Training Course in Sexual and Reproductive Health Research
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HPV infection, Cervical Cancer and HPV vaccines

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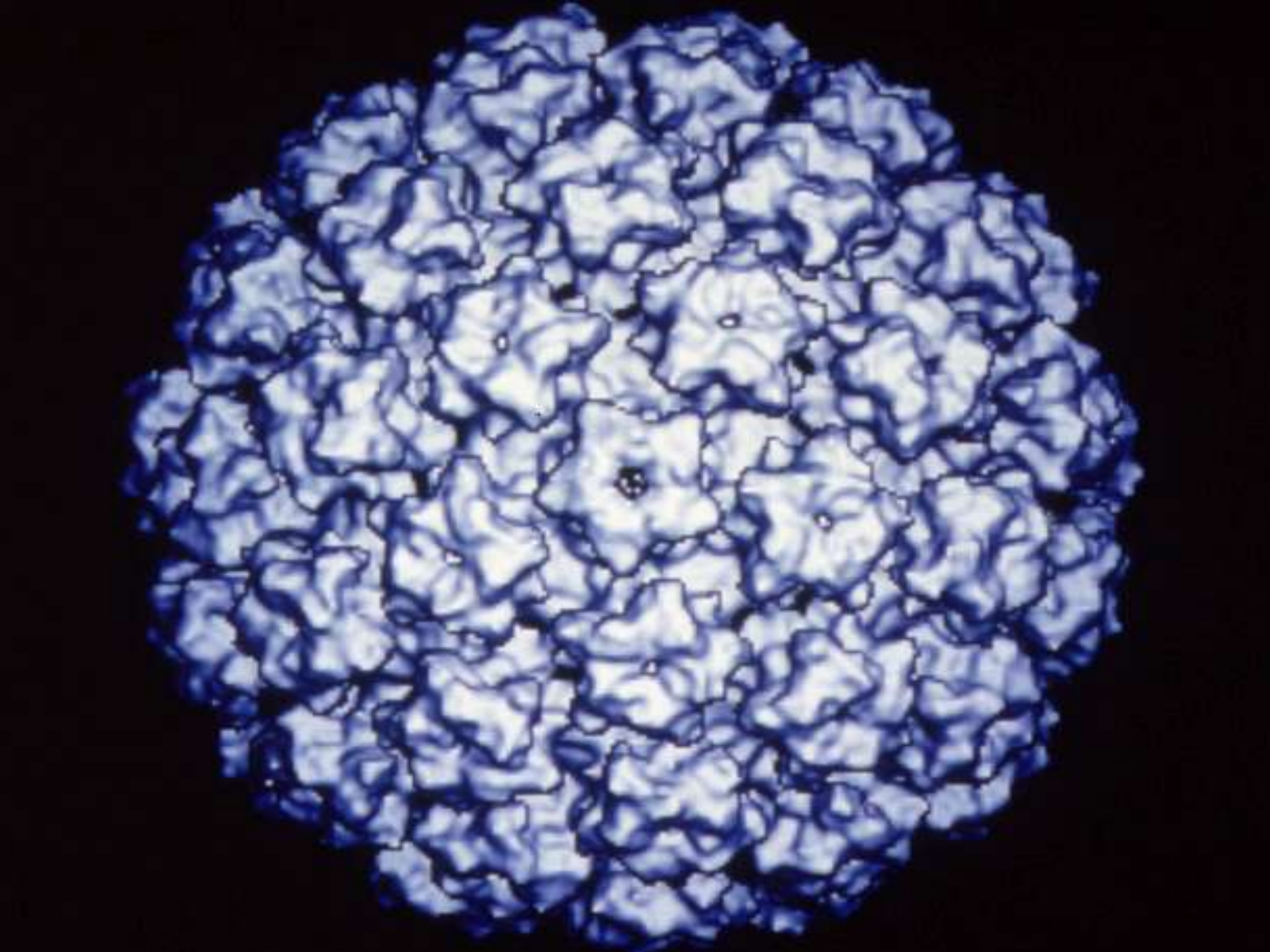
World Health Organization
On behalf of the WHO HPV vaccine group

World Health Organization

Presentation

- HPV natural history
- HPV disease and burden
- Vaccine Efficacy
- Vaccine Immunogenicity
- Vaccine Safety
- Ongoing studies



HPV

Over 100 types of HPV, most are not associated with cervical cancer or genital warts

Most genital HPV infections are transient and are not associated with persistent cervical disease

Transmission of genital HPV

- **Mainly sexual**
  - **genital warts in couples**
  - **rare in virgins**
  - **increases with number of sexual partners**
  - **HPV concordance in couples**
  - **Highly contagious**
- **Vertical transmission**
  - **rare**

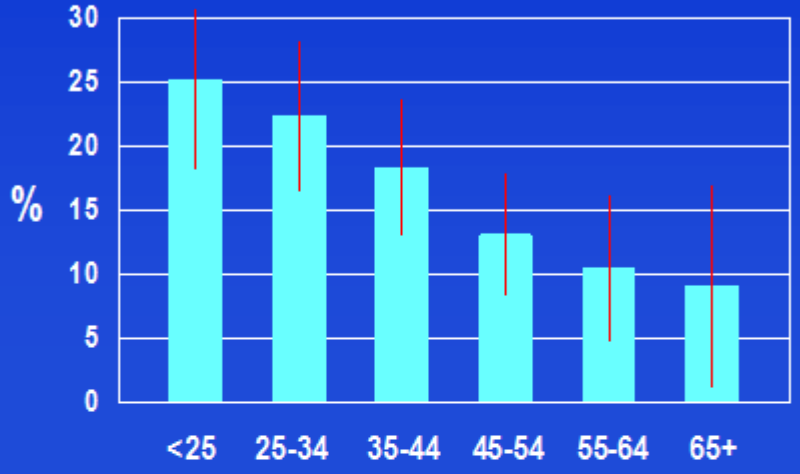
HPV Natural History

- **Cumulative risk HPV *(Woodman, Lancet 2001)* :**
  3 years: 44% / 5 years: 60%

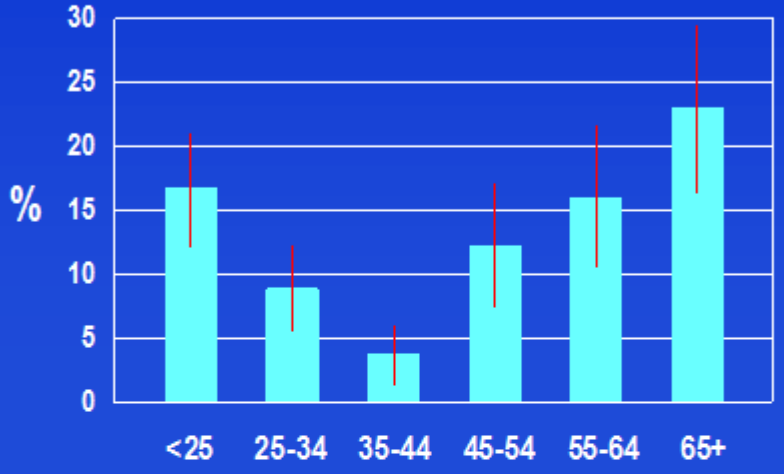
  1075 women (HPV- at entry) / 15-19 years
- **Mean carriage: 4-8 months**
- **Multiple infections common**
- **Age distribution : generally decreasing in older ages**
  but studies *(Lazcano-Ponce, 2000)*
  peak at <25 years
  increase from 45 years birth cohort *(Peto et al 2000)*

