

HPV infection, Cervical Cancer and HPV vaccines

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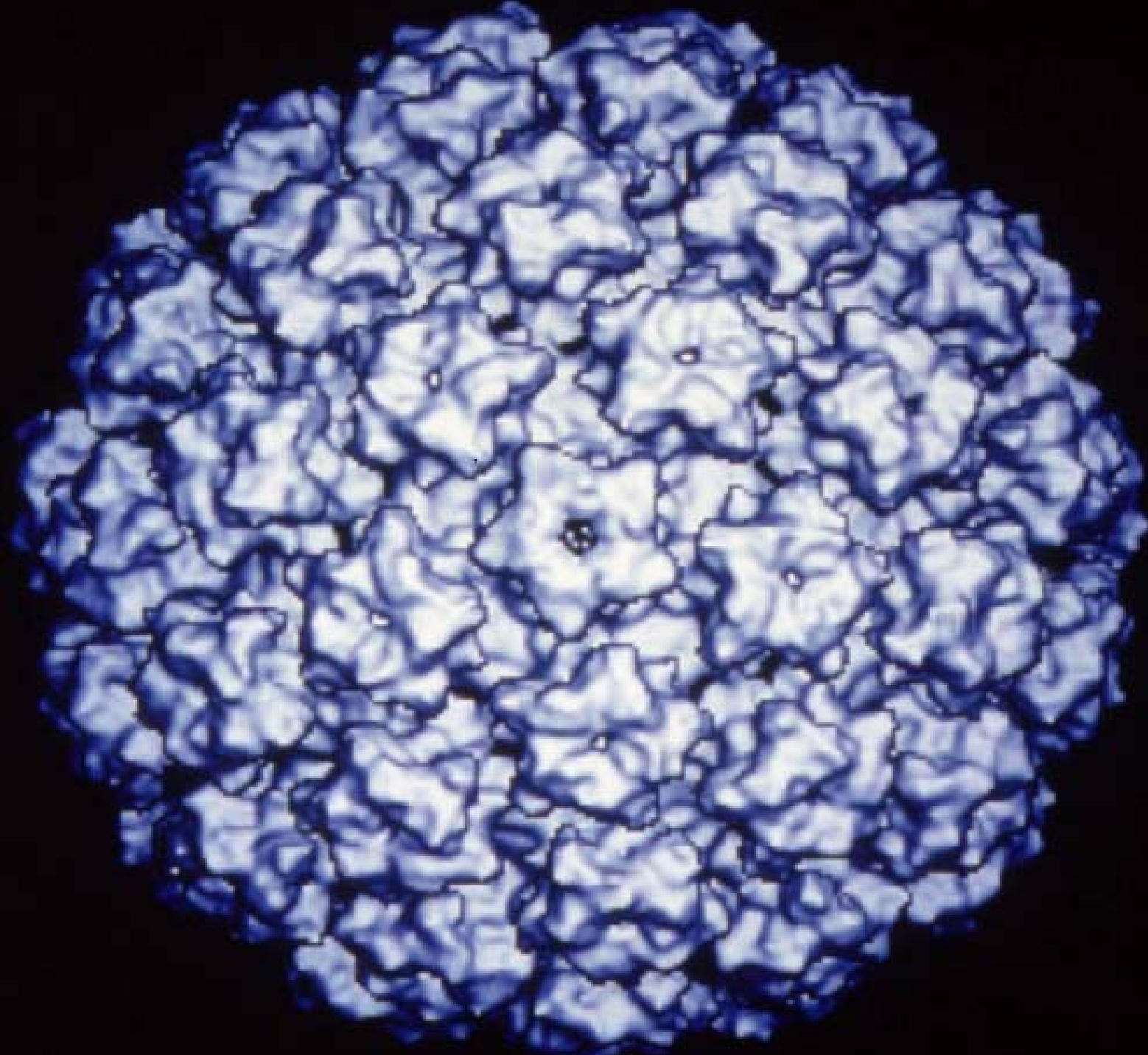
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Transmission of genital HPV

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



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HPV Natural History

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

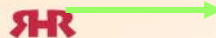
1075 women (HPV- at entry) / 15-19 years

- **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)



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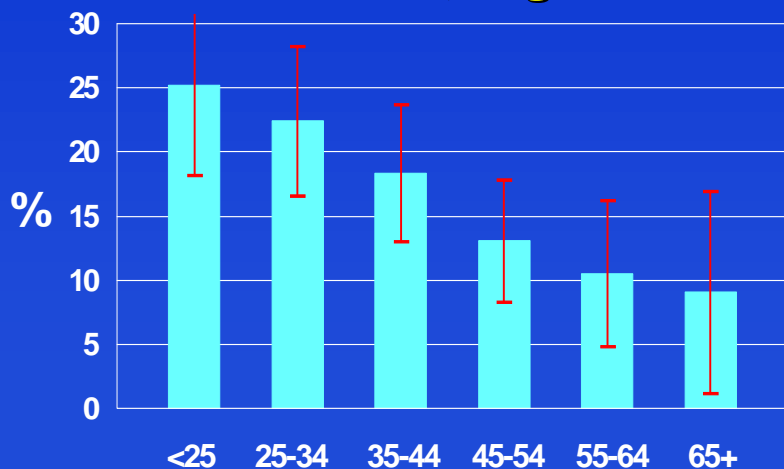
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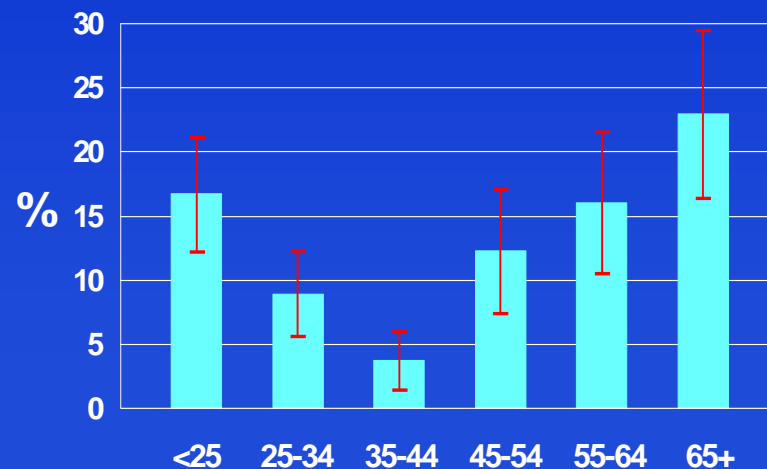
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Prevalence of HPV DNA in the general female population

