

HPV Vaccination: What's all the fuss about!

Katharina Kieser

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Division of Gynecologic Oncology

QEII Health Sciences Center

Outline

- HPV and cervical carcinogenesis
- Vaccine development
- Application of Vaccine
 - Pre-exposure
 - Post-exposure
 - clinic
- Impact on Screening programs
- How do I get my patient vaccinated?

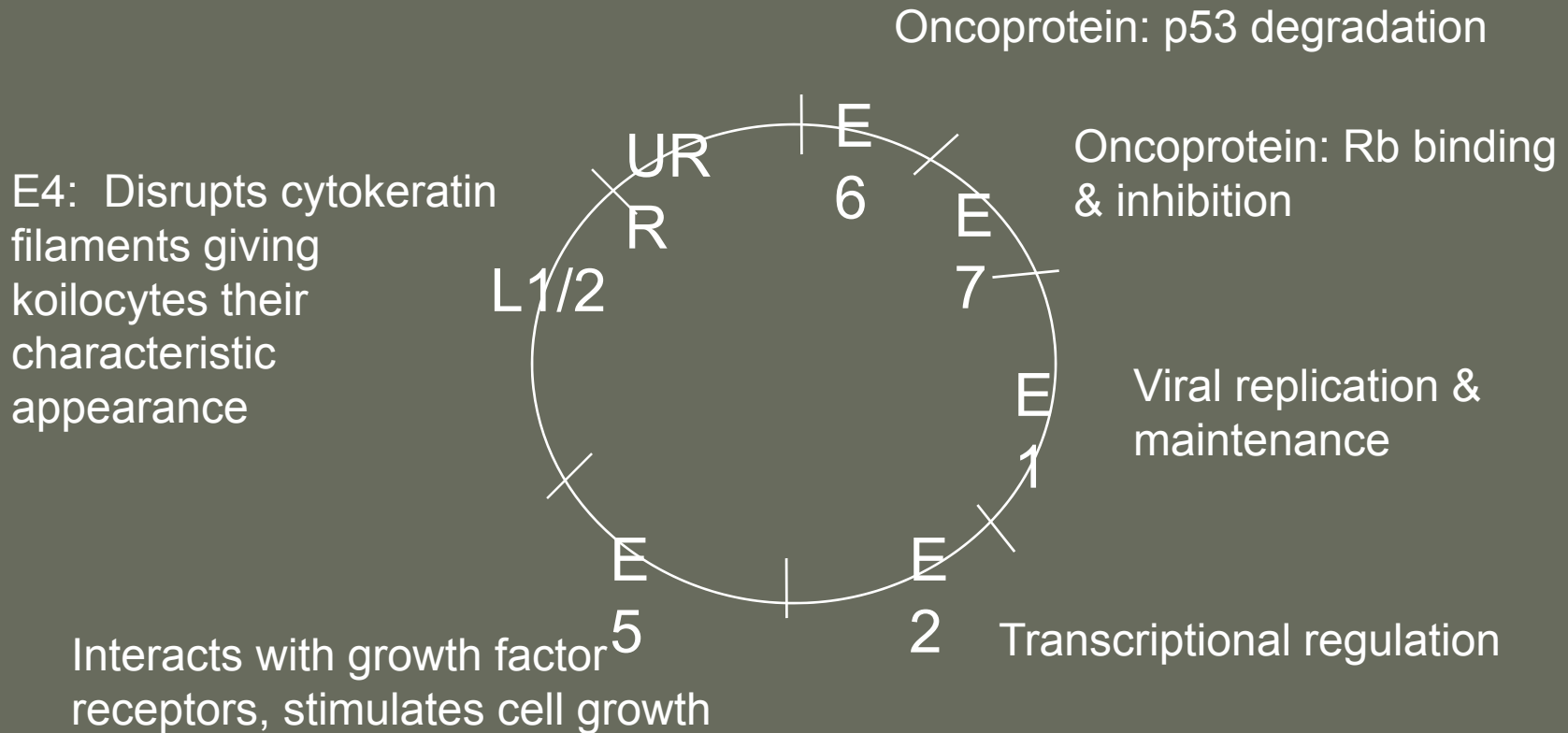
HPV

Non-enveloped double stranded DNA virus

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

- > 100 types identified
- ~30-40 anogenital
 - 15-20 oncogenic types, including 16, 18, 31, 33, 35, 39, 45, 51, 58
 - HPV 16 (54%) and HPV 18 (13%) account for most of the cervical cancers worldwide
 - Non-oncogenic types include 6, 11, 40, 42, 44, 54