Prevalence of HPV DNA in the general female population

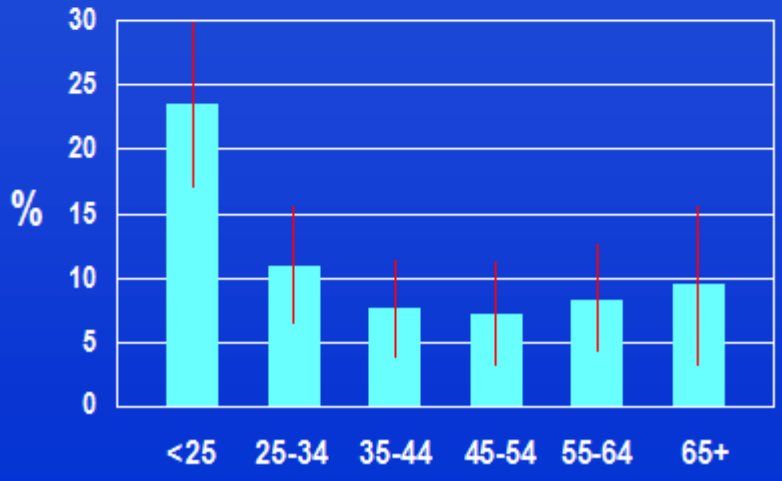
Concordia, Argentina



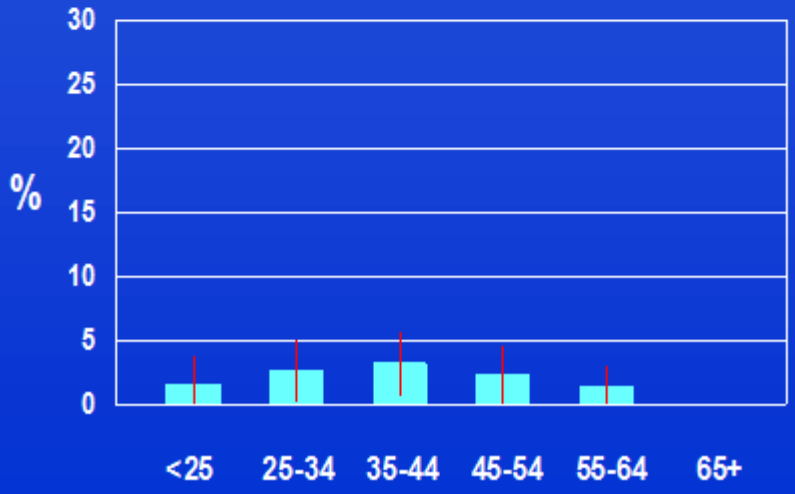
Morelos, Mexico



Ho Chi Minh, Vietnam



Hanoi, Vietnam



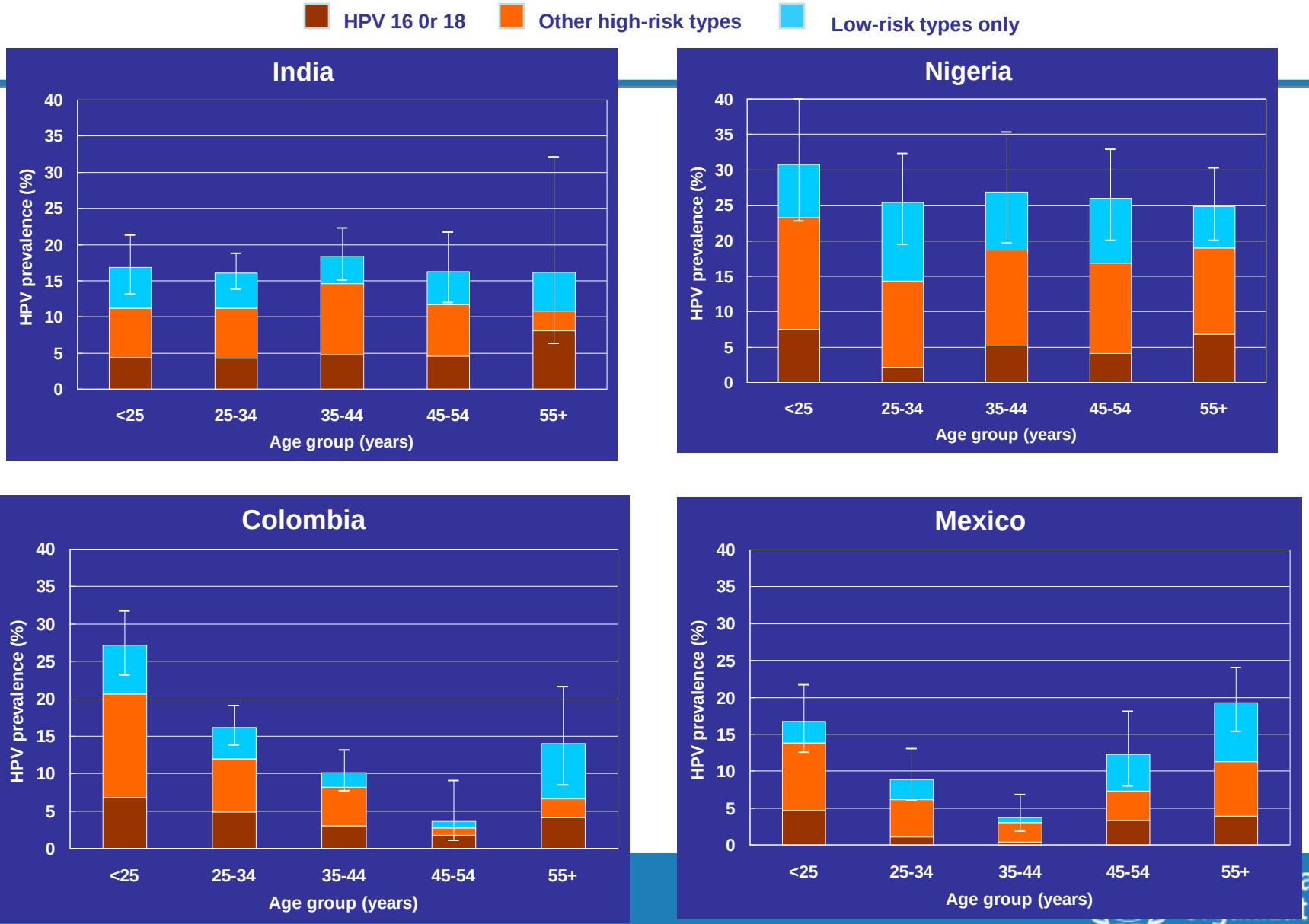
Genital HPV infection: clinical manifestations

- Latent infection
- Genital warts
- Intraepithelial neoplasia (cervical, vaginal, vulvar, anal)
  - I or mild dypslasia
  - II or moderate dysplasia
  - III or severe dysplasia
- Carcinoma in situ
- Invasive cancer

Latent HPV infection

- Only detectable with molecular techniques
- Very common among young women
- Associated with most genital HPV types
- Frequently have normal pap smears

Prevalence of cervical HPV DNA by age and HPV type in women with normal cytology: IARC Multi-centre HPV Prevalence Survey



Genital warts

- Very common – exact numbers unknown
- Increasing incidence in some areas
- Highly contagious
- 90% associated with HPV types 6 and 11
- Not associated with cervical cancer

Cervical neoplasia and HPV

- Most of intraepithelial neoplasia is transient, like HPV infection
- More than 98% of cervical neoplasia have detectable HPV DNA
- Relative risks of >65 in case-control studies for HPV and cervical cancer
- Extensive laboratory evidence