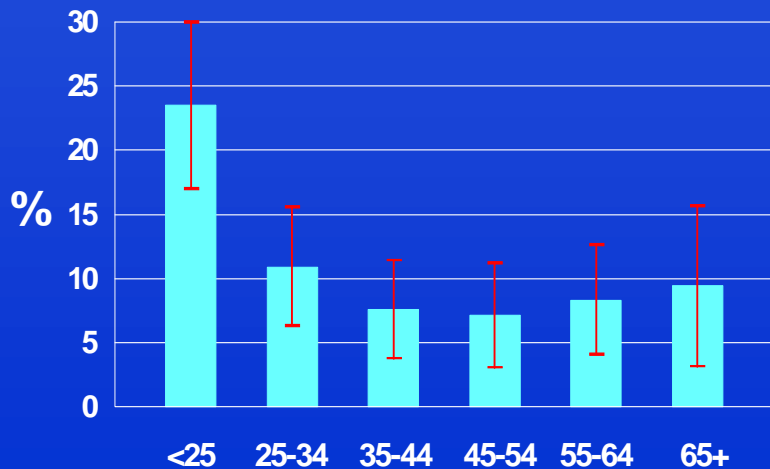
Concordia, Argentina



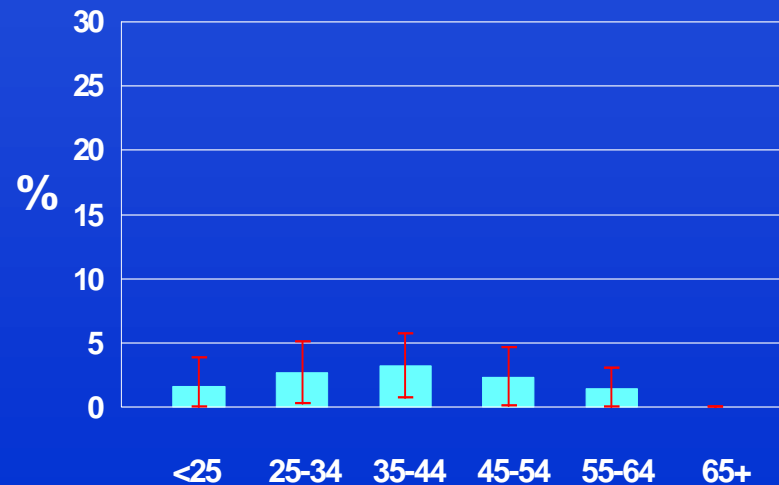
Morelos, Mexico



Ho Chi Minh, Vietnam



Hanoi, Vietnam



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



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Genital HPV infection: clinical manifestations

- Latent infection
- Genital warts
- Intraepithelial neoplasia (cervical, vaginal, vulvar, anal)
 - I
 - II
 - III
- Invasive cancer



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Subclinical HPV infection

- **Only detectable with molecular techniques**
- **Very common among young women**
- **Associated with most genital HPV types**



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Genital warts

- **Very common**
- **Increasing incidence in some areas**
- **Highly contagious**
- **Associated with HPV types 6 and 11**
- **Not associated with cervical cancer**



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HPV and cervical neoplasia

- **More than 95% of cervical neoplasia have detectable HPV DNA**
- **Relative risks of >65 in case-control studies**
- **Extensive laboratory evidence**



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IARC: HPV and cervical cancer

Country	HPV positives (%)		ORa* (95 % CI)
	Cases	Controls	
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

IARC Monograph on HPV (1995)

- HPV 16 and 18 are human carcinogens (Group 1)
- HPV 31 and 33 are probably carcinogenic (Group 2A)
- Some HPV types other than 16, 18, 31 and 33 are possibly carcinogenic (Group 2B)
- There is evidence suggesting lack of carcinogenicity to the cervix of HPV 6 and 11 (Group 4)



