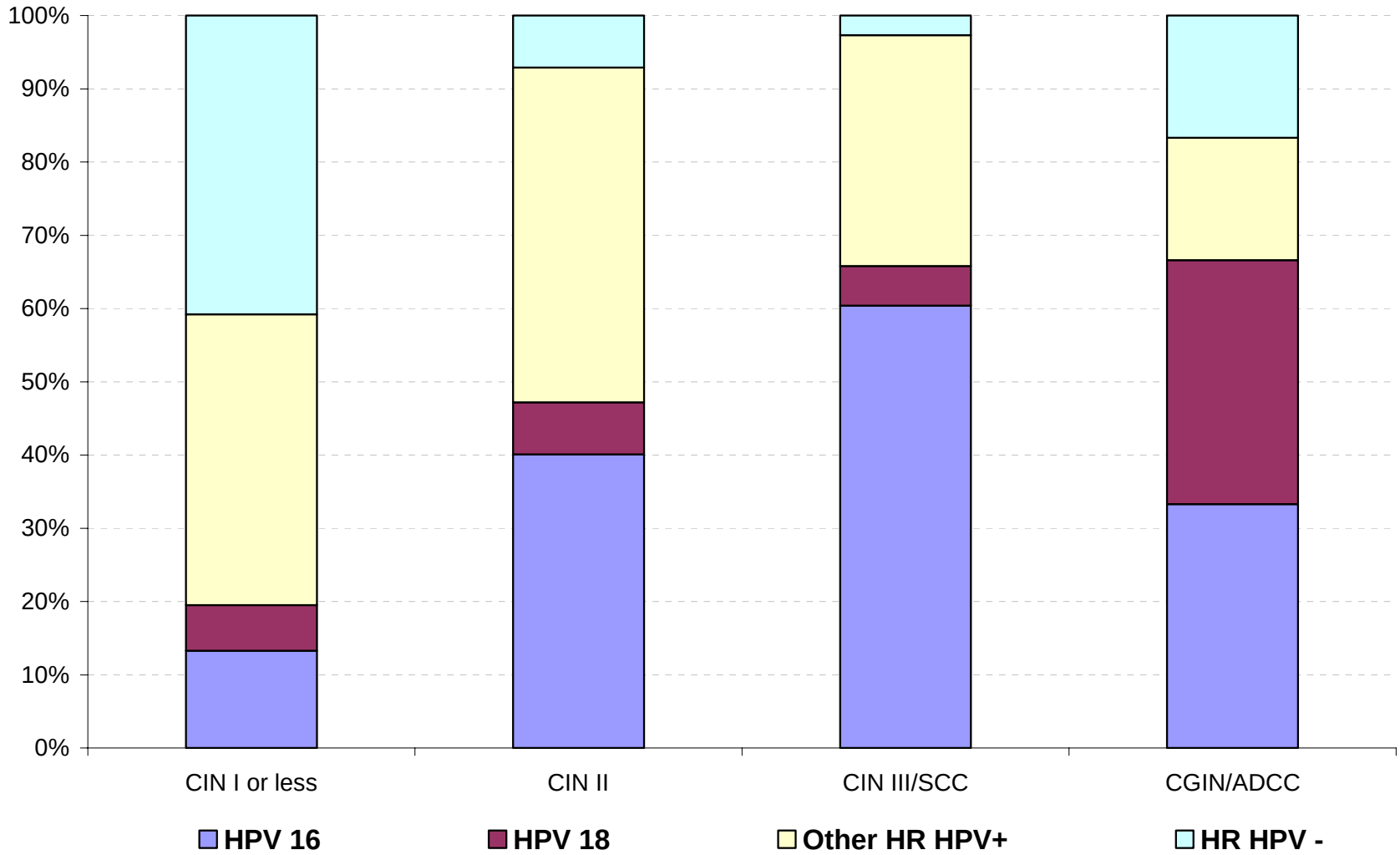


Source: ICSP 2005

Comparative data

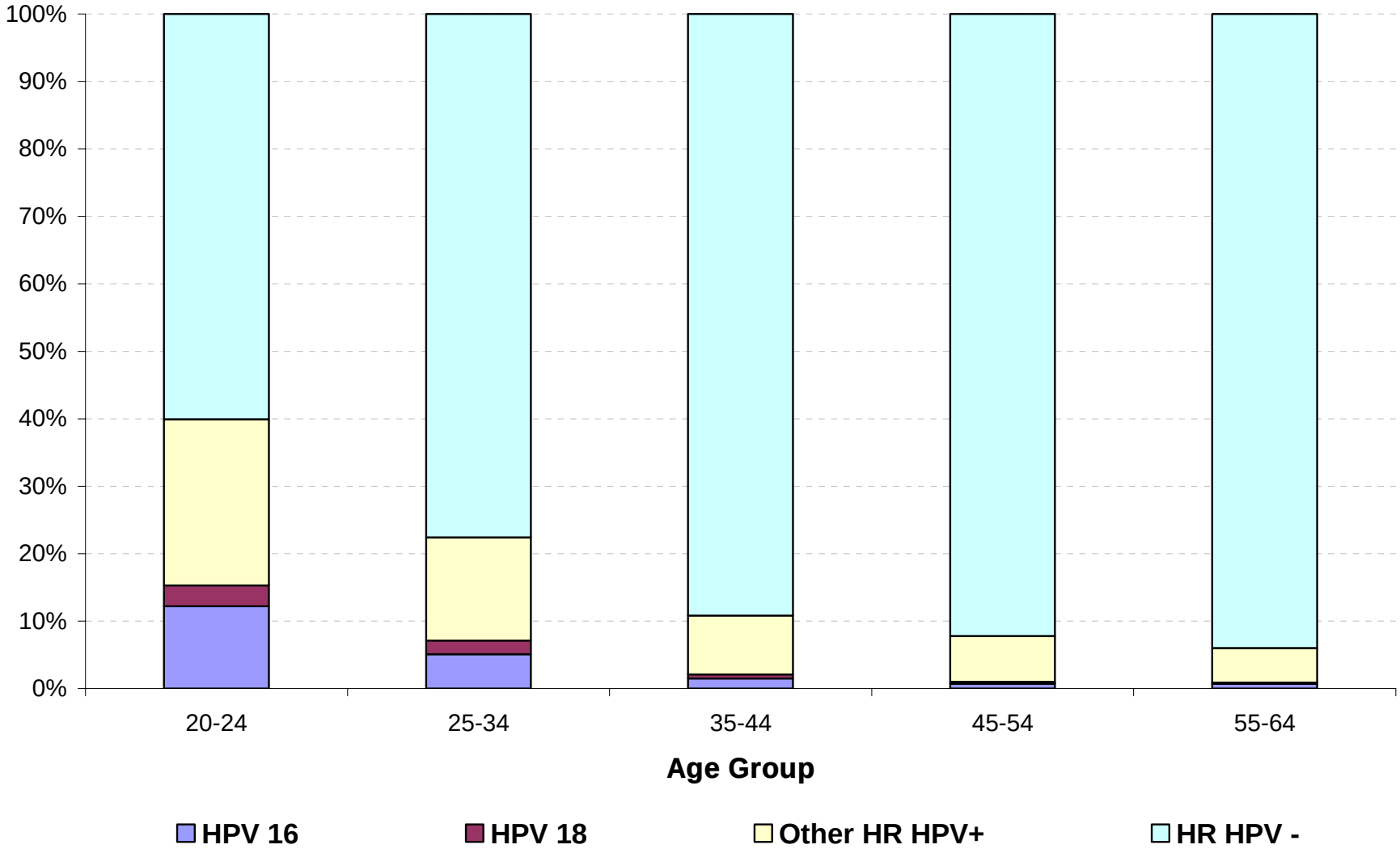
UK

Prevalence of HPV 16, 18 and other HR types by histology



Source: Kitchener et al. Br J Can; 2006

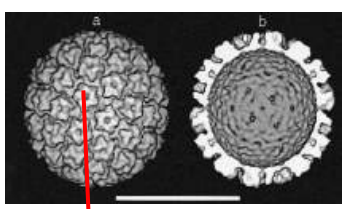
Prevalence of HPV 16, 18 and other HR types by histology