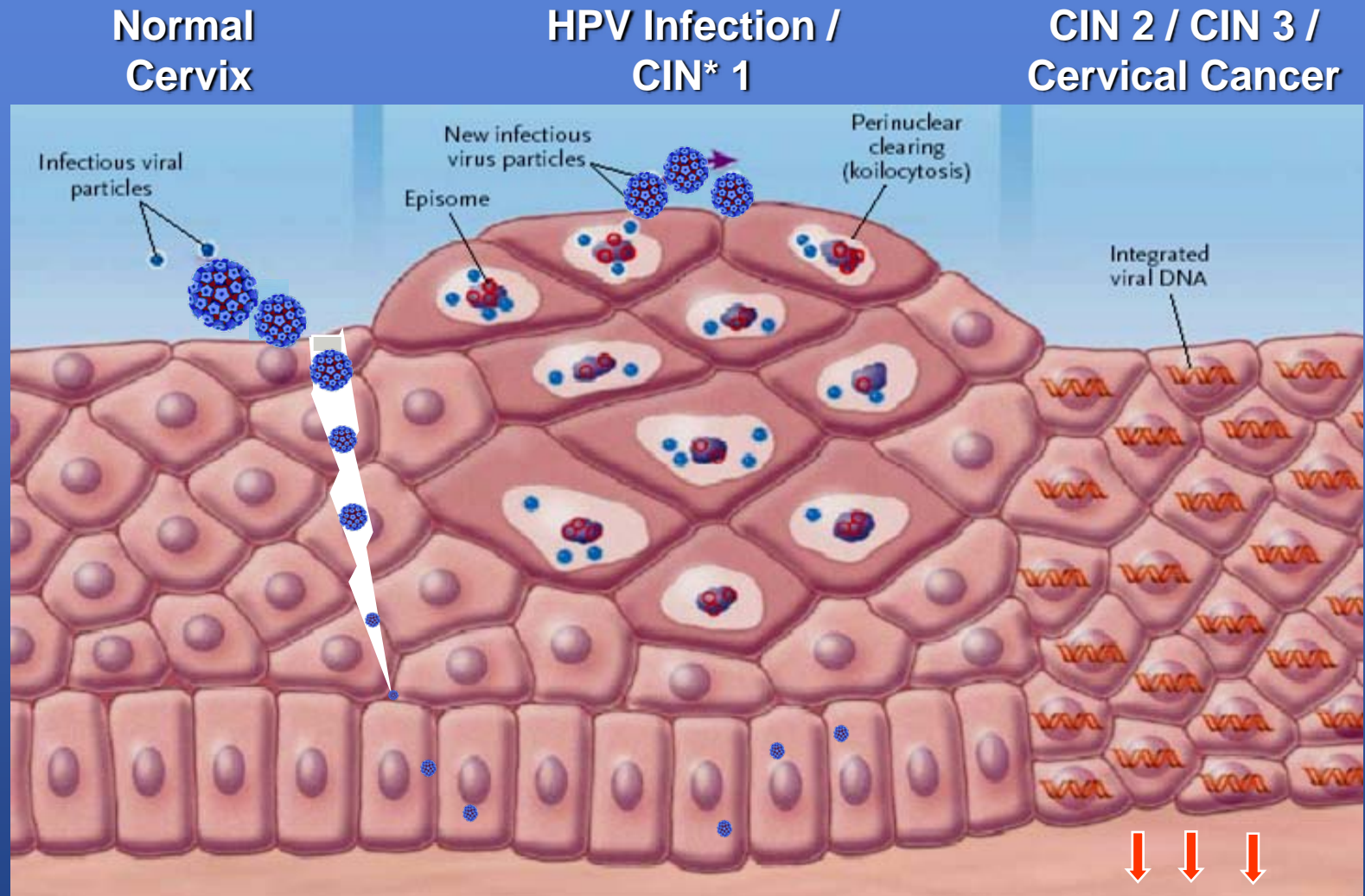
Infection



Infection

- 8000 base pair, double stranded DNA episome is replicated with host genome
- HPV infects basal cells of cervical epithelium
 - Micro abrasion at transformation zone
- Infected daughter cells migrate to upper epithelium