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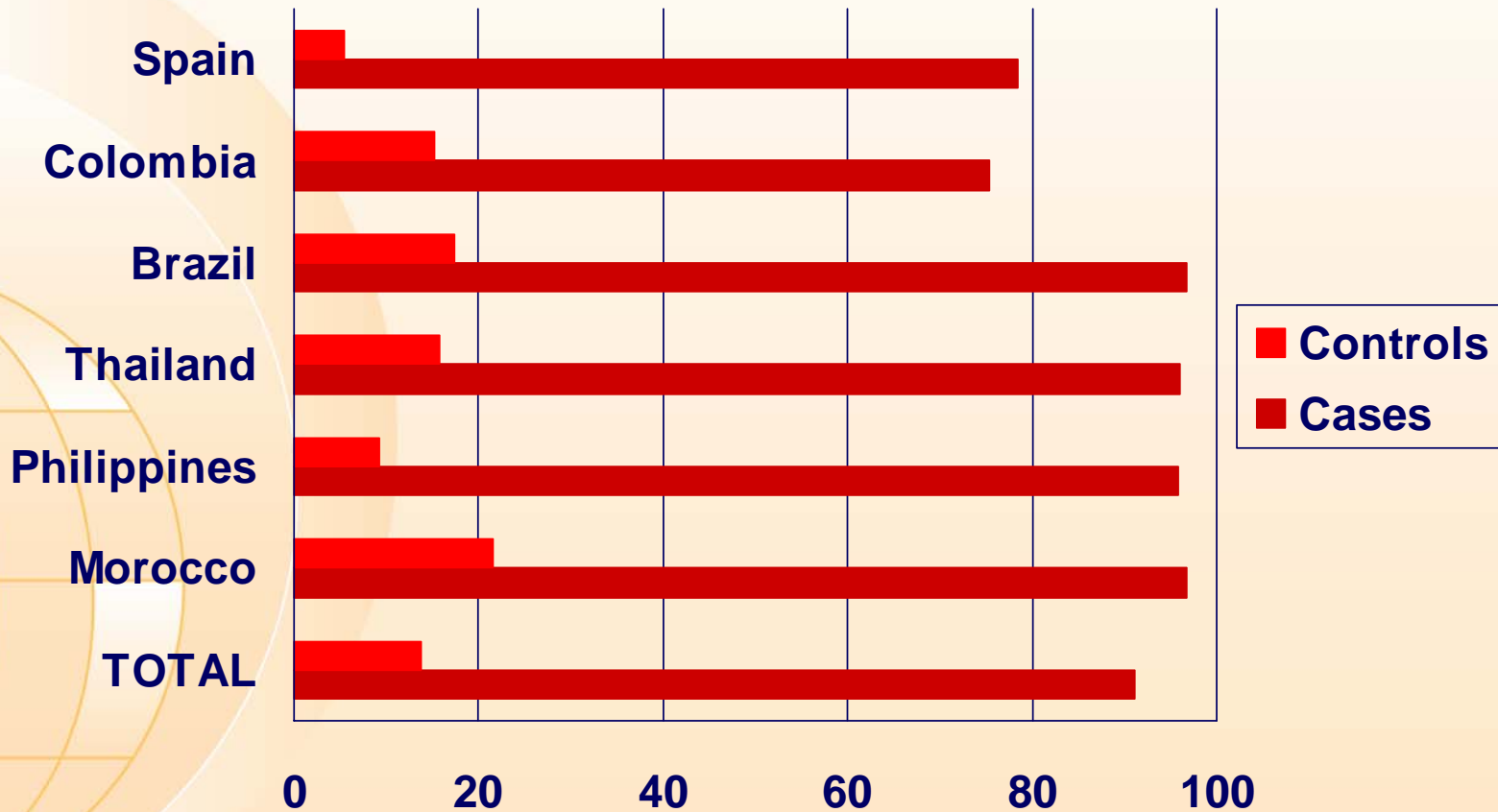


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IARC: HPV-DNA Prevalence



(Munoz et al., IARC)



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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 %

HPV-associated cancers

Of the total estimated HPV-attributable cancers in the world, 94% affect women and 80% occur in developing countries.



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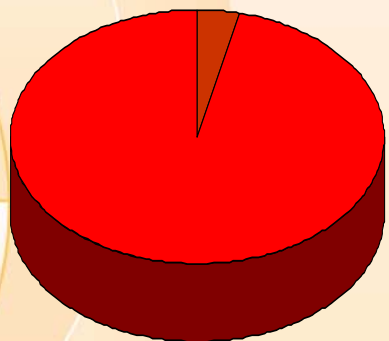
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CERVIX CANCER (2002)

Developed

83,400 cases

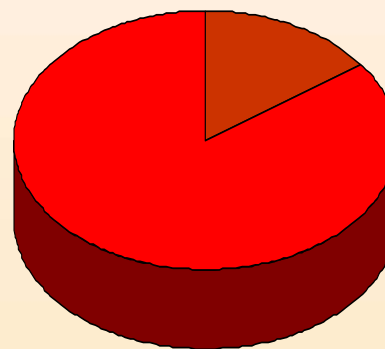
3.6% of all
cancers



Developing

409,400 cases

15.0% of
all cancers



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Cervical cancer Age-adjusted survival (%)

● US	70%	● Thailand	58%
● W. Europe	66%	● S. America	55%
● Japan	65%	● India	42%
● E. Europe	51%	● Sub S. Africa	21%
● All developed	61%	● All developing	41%