HPV-associated cancers

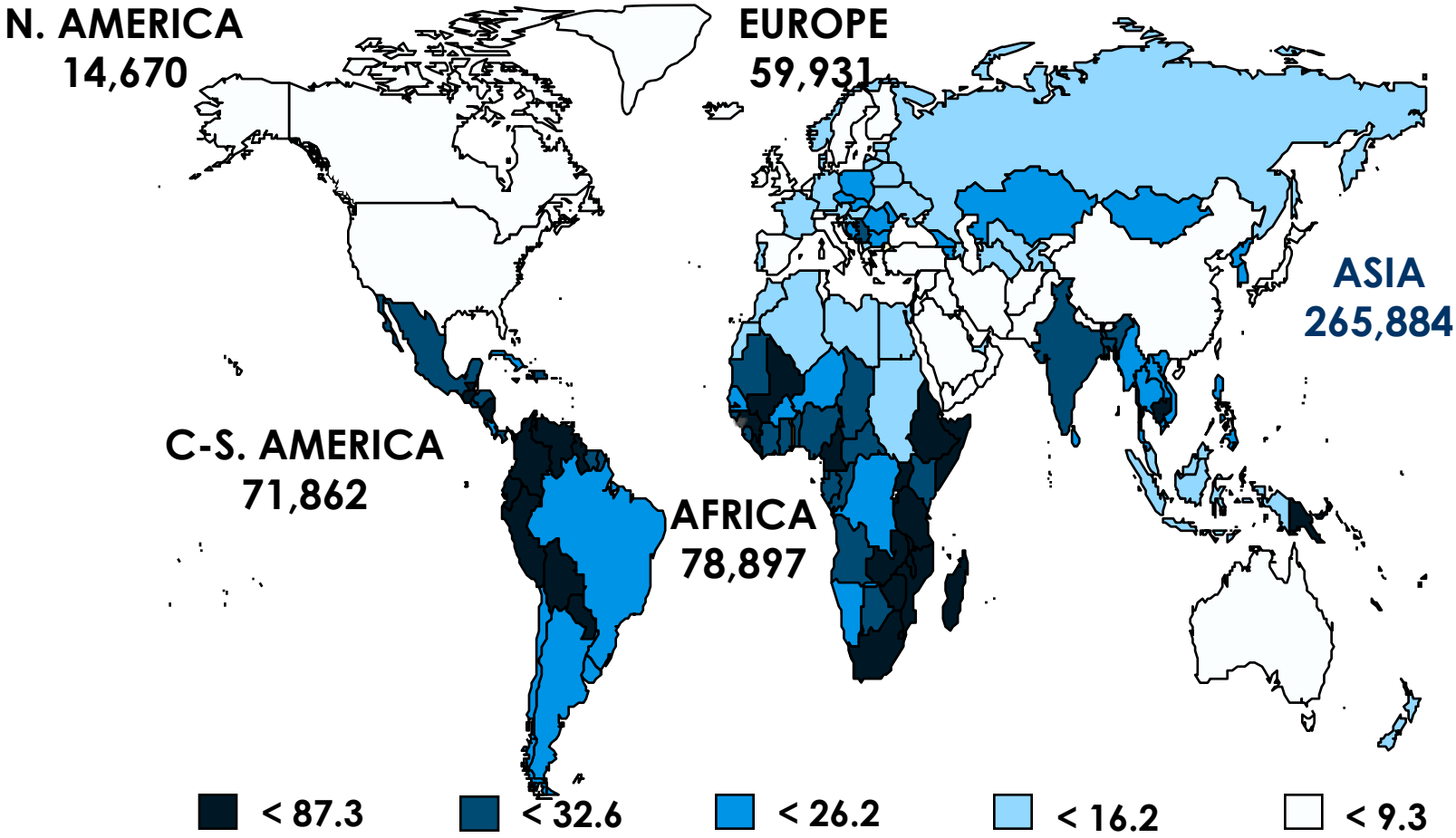
Of the total estimated HPV-attributable cancers in the world, 80% occur in developing countries.

HPV-Attributable Cancers, 2002

		HPV Attributable Cancers	
Site	Attributable to HPV (%)	Developed countries	Developing countries
Cervix	100	83,400	409,400
Penis	40	2,100	8,400
Vulva/Vagina	40	7,300	8,700
Anus	90	13,100	14,300
Mouth	3	2,700	5,500
Oral/pharynx	12	2,900	3,300
All sites		111,500	449,600

Parkin. Int J Cancer 2006 Slide courtesy of L. Markowitz

Estimated number of cervical cancer cases by region - 2002

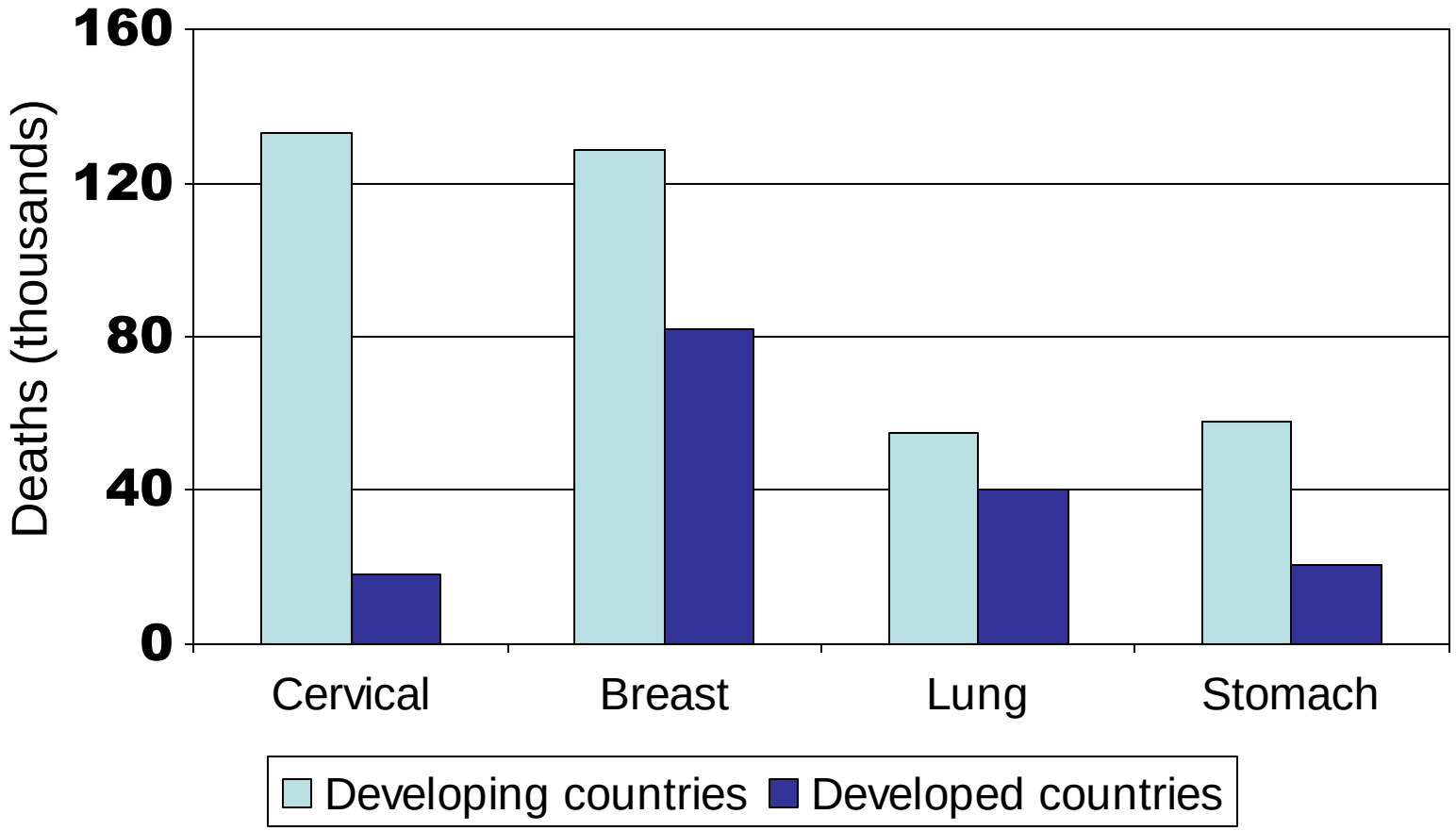


GLOBOCAN 2002

Age-adjusted incidence rates per 100,000 women per year

World Health Organization

Comparison with other cancers: number of deaths among women 25-64 years old



IARC, 2005 (based on: Yang B et al. *Int J Cancer*. 2004; 109: 418-424.)