- Virions are assembled in surface cells and spread with cell sloughing

Spectrum of Changes in Cervical Squamous Epithelium Caused by HPV Infection¹



*CIN = cervical intraepithelial neoplasia

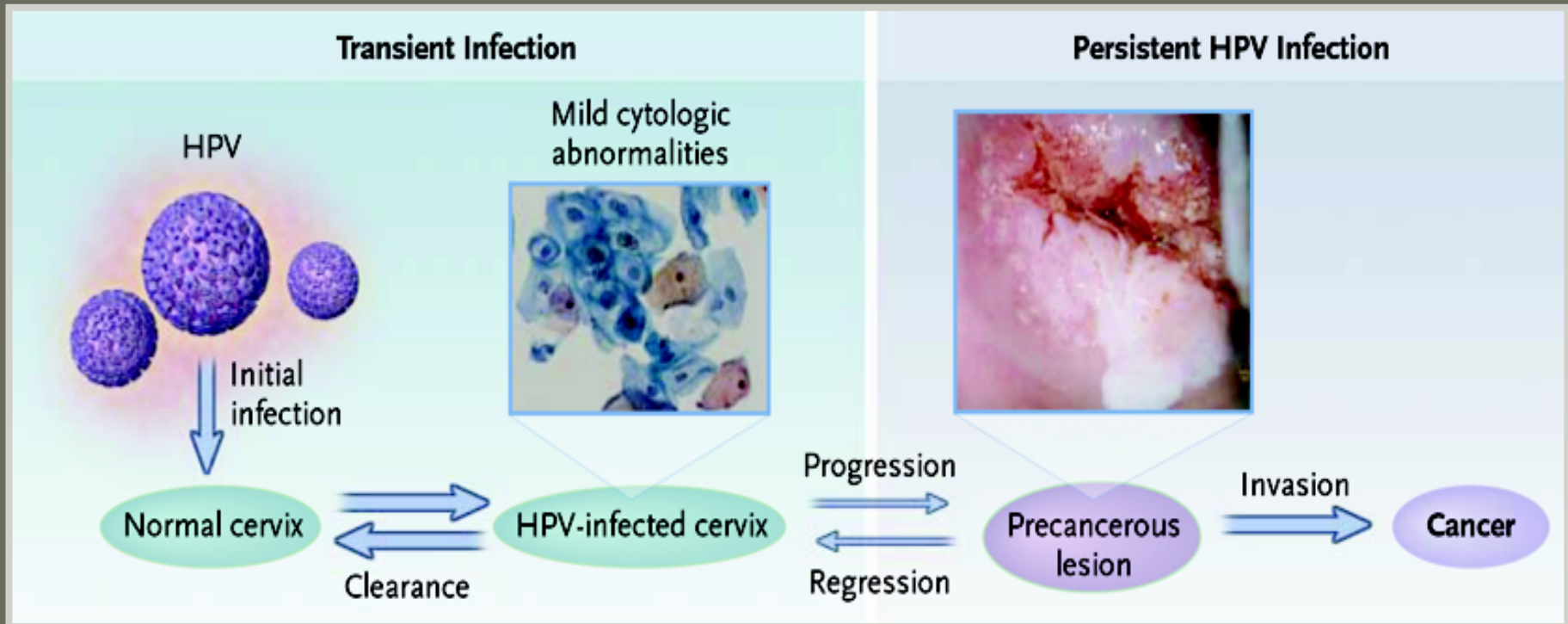
Cervical Cancer Is Essentially Caused by Oncogenic HPV