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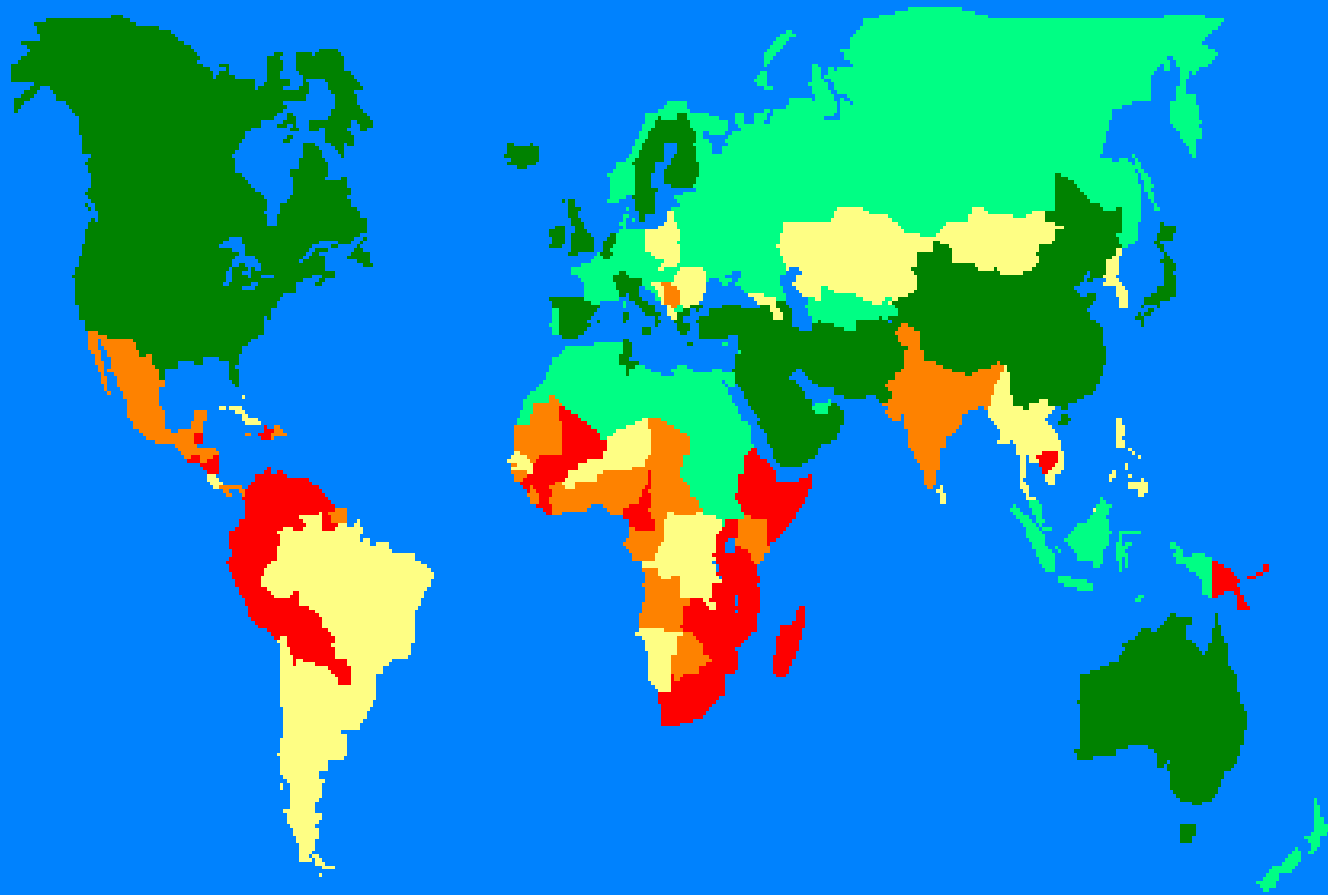
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CANCER OF CERVIX UTERI: 493,000 cases in 2002 (4.5% total)