World Health Organization

(Munoz et al., IARC)

IARC: HPV and cervical cancer

Country	HPV positives (%) Cases	Controls	ORa* (95 % CI)
Brazil	96.8	17.4	157.8 (63.1 - 394.8)
Colombia	75.4	15.3	17.4 (11.3 - 26.8)
Paraguay	97.6	23.0	149.5 (41.8 - 534.5)
Peru	94.9	17.7	98.3 (44.9 - 215.2)
Mali	96.9	33.3	108.8 (10.6 - 1111)
Morocco	96.8	21.6	105.6 (41.6 - 267.8)
Thailand	96.0	15.7	143.7 (75.9 - 272.1)
The Philippines	95.9	9.2	247.8 (130.7 - 469.9)
Spain	78.5	5.4	63.0 (36.4 - 108.9)
Total	91.1	13.8	**79.6 (63.7 - 99.6)

ORa* = OR adjusted for age

ORa** = OR adjusted for age and country

Cervical Cancer Burden by Country Income

Country Grouping	Estimated Cases, 2002	Percent Share
Low income countries of which: India	264,931 (132,082)	54% (27%)
Lower middle income	112,232	23%
Upper middle income	60,223	12%
High Income	54,402	11%
Total	491,788	100%

- Majority of cervical cancer cases are in low income countries
- Possible target populations: Developing countries: 52.5 million girls
  High-income countries: 6.5 million girls

Source: 2002 Globocan data and PATH staff estimates Slide courtesy L. Markowitz

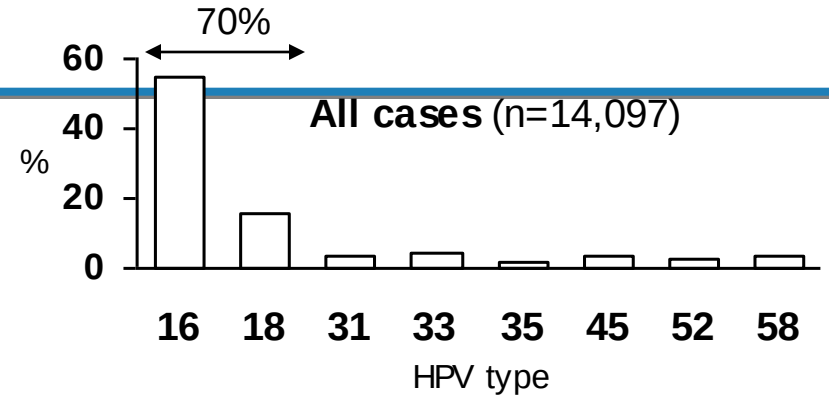
World Health Organization

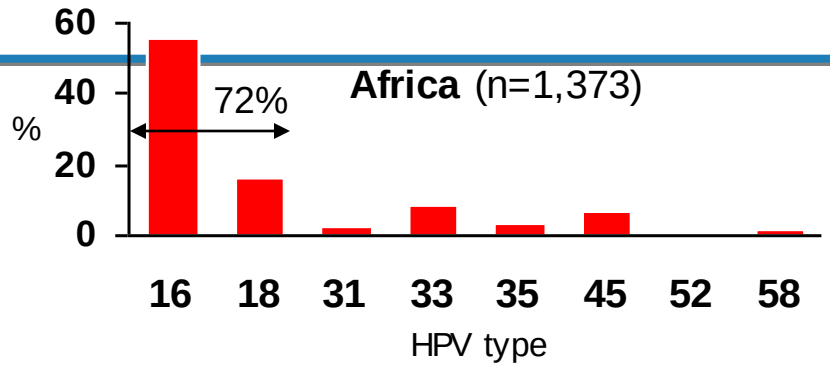
Conditions associated with HPV types 16,18, 6, 11

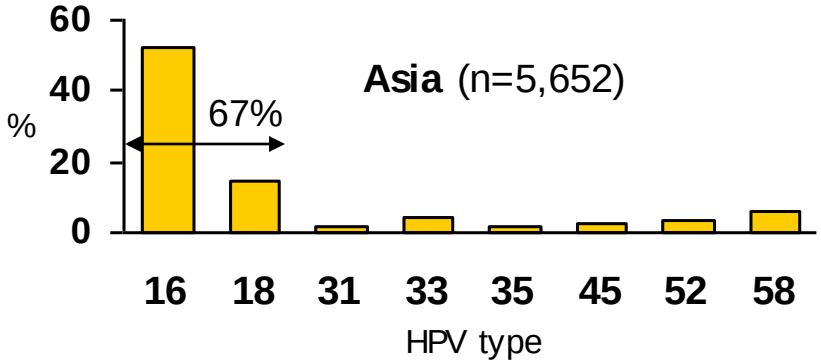
HPV 16, 18	Estimated attributable %
– Cervical cancer	70 %
– High grade cervical abnormalities	50 %
– Low grade cervical abnormalities	30 %
– Anal cancer	~70 %
– Vulva / Vagina / Penile	~40 %
– Head and neck cancers	~3-12 %
HPV 6, 11	
– Low grade cervical abnormalities	10 %
– Genital warts	90 %
– Recurrent respiratory papillomatosis (RRP)	90 %

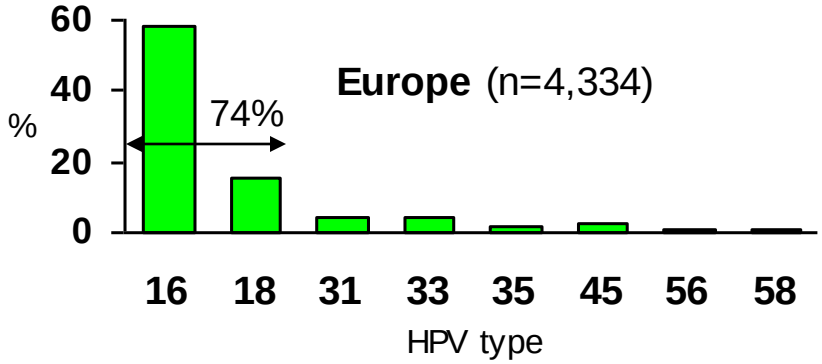
Clifford, BJ Ca 2003; Munoz Int J Cancer 2004; Brown J Clin Micro 1993; Carter Cancer Res 2001; Clifford Cancer Epi Biomarkers Prev 2005; Gissman Proc Natl Acad Science 1983; Kreimer Cancer Epidemiol Biomarkers Prev 2005

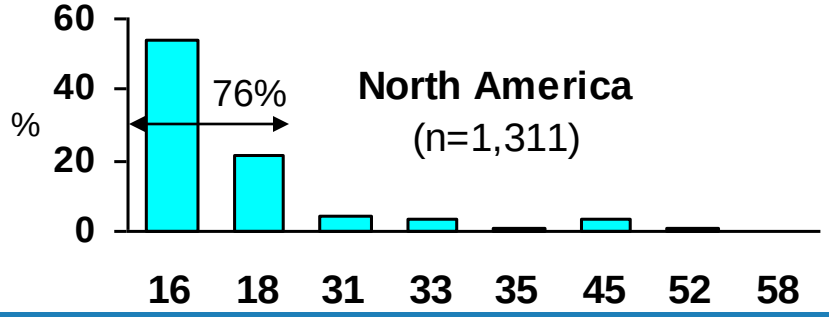
8 most common HPV types in 14,097 cases of invasive cervical cancer by region