- Infection with oncogenic HPV types is the most significant risk factor in cervical cancer etiology.¹
- Analysis of 932 specimens from women in 22 countries indicated prevalence of HPV DNA in cervical cancers worldwide = 99.7%.²
 - Tissue samples were analyzed for HPV DNA by 3 different polymerase chain reaction (PCR)–based assays, and the presence of malignant cells was confirmed in adjacent tissue sections.²

HPV and Cancer¹

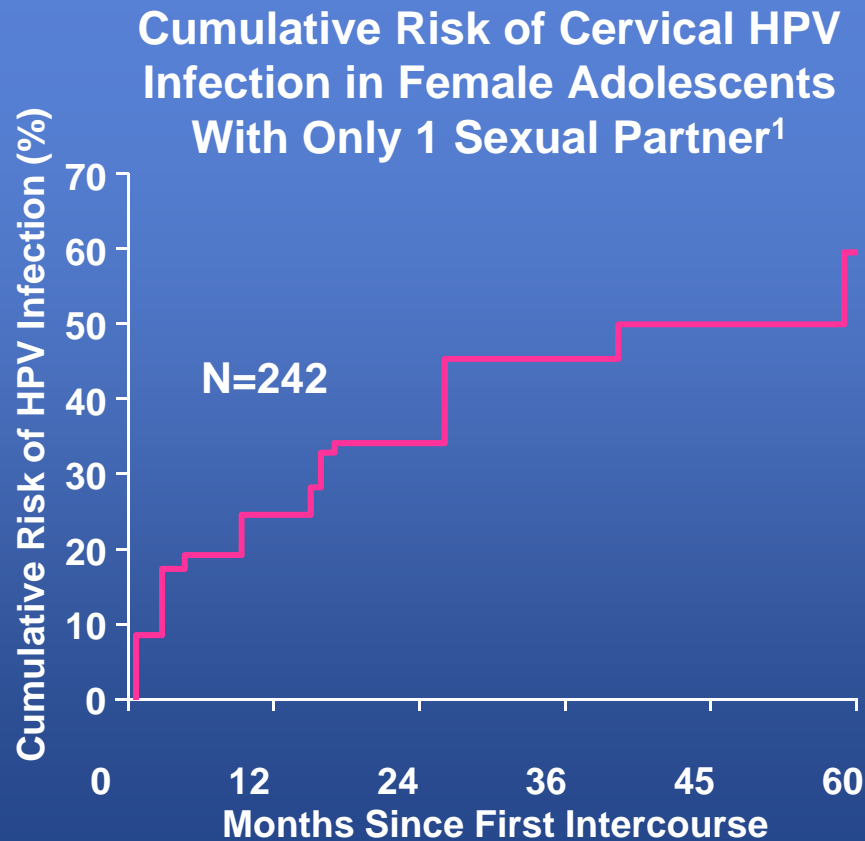
Cancer	% Associated with Certain HPV Types
Cervical*	≥95%
Vaginal*	50%
Vulvar*	>50%
Penile	50%
Anal	>70%
Oropharyngeal	20%
Nonmelanoma skin/cutaneous squamous cell	90%**