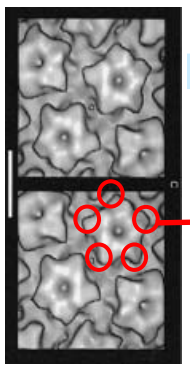
Source: Kitchener et al. Br J Can; 2006

HPV Vaccine(s)

HPV Vaccine



L1



5 x L1

L1-external protein

The vaccine mimics the virus shell

Virus-Like Particle (VLP)

L1 capsomere

L1 protein

5 x L1

72 capsomeres

(Atomic force microscopy image of a single VLP)

Expression and self assembly in a recombinant eukaryotic vector

Source: Dr. Kate Soldan, HPA

The Vaccines

- Merck/Sanofi-Pasteur MSD
  - Gardasil™
  - HPV types 6, 11, 16 & 18
- GlaxoSmithKline
  - Cervarix™
  - HPV types 16 & 18

	***Cervarix*™, GlaxoSmithKline Bivalent 16, 18**	***Gardasil*™, Sanofi Pasteur MSD Quadrivalent 16, 18, 6, 11**
Adjuvent; schedule in months	AS04; 0, 1, 6	Alum; 0, 2, 6
Total follow-up reported	27 months [1] 53 months [3]	37 months [2] 60 months [4]
Total number of women in vaccine: placebo groups	560:553 [1] 393:383 [3]	277:275 [2] 241 [4]
Countries	USA & Canada (n=607), Brazil (n=506)	USA (n=251), Brazil (n=187), Europe (n=114)
Criteria for inclusion in efficacy analyses (per protocol)	15-25 years, healthy, no more than 6 sexual partners, no history of cervical abnormality/disease, DNA negative and sero-negative for HVP16/18 at enrolment (*received 3-doses, negative for HPV 16/18 DNA at month 6*)	16-23 years; healthy, no more than 4 sexual partners, no history of cervical abnormality/disease, DNA negative and sero-negative for HPV6/11/16/18 at enrolment (*no protocol violation, negative for HPV 6/11/16/18 DNA up-to month 7*)

[1] Harper DM et al Lancet. 2004. [2] Villa LL et al Lancet Oncol. 2005. [3] Harper DM et al Lancet 2006. [4] Villa et al. EUROGIN 2006.

Source: Soldan et al, HPA

Efficacy (95% confidence interval) [number of cases in vaccine group: number of cases placebo group]

		***Cervarix*™, GlaxoSmithKline Bivalent 16, 18**	***Gardasil*™, Sanofi Pasteur MSD Quadrivalent 16, 18, 6, 11**
Efficacy against persistent infections (~6 months)		HPV 16/18	HPV 6/11/16/18
	- Per protocol	96%(75-100) [1:23]	89% (70-97) [4:35]
	- Intention to treat	94% (78-99) [2:34]	88% (72-96) [6:47]
Efficacy against disease endpoint		HPV 16/18 related cervical IN	HPV 6/11/16/18 related cervical, vulval/vaginal IN, or warts
	- Per protocol	-	100% (16-100) [0:6]
	Intention to treat	100% (42-100) [0:8]	100% (56-100) [0:10]
Geometric mean antibody titre at last reported follow-up compared to that of natural infection (per protocol)		Month 51-53 HPV16: 17-fold HPV18: 14-fold	Month 36 HPV16:18-fold HPV18: 2-fold
Patients reporting serious adverse events		22(4%):19 (3.5%)(months 0-27) 16 (4%):19 (5%)(months 27-53) None related to vaccination.	2(1%):2(1%) (months 0-36) None related to vaccination.
Injection site adverse events		499(94%):472(88%)	234(86%):212 (77%)

Harper DM et al Lancet. 2004. Villa LL et al Lancet Oncol. 2005. Harper DM et al Lancet 2006. Villa et al. EUROGIN 2006