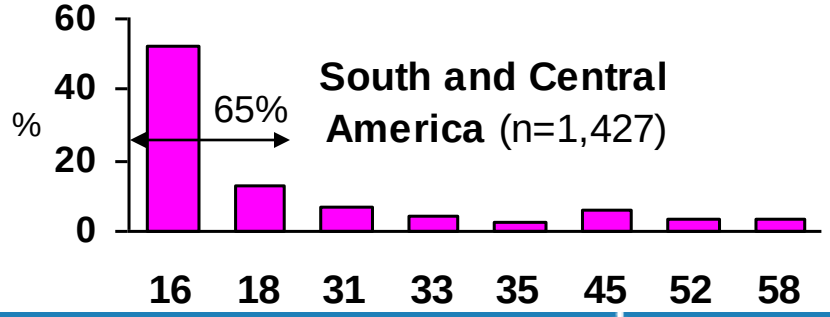










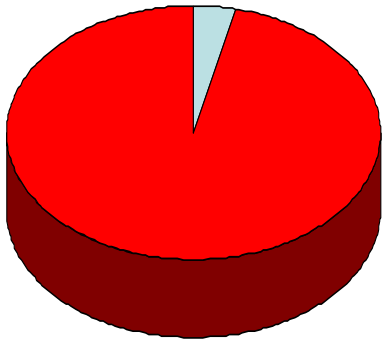


CERVIX CANCER (2002)

Developed

83,400 cases

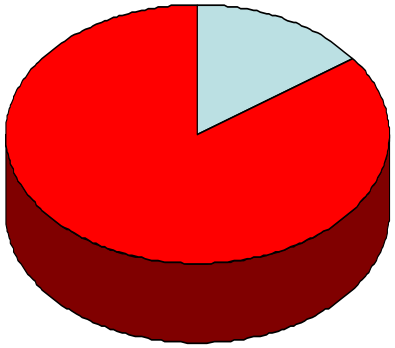
3.6% of all cancers



Developing

409,400 cases

15.0% of all cancers



Cervical cancer
Age-adjusted survival (%)

- US 70%
- W. Europe 66%
- Japan 65%
- E. Europe 51%

- Thailand 58%
- S. America 55%
- India 42%
- Sub S. Africa 21%

- **All developed 61%**
- **All developing 41%**

HPV and Cervical Cancer

- **Virtually all cervical cancer cases (99%) are linked to genital infection with human papillomavirus (HPV), which is the most common viral infection of the reproductive tract**
- **HPV is highly transmissible. Most individuals acquire the infection at some time in their lives.**
- **The peak incidence of HPV infection occurs between the ages of 16 and 20 years, soon after the onset of sexual activity**
- **A vaccine is now available that protects against infection and diseases associated with HPV**

New directions for primary prevention of cervical cancer: Two licensed HPV vaccines – Key findings

- **Vaccines efficacy extremely high against HPV vaccine-type disease in HPV naive women (+/-100% for HPV related diseases - two vaccines)**
- **In women already exposed to HPV type 16/18, vaccines are much less effective**
- **Good antibody persistence at least 5 years**
- **Acceptable safety profile**

What are HPV vaccines and how have they been evaluated?

- **HPV vaccines are prepared from virus-like particles using recombinant technology**
- **They are non-infectious**
- **Current HPV vaccines are designed to protect against HPV 16 and 18; one also protects against low-risk types 6 and 11**
- **They have been evaluated in large randomized, placebo-controlled, double-blind clinical trials conducted in many countries**

Prophylactic HPV VLP Vaccines

	Quadrivalent (Merck)	Bivalent (GSK)
Vaccine Type	**HPV 6/11/16/18**	**HPV 16/18**
Manufacturing	**Yeast - S. *cerevisiae***	**Baculovirus**
Composition	**20 µg HPV 6** **40 µg HPV 11** **40 µg HPV 16** **20 µg HPV 18**	**20 µg HPV 16** **20 µg HPV 18**
Schedule	**0,2,6 months**	**0,1,6 months**
Adjuvant	**Alum:** **225 µg Aluminum Hydroxyphosphate Sulfate**	**AS04:** **500 µg Aluminum Hydroxide 50 µg 3-deacylated Monophosphoryl Lipid A**

VLP: virus-like particle

Global HPV vaccine licensure status, Dec 2008

WHO Region	Quadrivalent (109)	Bivalent (90)
Africa	Botswana, Burkina Faso, CAR, Cameroon, Chad, Congo, DR Congo, Cote d'Ivoire, Equatorial Guinea, Ethiopia, Gabon, Guinea-Conakry, Kenya, Malawi, Mauritania, Mauritius, South Africa, Togo, Uganda	Cote d'Ivoire, Gabon, Ghana, Kenya, Namibia, Nigeria, Senegal, South Africa, Uganda
Americas	Argentina, Aruba, Bahamas, Barbados, Bermuda, Bolivia, Brazil, Canada, Cayman Is, Chile, Colombia, Costa Rica, Curação, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Jamaica, Mexico, Nicaragua, Panama, Peru, Puerto Rico, Trinidad/Tobago, Uruguay, USA	Argentina, Aruba, Brazil, Chile, Colombia, Curação, Dominican Republic, El Salvador, Guatemala, Guyana, Honduras, Mexico, Nicaragua, Panamá, Peru, Suriname, Trinidad/Tobago, Uruguay
Europe	EU (27), Belarus, Bosnia, Croatia, Georgia, Iceland, Israel, Macedonia, Montenegro, Norway, Russian Federation, Serbia, Switzerland, Turkey, Ukraine	EU (27), Albania, Azerbaijan, Belarus, Bosnia, Croatia, Georgia, Iceland, Israel, Kazakhstan, Macedonia, Moldova, Norway, Russian Federation, Serbia, Turkey, Ukraine
Middle East	Bahrain, Egypt, Jordan, Kuwait, Morocco, Pakistan, Saudi Arabia, UAE	Bahrain, Egypt, Kuwait, Morocco, Saudi Arabia, UAE
SE Asia	India, Indonesia, Thailand	Bangladesh, India, Indonesia, Myanmar, Thailand
W Pacific	Australia, HK, Macau, Malaysia, New Zealand, Philippines, Singapore, South Korea, Taiwan, Vietnam	Australia, HK, Malaysia, New Zealand, Philippines, Singapore, South Korea, Taiwan, Vietnam

Due to importation, distribution, and other regulatory requirements, as well as price negotiations, a licensed vaccine may not necessarily be marketed in a given country.

HPV Vaccines: Selected Aspects of Clinical Development Programs

Vaccine/ Manufacturer	Phase II Efficacy Trials females	Phase III Efficacy Trials females	Adolescent Immunogenicity Safety Trials	Efficacy (and immunogenicity) females > 25 years
Quadrivalent ***Merck***	**16-23 yrs**	**16-26 yrs**	**9-15 yrs**	**24-45 yrs**
Follow-up to date	**5 years**	**3.7 years**		
Bivalent ***GSK***	**15-25 yrs**	**15-25 yrs**	**10-14 yrs**	**26-55 yrs**
Follow-up to date	**6.4 years**	**14.8 months**		

Efficacy - Quadrivalent HPV Vaccine

- **Phase II trials, 5 year follow-up**

- **Phase II/III trials, end-of-study data**

Quadrivalent HPV Vaccine Efficacy

Per-Protocol Population (Combined Phase II/III studies)

Prevention of HPV 6/11/16/18-related outcomes

Endpoint	Vaccine (N=9075)	Placebo (N=9075)	% Efficacy	(95% CI)
CIN 2/3 or AIS	2	112	**98**	(94, 100)
VIN 1-3, VaIN 1-3 or EGL	2	227	**99**	(97, 100)

Per protocol analysis: includes participants who received all 3 doses, no protocol violations, vaccine HPV type DNA and seronegative through 1 month after dose 3

CIN= cervical intraepithelial neoplasia; AIS=adenocarcinoma in situ;
VIN= vulvar intraepithelial neoplasia; VaIN= vaginal intraepithelial neoplasia; EGL= external genital lesions (includes warts)