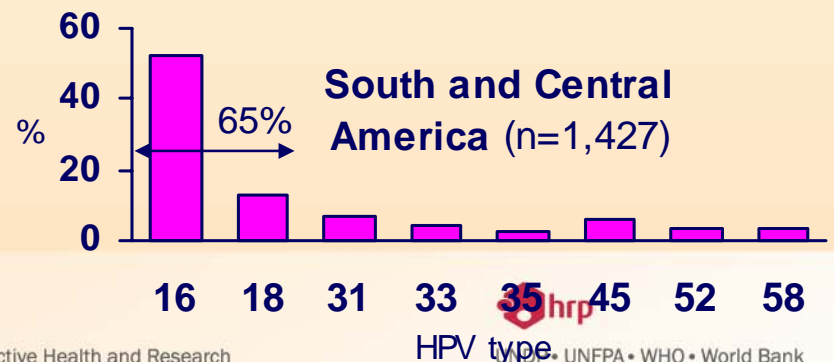
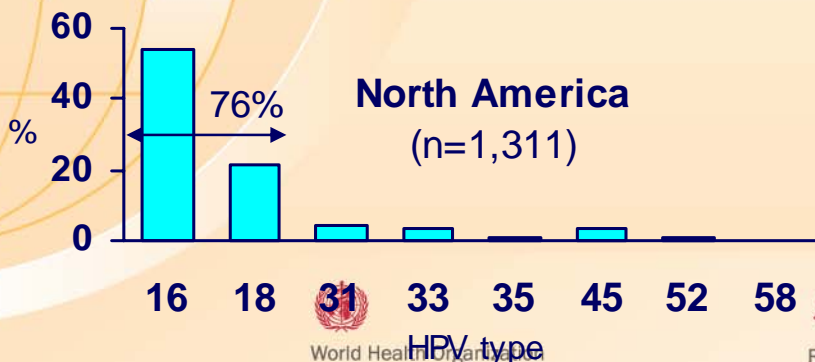
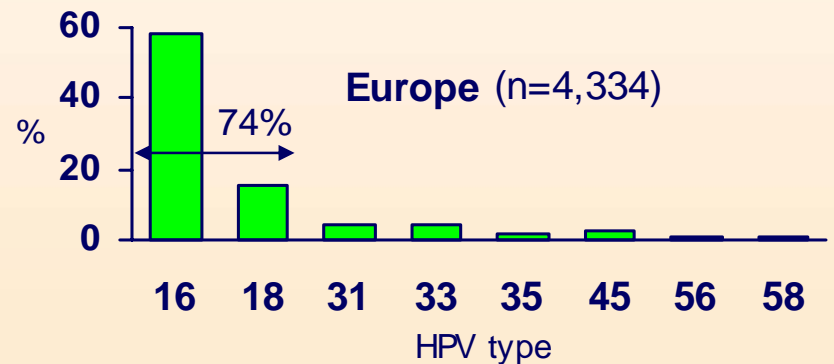
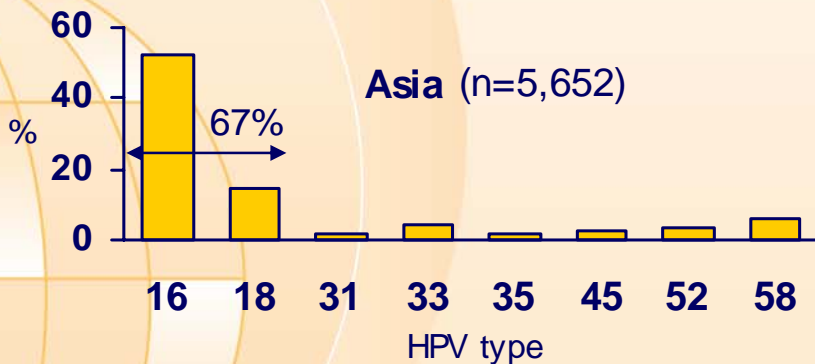
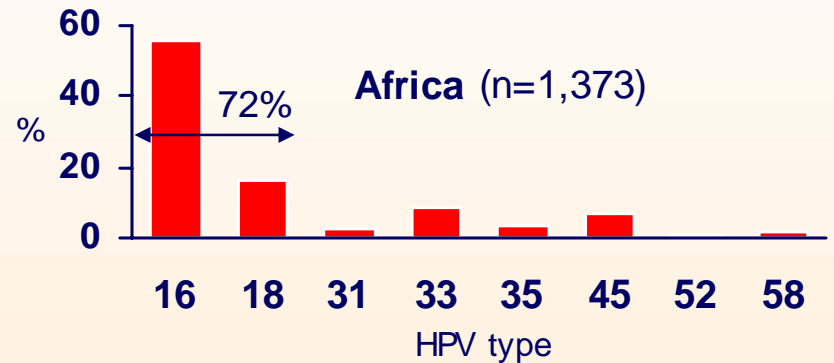
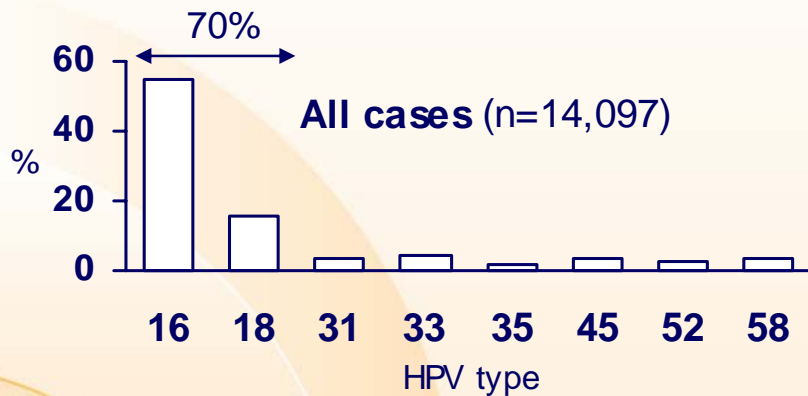
Incidence of Cervix uteri cancer: ASR (World) (All ages)



■ < 9.3 ■ < 16.2 ■ < 26.2 ■ < 32.6 ■ < 87.3 per 100,000 women

GLOBOCAN 2002

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



Many studies of HPV genotype distribution in cervical cancer around the world, but:

- Relative gaps in Central Asia, Africa and Eastern Europe
- Not enough known about genotype distribution in cancer cases among HIV-infected individuals, especially outside north America