Source: Soldan et al

Phase III trials

- Double-blind placebo controlled
- Europe, North, Central and South America and Asia
- End-points: incident and persistent HPV (2-3 yrs), cytological and histological lesions (2-5 yrs)
- Women aged 16-23
- Safety: generally well-tolerated, no adverse events related to vaccine
- Immunogenicity: high-titre anti-HPV responses
- Efficacy: Close to 100%. Reduction in vaccine type infections (in naïve women), reduction in CIN 2/3

Sanofi Pasture MSD In progress

- Phase III programme to evaluate clinical and public health impact in adolescents and young women (16-23), ~25,000 subjects in 33 countries (150 sites), long-term efficacy

Lowndes CM. Vaccines for cervical cancer. Epidemiol Infect. Feb 2006.

Merck: Pivotal clinical trials/analyses

The FUTURE* I study

- phase III efficacy study
- focus on external genital lesions (EGL)

The FUTURE* II study

- phase III efficacy study
- focus on cervical intraepithelial neoplasia (CIN)

Combined data

- combined analysis of 4 phase II/III efficacy data set

1. phase II proof of principle study with quadrivalent HPV6/11/16/18 L1 VLP vaccine
2. phase II proof of principle study with monovalent HPV16 L1 VLP vaccine
3. & 4. phase III efficacy studies FUTURE* I & FUTURE* II

Primary endpoint:

- combined incidence of HPV 16/18-related CIN 2/3, AIS, or cancer

Phase II/III efficacy data combined analysis

Results - Per protocol population - CIN

Endpoint	HPV Vaccine Cases	Placebo Cases	Vaccine Efficacy	95% Confidence Interval	P-value[1]
HPV 16/18-related CIN 2/3+ or AIS	N=8487	N=8460	100%	92.9–100	<0.001
	0	53			
HPV 16/18-related CIN 1[2]	N=7858	N=7861	93.1%	81.4-98.2	
	4	58			

Subjects may be counted in >1 row

1. Ault, K. European Journal of Cancer Supplements October 2005; Vol 3 (4): 4
2. Sanofi Pasteur MSD Data on File 2006 (06/006).

Phase II/III efficacy data combined analysis

Results - Per protocol population – External Genital Lesions

Endpoint	HPV Vaccine Cases	Placebo Cases	Vaccine Efficacy	95% Confidence Interval
HPV 6/11/16/18-related VIN 2/3	N=7897	N=7899	100%	41.4-100
	0	8		
HPV 6/11/16/18-related VaIN 2/3	N=7858	N=7861	NS	
	0	5		
HPV 6/11/16/18-related genital warts	N=7897	N=7899	98.9%	93.7-100
	1	91		

Subjects may be counted in >1 row

Licensure

GardasilTM Sanofi Pasteur MSD - licensed by EMEA for Europe, September 2006 and FDA for US, June 2006
Australia & other countries

EMEA The approved indication is:
prevention of
• High-grade cervical dysplasia (CIN 2/3)
• Cervical carcinoma
• High-grade vulvar dysplastic lesions (VIN 2/3), and
• External genital warts (condyloma acuminata)
casually related to Human Papillomavirus (HPV) types 6, 11, 16 and 18.
The indication is based on the demonstration of efficacy of GARDASIL in adult females 16 to 26 years of age and on the demonstration of immunogenicity of Gardasil in 9- to 15-year old children and adolescent. Protective efficacy has not been evaluated in males.