Reisinger, PAS & ASPR 2008 slide courtesy of L. Markowitz

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Quadrivalent HPV Vaccine Efficacy

Per-Protocol Population (Combined Phase II/III studies)

Prevention of HPV 6/11/16/18-related outcomes

Endpoint^	Vaccine (N = 9075)	Placebo (N = 9075)	% Efficacy	(95% CI)
HPV 6/11/16/18-related CIN or AIS	9	225	**96**	(92, 98)
By Type				
HPV 6-related	0	47	**100**	(92, 100)
HPV 11-related	0	12	**100**	(65, 100)
HPV 16-related	8	137	**94**	(89, 98)
HPV 18-related	1	61	**98**	(91, 100)
By Disease				
CIN 1	7	170	**96**	(91, 98)
CIN 2/3	2*	110	**98**	(93, 100)
AIS	0	7	**100**	(31, 100)

^ Subjects counted once/per row, but may be in > 1 row

* One case co-infected with HPV 52; one case co-infected with HPV 51 & 56

Efficacy - Bivalent HPV Vaccine

Phase II trial, 6.4 year follow-up

Phase III trial, 14.8 month follow-up

Bivalent HPV Vaccine - Phase II Trial

Prevention of HPV 16/18-related outcomes

Mean follow-up 6.4 years; 776 females

Endpoint	Vaccine	Control	% Efficacy	(95% CI)
Incident Infection	4	70	**95**	(87.4-98.7)
12 Month Persistence	0	20	**100**	(81.8 – 100)
CIN2/3 or AIS	0	9	**100**	(51.3 – 100)

Restricted to females who were HPV 16/18 seronegative and DNA negative to 14 oncogenic types at enrollment in initial or extended follow up phase II studies

CIN 2/3 = moderate/high-grade cervical intraepithelial neoplasia;
AIS = adenocarcinoma in situ

Bivalent HPV Vaccine - Phase III Trial

Prevention of HPV 16/18-related outcomes

Mean follow-up 14.8 months

Endpoint	Vaccine N	Vaccine cases	Control N	Control cases	Vaccine Efficacy %	Vaccine Efficacy (97.9%CI)
CIN2/3 or AIS	7788	2	7838	21	**90**	(53-99)

- Total vaccinated cohort analysis: includes participants who received at least one dose, cases counted one day after dose one, HPV 16/18 seronegative and DNA negative at baseline

- Two cases in vaccine group co-infected with another oncogenic type. Post-hoc analysis, including only lesions believed causally associated with vaccine types showed 100% efficacy

Paavonen et al. Lancet 2007;369 slide courtesy of L. Markowitz

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What about data in males? Quadrivalent Vaccine

- Randomized, double-blind, placebo-controlled trial of 4,065 men 16-26 yo
  - Efficacy against persistent genital infection with 6/11/16/18 was 85.6% (95% CI 75.1, 92.2)
  - Efficacy against genital warts and pre-cancer associated with 6/11/16/18 was 90.4% (95% CI 69.2, 98.1)

Giuliano and Palefsky, Abstracts presented at Eurogin Nov 2008

HIV-Infected Children Immunogenicity and Safety Quadrivalent Vaccine

- 120 HIV-infected boys and girls 7-11 years
- Enrolled in the US, some on anti-retrovirals
- Seroconversion >99.5%
- GMTs lower than in HIV-uninfected historical controls - significant for HPV 6 and 18
- Local adverse events similar to HIV-uninfected
- Fluctuations in CD4% and plasma HIV RNA not different from HIV-infected controls

What is the immune response to HPV vaccine?

- The major basis of protection is neutralizing antibody
- Robust data are only available after three doses
- HPV vaccines induce serum antibodies in virtually all vaccinated individuals, that persist for >= 5 years
- Antibody levels are many-fold higher in vaccinated individuals at all ages than after natural infection
- Antibody levels are higher after vaccination of young adolescents (<15 years old) than older women
- The minimum protective antibody level is not known

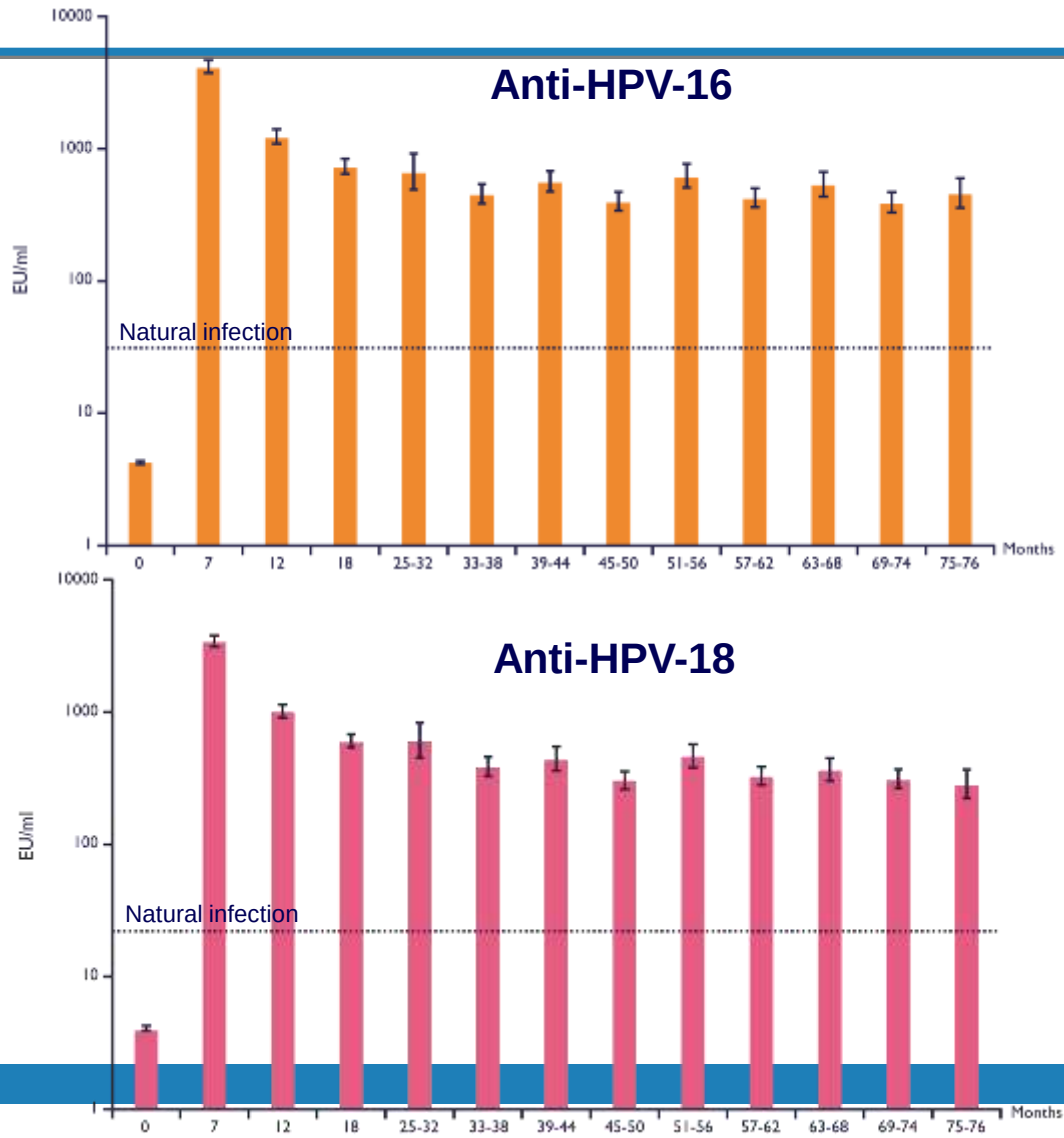
Seropositivity at months 7 and 36 after vaccination