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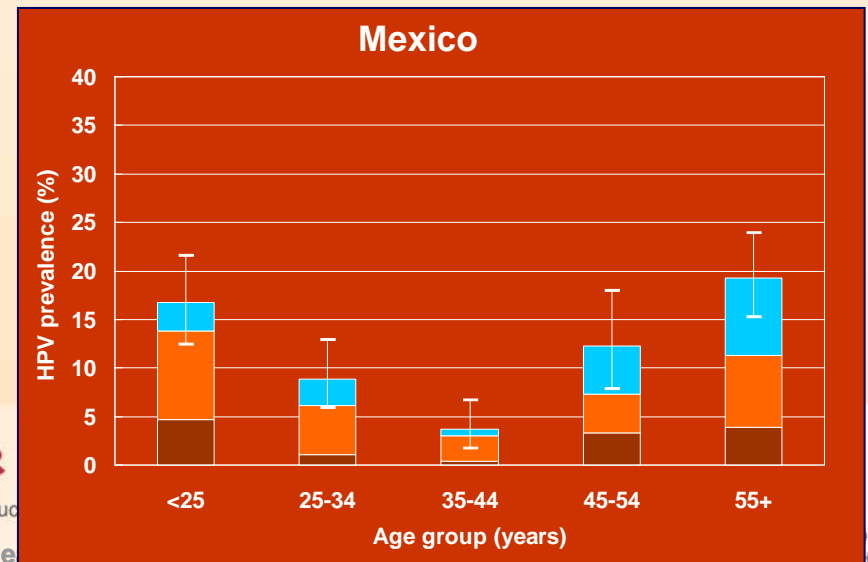
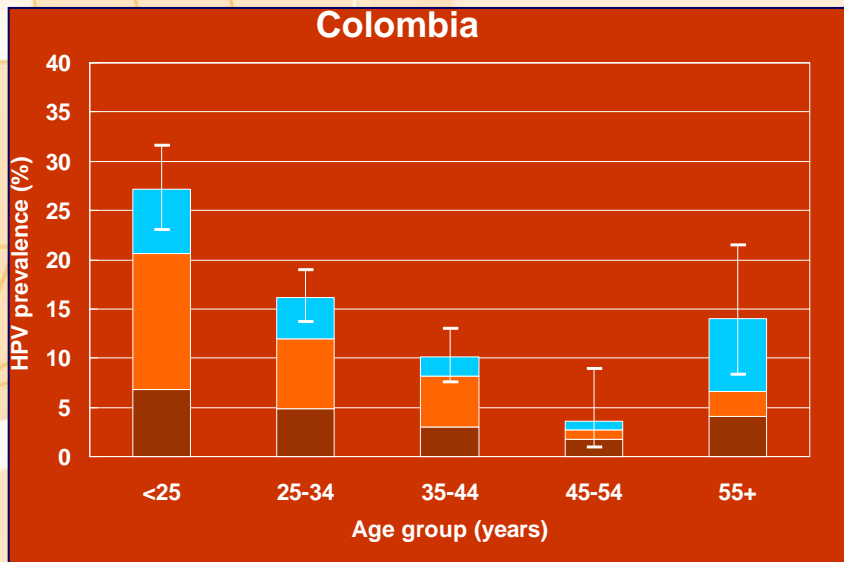
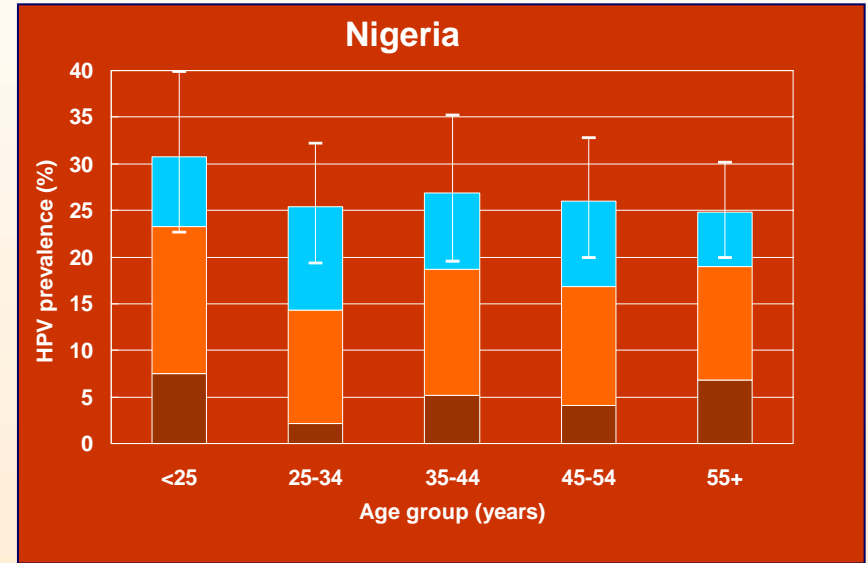
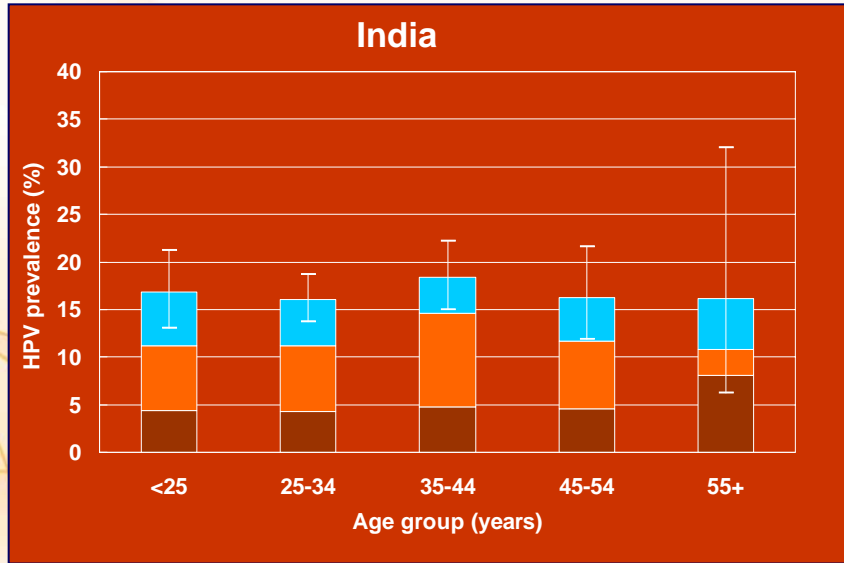
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Prevalence of cervical HPV DNA by age and HPV type in women with normal cytology: IARC Multi-centre HPV Prevalence Survey

■ HPV 16 or 18
 ■ Other high-risk types
 ■ Low-risk types only



HPV vaccines

- **June 8, US FDA approved quadrivalent HPV (type 6, 11, 16, 18) Recombinant vaccine**
- **Use: women 9-26 years**
- **Indication: prevention of HPV related diseases:**
 - **Cervical cancer**
 - **Genital warts**
 - **Precancerous or dysplastic lesions (AIS, CIN 2/3, CIN 1, VIN 2/3, VaIN 2/3)**



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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
- No trials done in Africa



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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



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What is HPV vaccine efficacy against vaccine-type infection/disease in HPV-naïve women aged 15-26 years?

- Data from the large phase III trials are only available for the quadrivalent vaccine
- Efficacy against persistent infection due to types 16 or 18 is over 90% in women who received 3 doses
- Efficacy against CIN 2 (bivalent), or against CIN 2/3/AIS (quadrivalent), due to types 16 or 18 is close to 100%, with a high degree of certainty for the quadrivalent vaccine.