FDA INDICATIONS AND USAGE
GARDASIL is a vaccine indicated in girls and women 9-26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types 6, 11, 16, and 18:
• Cervical cancer
• Genital warts (condyloma acuminata)
and the following precancerous or dysplastic lesions:
• Cervical adenocarcinoma in situ (AIS)
• Cervical intraepithelial neoplasia (CIN) grade 2&3
• Vulvar intraepithelial neoplasia (VIN) grade 2&3
• Vaginal intraepithelial neoplasia (VaIN) grade 2&3
• Cervical intraepithelial neoplasia (CIN) grade 1

CervarixTM, GlaxoSmithKline – license awaited EMEA opinion expected early 2007

Vaccine Programme

What needs to be considered

Data expected

- Final reports of Phase II studies – efficacy, persistence, booster immunogenicity
- Further reports from Phase III studies – including protection in non-naïve
- Type-specific efficacy for non-vaccine types
- Mid-adult women's efficacy study, subjects 25-45 years
- Efficacy in 16-23 year old men
- Immunogenicity and safety in HIV infected children
- Concomitant administration of other vaccines
- Long-term follow-up studies, e.g. Nordic cancer registries (till 2018+)
- ?Immune correlates of protection

Further work

- Second-generation vaccines with additional HR types
- Therapeutic vaccines

Further Data from trials - Population-based long-term efficacy trials

Nordic HPV vaccine trials

2002-04: ~55,000 16-23yr old females, randomised to i) quadrivalent HPV vaccine or placebo, or ii) bi-valent HPV vaccine or HAV vaccine. Active follow-up 6 mthly for 4 yrs, then national cancer registry-based follow-up

2003-2005: cohort of unvaccinated 18-45yr old females for registry based follow-up (CIN3+)

Costa Rica (Guanacasta)

2004-05: ~7.500 18-25 yr old females randomised to bivalent HPV vaccine or HAV vaccine, Follow-up annually for 4 yrs.

Lehtinen *et al.* Studies to assess the long-term efficacy and effectiveness of HPV vaccination in developed and developing countries. *Vaccine 24S3 2006*

Gaps in our understanding

1. Vaccine safety: long-term safety, vaccination of women during pregnanacy
2. Vaccine efficacy: duration. Other types, existing infections, males
3. Design considerations for post-licensure studies of safety and efficacy: ethics of placebo controlled trials
4. Vaccine effectiveness: real-world impact, whole population, compliance.
5. Logistics of HPV vaccine implementation: optimal strategies to reach pre-/early-adolescents, 3-dose(6 mth) schedule
6. Vaccine acceptability: all, high-risk and hard to reach populations
7. Alternative delivery approaches and 2nd generation vaccines: simplified schedules, simplified administration, more types, addition of therapeutic components, validation of early immunological/virological surrogates
8. Natural history of HPV and cervical neoplasia post vaccine introduction: type-replacement

Hildesheim *et al.* Research needs following initial licensure of virus-like particle HPV vaccines. *Vaccine 24S3 2006*

Questions regarding effectiveness

1. What proportions of cervical cancer and other HPV related disease in a region or country are attributable to the HPV types targeted by the available vaccines?
2. What fraction of cervical cancer overall will be prevented by a vaccine against HPV 16 and 18?
3. Will immunity induced by vaccines alter the distribution of other, non-vaccine HPV types?
4. Will a vaccination programme against a sexually transmitted infection prove acceptable to adolescents who are not yet sexually active their parents?
5. Should teenage boys be vaccinated as well as teenage girls?
6. Will booster vaccinations be necessary, and if so, when?
7. How will a vaccination programme affect current programmes for cervical cancer screening, and how and when should screening change in response?
8. What benefits might vaccination confer on adults who are already infected with HPV?
9. Should older sexually active adults be included as part of a catch-up campaign at the outset of a vaccination programme?
10. Should any catch-up campaign be aimed at specific subgroups of the population?
11. What will be the cost effectiveness of various strategies for vaccination programmes?

Lowndes & Gill, Cervical cancer, human papillomavirus, and vaccination. BMJ 2005

Impact on non-vaccine types? - Cross protection?

- **Harper** *et al*, Lancet 2006
  - *Cervarix*™ (GlaxoSmithKline – bivalent vaccine)

    Cross-protection against infection with
    - HPV type 31 - 55% (95%CI 12-78)
    - HPV type 45 - 94% (95%CI 63-100)

- **Munoz** *et al*, Paris 2006
  - *Gardasil*™ (Sanofi Pasteur MSD – quadrivalent vaccine)

    Increases in titres of type-specific antibodies for

    HPV types 31, 45, 52 and 58

  - Interactions?