Natural History of HPV Infections

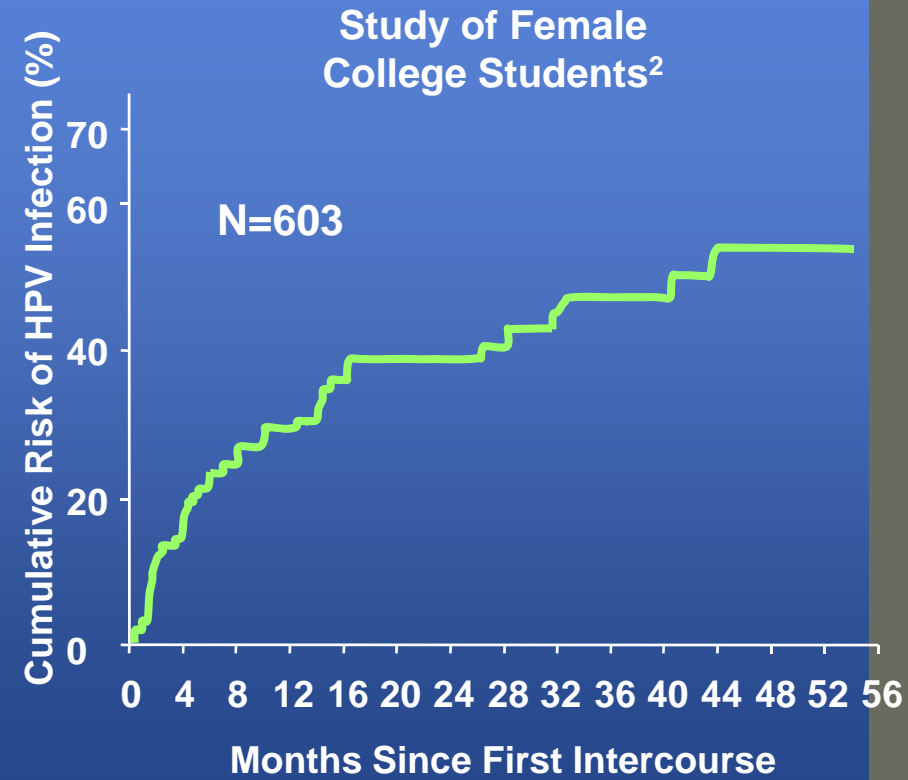


Wright and Schiffman (2003) NEJM

Risk of Acquiring HPV After First Intercourse



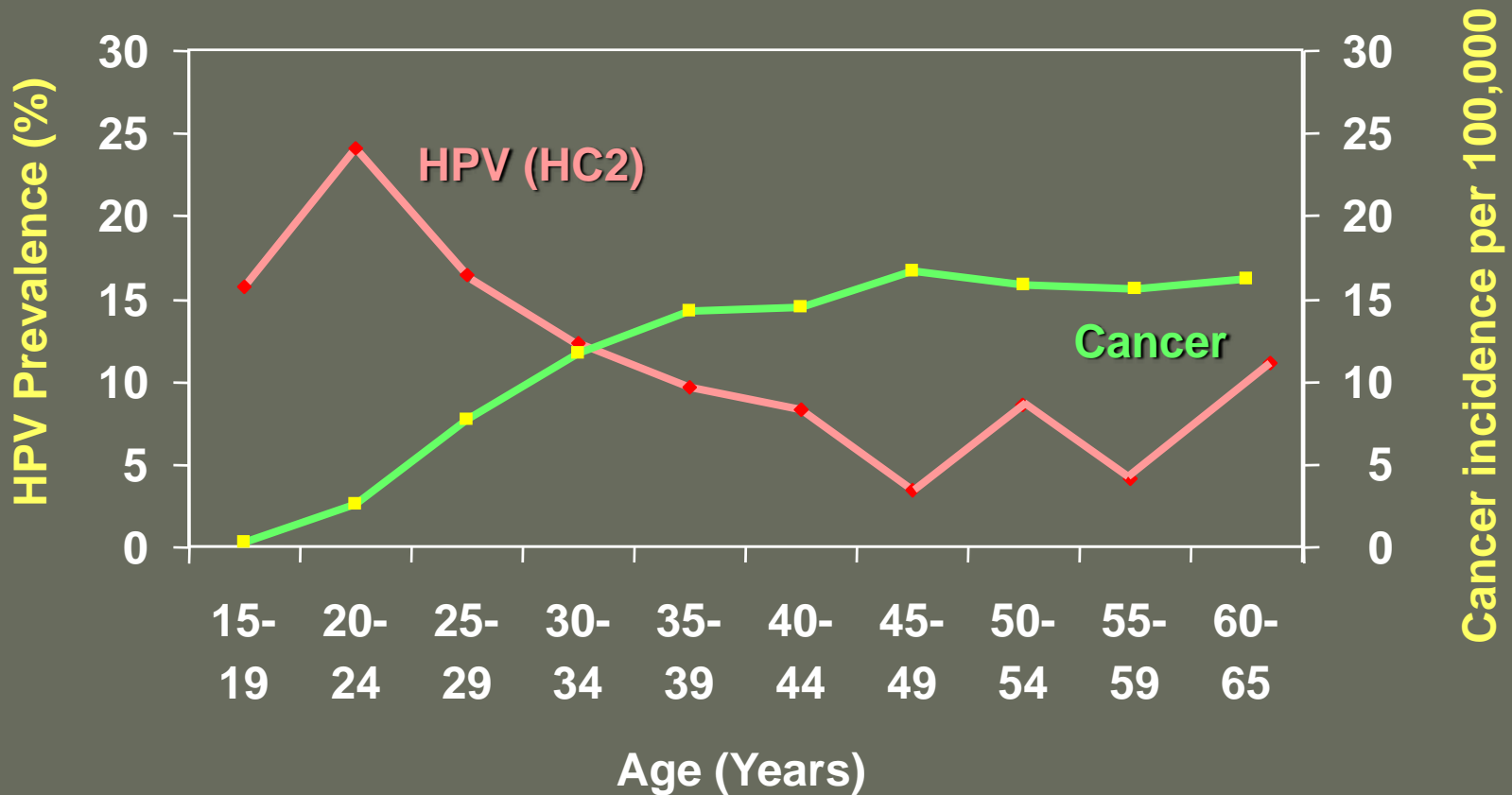
Adapted from Collins et al.¹



Adapted from Winer et al.²

1. Collins S, Mazloomzadeh S, Winter H, et al. *BJOG*. 2002;109:96–98. 2. Winer RL, Lee S-K, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: Incidence and risk factors in a cohort of female university students. *Am J Epidemiol*. 2003;157:218–226. Adapted by permission of Oxford University Press.

HPV Prevalence and Cx Ca Incidence by Age



Sellors JW, et al. *CMAJ*, 2000;163:503.

Ries, et al. *2000 SEER Cancer Stats NCI*, 1973-1997.

Sellors JW, et al. *CMAJ*, 2002;167:871.

HPV Clearance

- In women 15-25 years of age ~80% of HPV infections are transient