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What is VE against HPV 16/18 related CIN 2+ in women who have already been exposed to those HPV types (quadrivalent vaccine)?

- 27% of women had evidence of prior exposure or ongoing infection with ≥ 1 of the 4 vaccine types
- Overall, no effect of vaccine was seen among women who had already been infected with HPV 16 and 18 against the relevant type-specific events
- Some evidence of varying effects in different subgroups of women according to the type of previous infection, but further data are needed.



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Is there any cross-protection against other types not included in the vaccine?

- For the bivalent vaccine, partial protection against new infections by two other types has been reported:
 - Type 45 : 95% (63,100)
 - Type 31 : 55% (12,78)
- For the quadrivalent vaccine, cross-neutralization has been reported against types 45 and 31 ([PL 1-6] Sunday, September 3, 2006)



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HPV vaccines – Key findings

- Vaccines efficacy extremely high against HPV vaccine type diseases in HPV naive women (+/-100% for HPV related diseases - two vaccines)
- In women already exposed to HPV type 16/18 much less effect
- Good antibody persistence for 3 to 5 years
- Acceptable safety profile



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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



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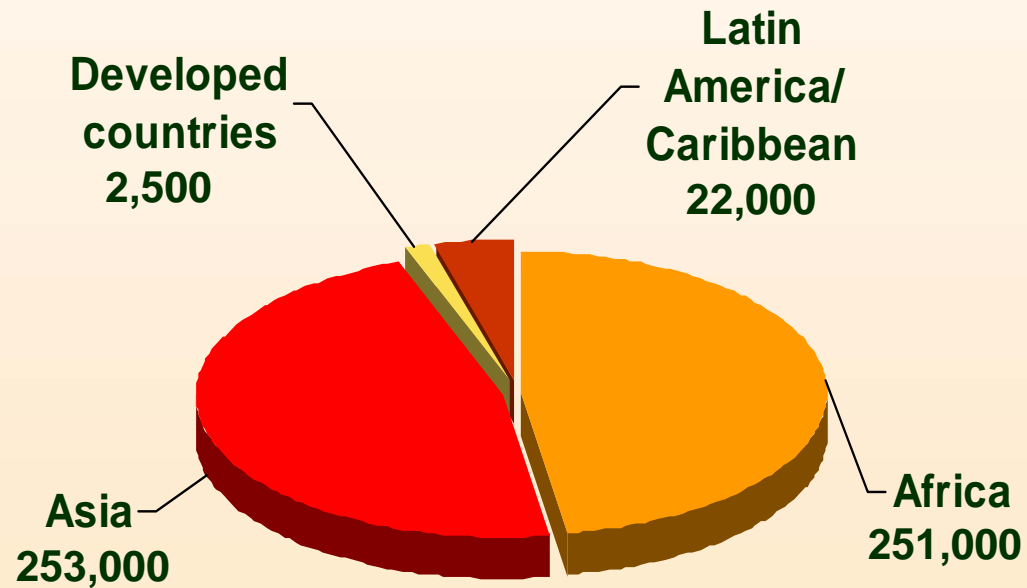
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Maternal mortality in 2000

Total maternal deaths = 529,000



(Source: WHO/UNICEF/UNFPA, 2003)



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Access to an affordable HPV vaccine

- **HPV vaccine is a critical public health need for all women - particularly to poorer women in less developed countries.**
- **How can these women get equitable access to an affordable, quality vaccine ?**
- **Will there be adequate quantities of vaccine available at an affordable price for developing country programmes ?**
- **What will be the role of existing programmes and services ?**



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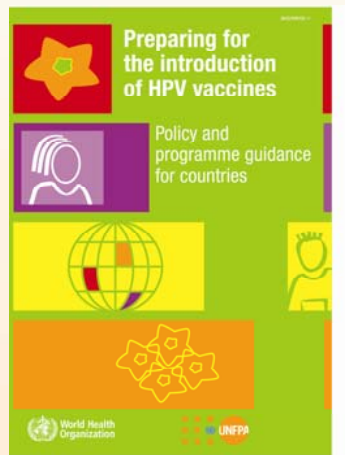
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WHO-UNFPA Consultation on Sexual and Reproductive Health programmes and HPV vaccines, March 2006

- **Broad-based consultation meeting**
 - **Guidance Note**
 - **Background Paper**
- **Consensus on key issues surrounding up-coming country introduction programmes**
- **Policy and Programmes, not a technical reference on vaccines or cervical cancer control**



Human papillomavirus and HPV vaccines Technical Information for Policy-makers and Health Professionals



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Features of HPV Vaccines

A Unique Opportunity

An Expensive Product

Introduction Challenges

Not Business as Usual



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Features of HPV Vaccines: Unique Opportunity

- ✓ HPV vaccination will bring national immunization programmes into socio-politically charged environment of sexual health among pre-teenage girls (and boys)
- ✓ Cancer control programmes will confront difficult decisions regarding prioritizing interventions for prevention of CxCa
- ✓ SRH programmes will need to develop new strategies for counseling young people and women receiving the vaccine
- ✓ Experience with introduction may serve as a model for eventual HIV vaccine, microbicides introduction



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Features of HPV Vaccines: An Expensive Product

- ✓ **Higher cost than traditional EPI vaccines**
- ✓ **Risk of HPV vaccine increasing health inequities**
- ✓ **Cost is important but should not be the sole criterion – additional benefits also are important**



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Features of HPV Vaccines: Introduction Challenges

Priority to country-specific considerations:

- ✓ **Affordability**
- ✓ **Accessibility**
- ✓ **Feasibility**
- ✓ **Acceptability**

Avoid harmful backlash against SRH, ARH

Update national cervical cancer control strategies



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Features of HPV Vaccines: Not Business as Usual

Partnerships,

Partnerships,

Partnerships.....