Conclusions

1. What is the burden of disease related to HPV in their country, or in a country of similar demographic circumstances in the same region
2. What are population attitudes towards cervical cancer and HPV
3. What is the peak age of infection with HPV, and what are the implications for the choice of target age group?
4. What is the number of doses needed to generate adequate immunity through high risk period, and in particular, is it possible to use a two-dose vaccination schedule instead of a three-dose schedule?
5. Might HPV vaccination be integrated in the infant immunization schedule, or at school entry, at any time in the future, with or without a booster dose just before the high-risk period?
6. Can the vaccine be administered simultaneously with other vaccines such as those containing measles and rubella vaccines and tetanus toxoid?
7. What are the cold chain requirements for the vaccine?
8. What is the cost of the vaccine, and what are the potential mechanisms to finance this?

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2. What fraction of cervical cancer overall will be prevented by a vaccine against HPV 16 and 18
3. Will immunity induced by vaccines alter the distribution of other non-vaccine HPV types
4. Will a vaccination programme against a sexually transmitted infection prove acceptable to adolescents who are not sexually active and their parents?
5. Should teenage boys be vaccinated as a well as teenage girls?
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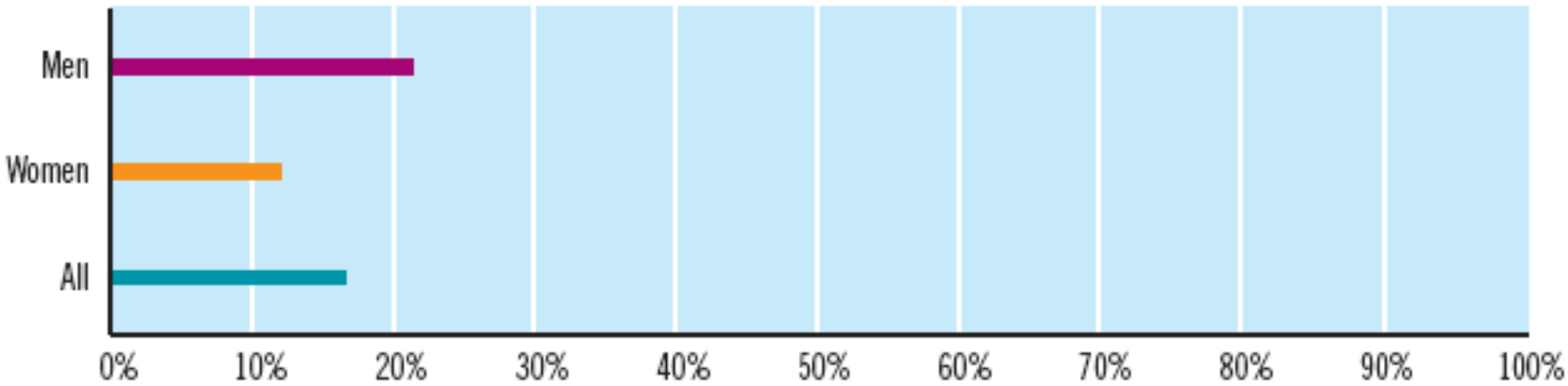
8. What benefits might vaccination confer on adults who are already infected with HPV?
9. Should older sexually active adults be included as part of a catch-up campaign at the outset of a vaccination programme?
10. Should any catch-up campaign be aimed at specific sub-groups of the population?
11. What will be the cost effectiveness of various strategies for vaccination programmes?

Will vaccination against HPV be acceptable?