 - Gradual development of cell-mediated immune response presumed mechanism
- In a study of 608 college women, 443 infected, 70% of new infections cleared within 1 year and 91% within 2 years
 - Mean duration of infection - 8 months
 - HPV 16 and 18 infections persist longer

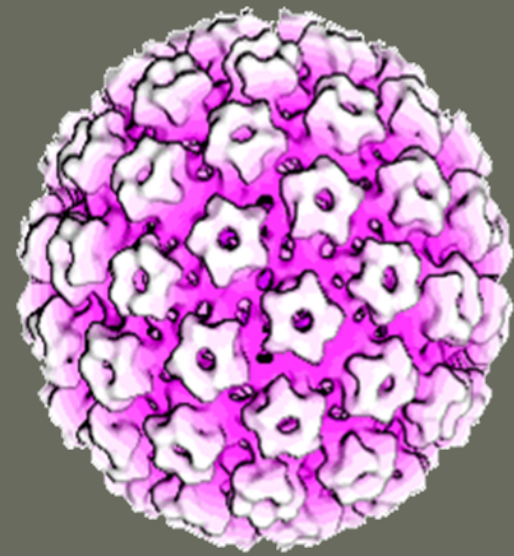
HPV Persistence

- Persistent infection is difficult to assess.
 - Detection of same HPV type DNA on 2 or more consecutive visits at least 4 months apart
 - Impossible to distinguish between 2 incident infections
- Persistence of high-risk HPV types may be crucial for the development of cervical precancer and cancer.
 - However, persistence may not be necessary for progression.
 - In one study of 2011 women 15–19 years of age, 5 women who were consistently HPV-negative progressed to high-grade CIN.
- Other associated factors
 - Infection with multiple HPV types