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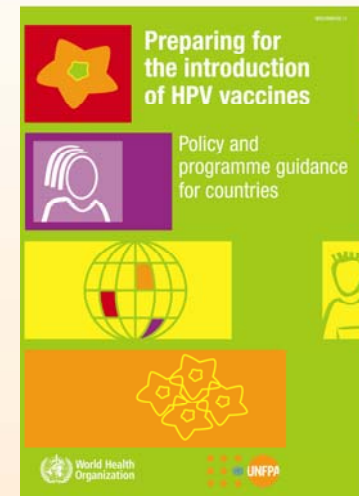


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Preparing for the HPV Vaccine

Three Key Areas:

1. **Advocacy, Information and Communication**
2. **Service Delivery**
3. **Stewardship and Financing**



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Advocacy: Providing information for evidence-based decisions

Lack of information



Lack of consumer demand



Lack of political will



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Advocacy, Information and Communication

- ❖ **Managing expectations and addressing concerns**
- ❖ **Basic consideration: How to present these new vaccines in clear and non-confusing health messages adapted to each country's sociocultural norms**
- ❖ **Promotion strategies based on country-specific circumstances**



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Service Delivery: Reaching Target Populations

- ✓ **School-based strategy attractive, first option, yet limited coverage in many settings**
- ✓ **Adolescent SRH programmes have experience reaching out-of-school youth**
 - **Lack service delivery experience and capacity required for HPV vaccines**
- ✓ **Community programmes can increase awareness, create linkages with services both public and private**
 - **Referral and Vouchers**
- ✓ **SRH Programmes can reach women (FP, MNH, cervical cancer screening) about need for HPV immunization of younger women and girls**



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Service Delivery: Partnerships Between Programmes

- ✓ HPV vaccine delivery should be built on structures already in place
- ✓ National Immunization Programmes likely to assume leadership in most settings
- ✓ Delivery strategies require partnership coordination mechanism between programmes
- ✓ These will need guidance and support to avoid bureaucratic politics



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Service Delivery: Monitoring and Evaluation

- ✓ Attention to data needs through both routine NIP surveillance and cancer registers
- ✓ Monitoring of vaccine coverage data and outcomes of post marketing surveillance
- ✓ Results from pilots and demonstration studies are important: Dissemination Strategies / Resources



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Health Systems Stewardship and Financing

- **Partnership:** A broad range of stakeholders should be involved in developing a strategy for comprehensive introduction of HPV vaccines – international and national levels
- **Money:** developing countries concern about ability to pay for the HPV vaccine and increased cost of introducing a new vaccine
- **Models** should be developed at country level to forecast demand and to estimate the financing and coverage needed to have an impact on disease at the population level
- **Securing international funding commitments for HPV vaccines (e.g. GAVI, UNICEF, PAHO revolving funds)**



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Exciting possibilities with new vaccines

But more data are necessary

- **Age:** can the vaccines be given to 4-6 year olds? Trials urgently needed eg of school-entry age groups
- **Males:** marginal benefits and costs of vaccinating males?
- **Cross protection** against persistent infection / CIN 2+ due to HPV 31, 45?
- **Duration of immunity** – booster needed?
- **Safety and efficacy** in immunocompromised persons (HIV+)? in pregnant women?
- **Simultaneous administration** with other vaccines esp TdaP, MMR
- **Logistics:** stability / cold chain/ potential for Uniject delivery
- **Cost**



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Conclusions

- **Exciting possibilities with new vaccines but more data are necessary**
- **Overarching consideration is to position the HPV vaccine within a comprehensive, integrated service delivery structure**
- **Because this vaccine "fits" in several different programmes, partnerships are key to any successful introduction**
- **HPV vaccine is one element of a cervical cancer control strategy**
- **Because of its cost, critical issues of equity associated with the new vaccine must be addressed**



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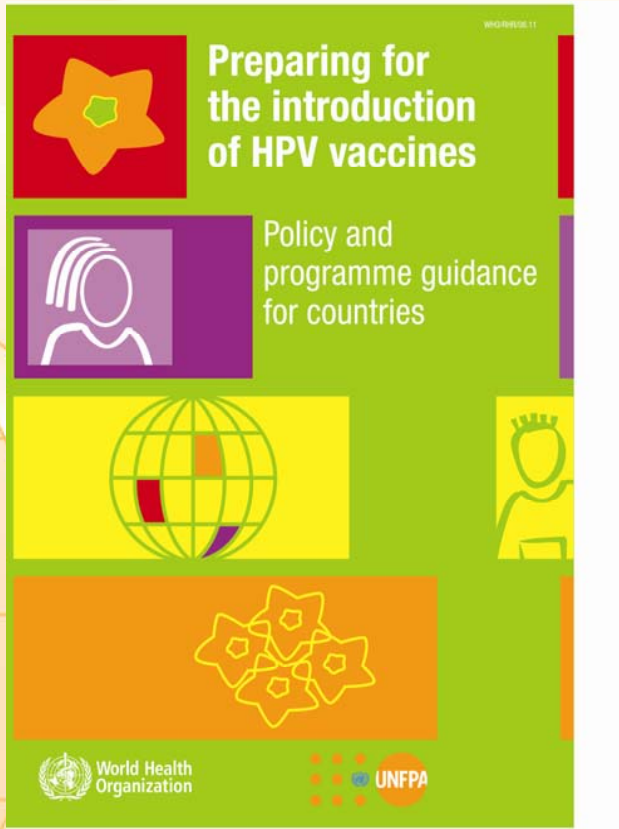
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WHO Working group on HPV vaccines

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UNFPA

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