- UK Department of Health, Immunisation Policy Monitoring & Surveillance
  - Fear of new vaccines **Yarwood** *et al* Vaccine 2005
  - Low awareness of HPV
  - Difficulties with concept of partial protection
  - Difficulties with 'sex jab' giving tacit permission for sex
  - Protectiveness of children's innocence (8-10yrs), when too old not to explain

- **Brabin** *et al* Vaccine. 2006.
  - Uptake of 80% may be achievable (11-12 yr olds)
  - Only 38% definitely approved
  - ~15% were opposed
  - Most parents lacked knowledge, some concerned about sexual health issues

Proportion of Irish men and women having sex before 17 years



Source: Irish Study of Sexual Health and Relationships

Age of sexual onset and number of sexual partners of Irish men and women in lifetime

	Males	Females	Total
Age at first sexual intercourse	%	%	%
Under 14 years	3.4	1.8	2.4
15-16 years	26.8	21.9	23.8
17 years or older	69.8	76.3	73.7
Number of sexual partners			
1-3 people	58.0	71.3	66.1
4-5 people	14.6	13.7	14.1
6 or more people	27.4	15.0	19.9

Source: CLAN Survey, 2003

Cost-effectiveness?

Insinga *et al* A preliminary assessment of the cost-effectiveness if a quadrivalent HPV vaccine in the United Kingdom using a multi-type transmission dynamic model. 23rd International HPV conference, 2006 (poster).
- in addition to screening programme
- assuming life-time duration of protection, coverage 85% by yr 5 (50% for catch-up), vaccine cost of £225 for 3 doses plus £11 admin.

"HPV vaccine can be efficiently added…catch-up can provide earlier and greater reductions....vaccinating females before age 12 with catch-up to 12-24s can be cost-effective"

Also **Myers** et al (2000), **Goldie** et al (2004) , **Hughes** et al (2002), **Taira** et al (2004), **Sanders & Taira** (2003), **Kulasingam & Myers** (2003), reviewed by **Newall** *et al* (in press)

Clear that following are important:
- type-specific acquisition rates 11 to 24 yrs
- duration of protection
- discounting of benefits
- ?impact on non-vaccine types

Priorities for work in progress

- Adequate local knowledge of **age/sex/type specific infection** and burden of disease, all women and women at most risk
  - Development and validation of assays
  - Surveys
- **Develop and parameterise models** to enable cost effectiveness analyses to inform use of vaccine and evolution of cervical cancer prevention strategies
- Understanding of issues relating to the **communication** and implementation of HPV vaccination
- Monitoring vaccination **effectiveness and impact** on epidemiology

United States Strategy

US Policy: CDC's Advisory Committee on Immunization Practices

Recommendations, August 2006:

- Quadrivalent HPV vaccine
- Routine, females 11-12 years
- Catch-up, females 13-26 years

Vaccine Strategy Options

- Routine 12 year-old females
- 12 year-old females plus 12-14 year-old female catch-up
- 12 year-old females plus 12-17 year-old female catch-up
- 12 year-old females plus 12-19 year-old female catch-up
- 12 year-old females plus 12-24 year-old female catch-up

Strategies in Europe …

WHO HPV laboratory network

- global reference laboratory in Malmö, Sweden.
- to facilitate the evaluation of HPV vaccination programmes and the monitoring and reporting of HPV infections and HPV-associated diseases using **laboratory methods** for HPV testing and typing that are **internationally comparable** and are **quality assured to meet international standards**.

Population based <u>effectiveness</u> trials (phase IV)

- Nordic countries: communities randomised to different vaccination strategies (HPV, HBV, girls, boys, catch-up)

Lehtinen *et al.* Studies to assess the long-term efficacy and effectiveness of HPV vaccination in developed and developing countries. *Vaccine 24S3 2006*

Further work….

France – (*Le Conseil Superieur d'Hygiene Publique de France)*

- 14 year-old females
- Or within 1 year of becoming sexually active

- Catch-up; 15-23 year-old females

Australia - (*Pharmaceutical Benefits Advisory Committee)*

- 3 cohort programme (school and community based;
  - 12-13 year-old females; **school based**
  - 13-18 year-old females; **school and community based**
  - Females <26 years; **community based**

Cohort	% reduction in lifetime risk of cervical cancer
Full potential of programme in 12-year old girls	64
First cohort of 12-year old girls vaccinated	46
24-year old women who receive catch-up vaccination	35
30-year old women who receive catch-up vaccination	17

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