Vaccine/HPV type	Month 7*	Month 36
Quadrivalent		
Anti-HPV 6	100%	96%
Anti-HPV 11	100%	98%
Anti-HPV 16	100%	99%
Anti-HPV 18	100%	74%+
Bivalent		
Anti-HPV 16	100%	99%
Anti-HPV 18	100%	99%

*** After all three doses + not associated with breakthrough infections**

Villa et al. Vaccine 2006 Harper et al. Lancet 2006

Bivalent Vaccine
ELISA Titers through 6.4 Years



≥98% of women remain seropositive for both HPV-16 & -18 up to 6.4 years

Poster C. Wheeler, ESPID May 13-16th , 2008

Slide courtesy of L. Markowitz

Is There Cross Protection?
(Protection against types other than 16 or 18)

Quadrivalent vaccine

- Evaluated as protection against CIN 2/3 and AIS

  VE against
  - 10 non-vaccine type-related CIN 2/3: 33% (95% CI: 6-52%)
  - types 31/45-related CIN 2/3: 59% (95% CI: 14-82%)

Bivalent vaccine

- Evaluated as protection against persistent infection

  VE against
  - 12 mos persistence with 12 non-vaccine types: 27% (97.9% CI: 0.5-47%)
  - 6 mos persistence with types 31/45: 60% (97.9% CI :21-81%)

Brown, International Papillomavirus Conference 2007
Paavonen et al. Lancet 2007;369 Jenkins, ICWC 2008 slide courtesy of L. Markowitz

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Safety Data

Quadrivalent HPV vaccine

Pooled data

Post licensure data

Bivalent HPV vaccine

Pooled data

Adverse events evaluated:

- Injection site
- Systemic
- Serious
- New medical conditions
- Pregnancy

Reports to the U.S. Vaccine Adverse Events Reporting System (VAERS) in Quadrivalent Vaccine Recipients June 2006 - August 2008

- >20 million doses distributed
- 10,326 VAERS reports, 6% were classified as serious
- Most common reports: syncope (15%), dizziness (14%), nausea (9%), injection site pain (8%)

- Deaths: 27 reports
  - 17 deaths verified; none appear to be caused by vaccine

- Guillain-Barré Syndrome (GBS): 52 reports
  - 13 confirmed: 7 also received other vaccine
  - Number of confirmed reports is within range expected by chance

- Transverse myelitis: 8 reports
  - Evidence insufficient to support causal relationship

Calugar and Slade, presented at October 2008 ACIP
http://www.cdc.gov/vaccinesafety/vaers/gardasil.htm slide courtesy L. Markowitz

World Health Organization

… SAGE recommendations published in January 2009

- http://www.who.int/wer/2009/wer8401_02.pdf

And safety report published by safety group in WHO:

- http://www.who.int/wer/2009/wer8405.pdf

Overall Recommendation

Routine HPV 16/18 vaccination should be included in immunization programmes of all countries where:

- prevention of cervical cancer and other HPV-related diseases is a public health priority
- vaccine introduction is programmatically feasible
- sustainable financing can be secured

If cost-effective analyses may guide a country's health decisions, countries should consider the cost-effectiveness of possible vaccination strategies in their country or region, when feasible.

Target populations

- The primary target population should be young adolescent girls.

- Because vaccination is most efficacious in girls who have not become sexually active and are naïve to HPV 16 and 18, programmes should determine primary target age group based on:
  - data on the age of sexual initiation
  - the feasibility of reaching young adolescent girls through schools, health-care facilities, or community-based methods.

- In most countries, this group would include girls within the age range of 10–13 years.

Target populations (cont'd)

Catch-up strategies for older adolescent females and young women are recommended to supplement routine vaccination of young adolescent females if such programmes are:

- feasible
- affordable
- cost-effective
- do not divert resources from
  - vaccinating the primary target population
  - existing, effective cervical cancer screening programmes

Rationale for HPV vaccine licensure and recommendations in developed countries

- High efficacy against persistent HPV infection and precancerous cervical lesions
- High efficacy against anogenital warts (quadrivalent vaccine)
- Good safety profile based on available data
- In some countries, vaccination is cost-effective when used to complement cytology screening
- Infrastructure exists to deliver vaccines through primary care systems, schools, or other settings

HPV vaccines - Challenges

HPV vaccination holds great promise for improving health in the world …

But existence does not mean :

1- Automatic acceptance and uptake

2- Access and affordability

In the reality of overburdened health systems …

How to ensure access to an affordable HPV vaccine?

- **HPV vaccine is a critical public health need for all women**
- **Inequity in developping countries is high particularly for poorer women in less developed countries**
- **Will the same women who access cervical cancer screening also get HPV vaccines?**
- **How can women get equitable access to an affordable, quality vaccine ?**
- **What will be the role of existing programmes and services ?**

Features of HPV vaccines: challenges and opportunities

- **HPV vaccination raise issues of cost and financing and programme delivery to adolescents**

- **But it may strengthen or support adolescent immunization programmes, through schools or other delivery systems, according to country-specific needs and socio-cultural context**
  - **Additional promotion as vaccine against STI may foster negative connotation**
  - **Likelihood of coincidental occurrence of various pathologies in close proximity to vaccinations (gynaecological and autoimmune disorder**

    → Need to be prepared

- **It may also link immunization with other public health interventions for adolescent (sexual health and other health interventions)**

Features of HPV vaccines: challenges and opportunities

- Sexual and reproductive health programmes can take the opportunity to develop new packages for counseling young people and women receiving the vaccine

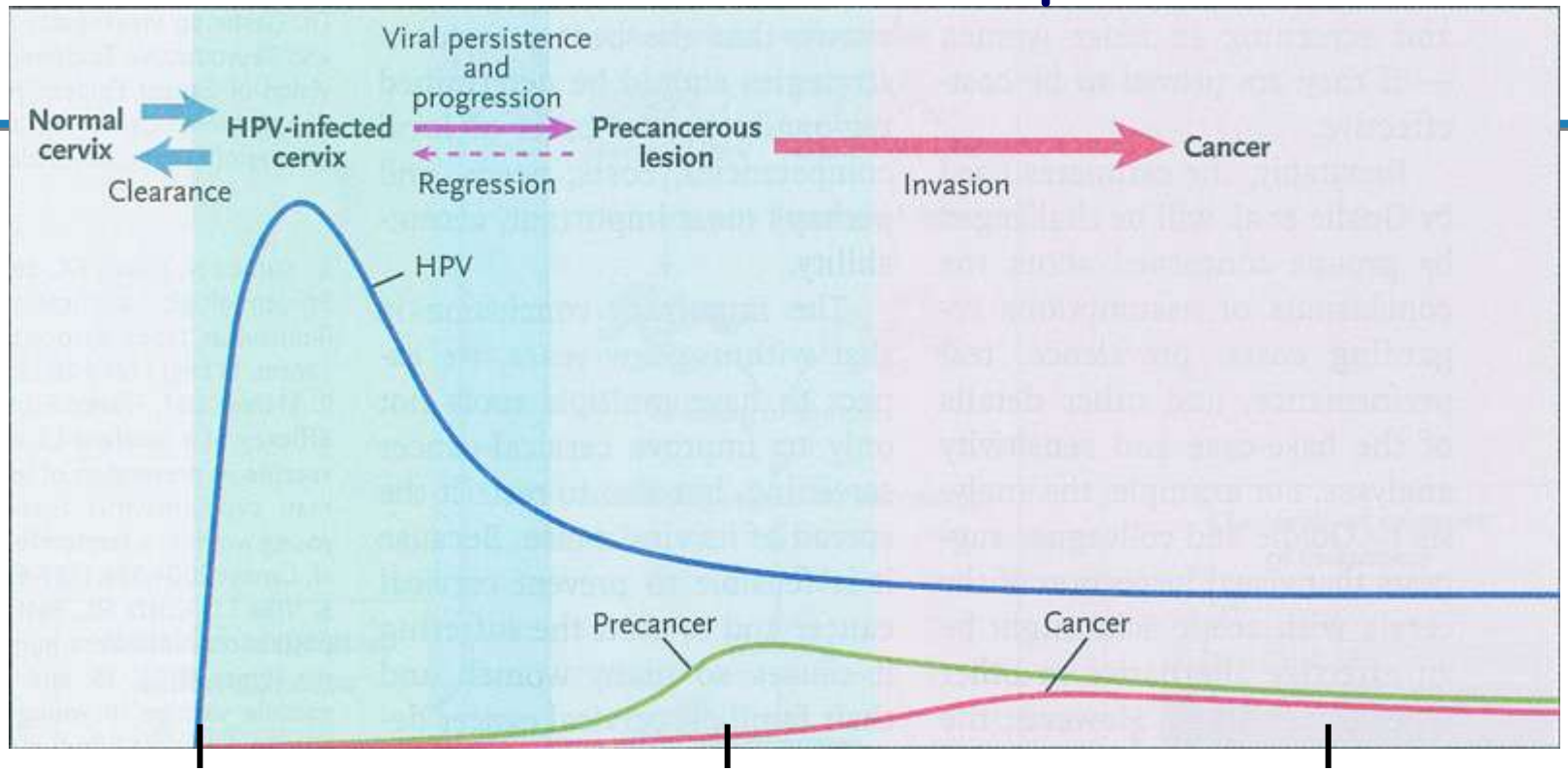
- But the gained experience with HPV vaccine introduction may serve as a model for other vaccines against STIs in the future

Features of HPV vaccines: challenges and opportunities

- Cancer control programmes will confront difficult decisions regarding prioritizing interventions for cancer prevention and control

- But HPV introduction may also help them to reinforce cervical cancer control programmes and cancer registries

Target age groups of different interventions and links with cervical cancer prevention



Vaccination
School health
Adolescent health

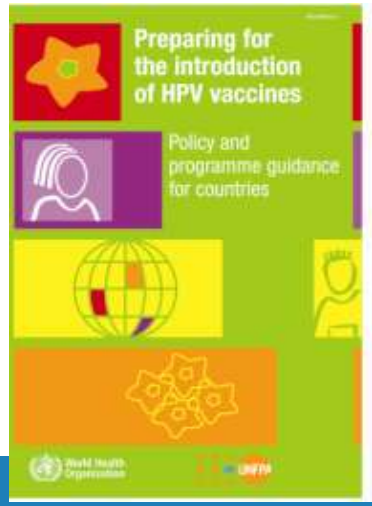
Screening

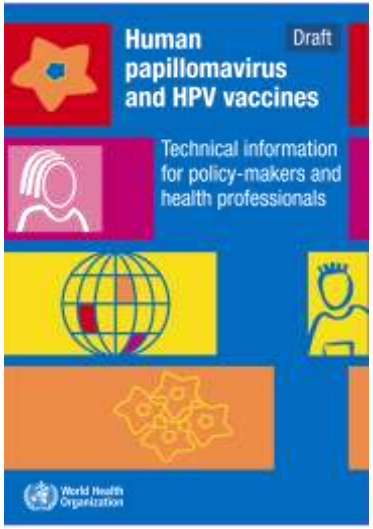
Treatment

Inter-disciplinary approach required to span cervical control interventions

We have a unique opportunity

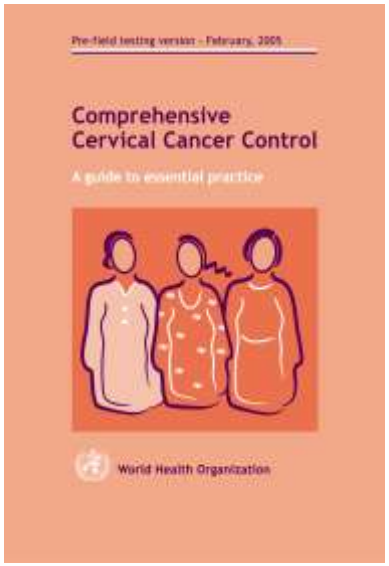
- **HPV vaccines have great potential to reduce global cervical cancer burden**
- **Vaccines complement other prevention and control methods (sexual risk reduction, screening, treatment)**
- **WHO is supporting vaccine introduction through:**
  - **Policy**
  - **Programmatic support**
  - **Research**
  - **Communication**



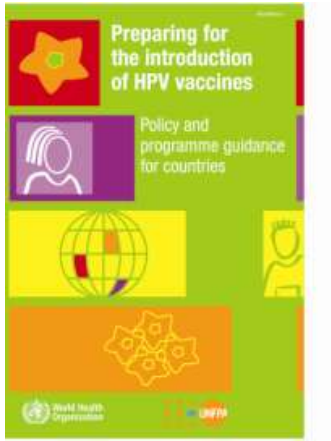


World Health Organization

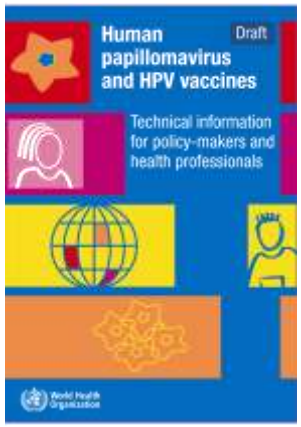
WHO Support for evidence based decision making



Comprehensive cervical cancer control For health professionals



Preparing for the introduction of HPV vaccins: policy and programme guidance for countries

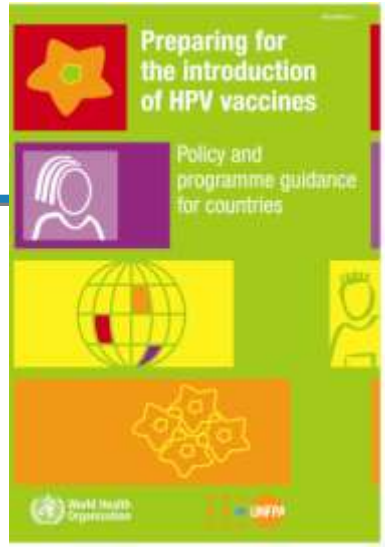


Human papillomavirus and HPV vaccines: technical information for policy makers and health health professionals

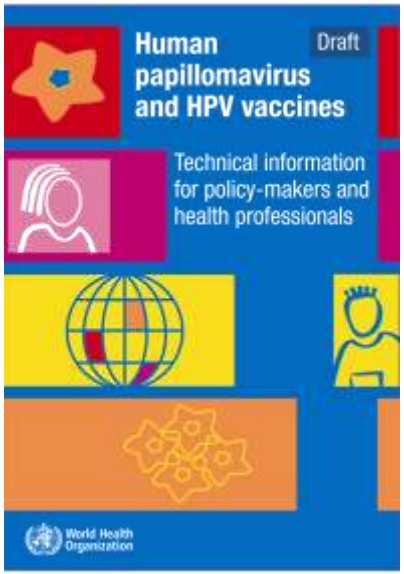
http://www.who.int/reproductive-health/publications/cancers.html

Conclusion

- Cancer is an increasing public health threat, in particular in low and middle income countries.
- WHO recommends the comprehensive and integrated approach to cervical cancer prevention in the context of national cancer plans.
- Cervical cancer control is part of the overall framework of the action plan and is a WHO priority.
- WHO aims to decrease inequity through appropriate access to care.
- Partnerships are essential for moving ahead.
- Because of its cost, critical issues of equity associated with the new vaccines must be addressed.



Acknowledgments



WHO Working group on HPV vaccines, including colleagues from:

- **Immunization**
- **Reproductive health**
- **Child and Adolescent health**
- **and Cancer control**