Current Cervical Cancer Prevention

- Secondary prevention, often opportunistic
- NS Rates:
 - 1 year 41%
 - 3 year 63%
- Unlikely to improve
- A VACCINE PROMISES TO BE REVOLUTIONARY IN ITS EFFECT ON CERVICAL CANCER

Prophylactic Vaccine



- Made from the L1 capsid VLP
 - 5 assemble to form capsomere
 - 72 form together into a sphere
- Gardasil (Merck) Quadravalent, 16, 18, 6, 11
- Cervarix (GSK) Bivalent 16, 18. (not yet clinically available)

Prophylactic Vaccines

- Both 100% effective in preventing CIN 2,3 disease related to the vaccine genotypes
- Gardasil 100% effective in preventing condyloma caused by HPV 6 and 11.
- Last for 5 years (so far)
- Very few vaccine related side effects

HPV Vaccines: Published data

	Gardasil (Merck)	Cervarix (GSK)
	Villa et al, Lancet Oncology (2005)	Harper et al, Lancet (2004)
Study type	RCT	RCT
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

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	277 vaccine vs. 275 placebo	560 vaccine vs. 553 placebo
Site	USA, Brasil, Europe	USA, Canada, Brasil
Age range	16-23	15-25
eligibility	No Hx of Cx lesions, few sexual partners	No Hx of Cx lesions, few sexual partners
<i>exclusion</i>	<i>none</i>	<i>Women who were HPV +ve at initial testing</i>
duration	Up to 35 months	Up to 27 months

HPV Vaccines: Published data

According to Protocol efficacy	Gardasil (Merck)	Cervarix (GSK)
<i>Preventing persistent vaccine specific HPV, cervicovag specimens</i>	89% <i>(P/V 47/6 events)</i>	100% <i>(P/V 0/16 events)</i>
HPV 6	100% (P/V 13/0)	N/A
HPV 11	NS (P/V 3/0)	N/A
HPV 16	86% (P/V 21/3)	100% (P/V 13/0)
HPV 18	89%	100%

HPV Vaccines: Published data

Intention to treat analysis	Gardasil (Merck)	Cervarix (GSK)
Efficacy in preventing persistent vaccine specific HPV infections	88%	88-95%
Efficacy in preventing type specific abnormal paps	Not reported	94%
CIN lesions	100% (P 7 events)	100% (p 6 events)
External genital warts	100%	N/A

Prophylactic Vaccines

- No real effect on existing disease, either preclinical, or against women with CIN

- Therefore

PROPHYLACTIC VACCINES BEST USED
BEFORE EXPOSURE

Vaccine Recommendations USA

- FDA approval in June:
 - Approved for women 9-26
- Advisory Committee on Immunization Practices Recommended:
 - Initial vaccination of women age 11-12 (9 yrs old OK)
 - Catch up should be offered to women up to 26
- Vaccines < 18 yrs old are covered by the federal government in the USA

Vaccine Implementation: Canada

- Health Canada Approved July 2006
- Available to physicians early September 2006
- National Advisory Committee on Immunization
 - ➔ Canadian Immunization Council
 - ➔ re universal programs that may be implemented by the Provinces.

Gardasil: Quadrivalent HPV Vaccine

- COST ~\$130 each vaccine dose
- Storage: 2-8°C, should not be frozen, protect from light. *NEED TO PRESERVE THE “COLD CHAIN”*
- Contraindications: hypersensitivity to the active substances or components
- Precautions:
 - May not be effective
 - Not for treatment of active warts, cervical cancer, CIN VIN, VAIN
 - Does not provide protection against non vaccine HPV types
 - Not recommended for use in pregnancy, Category B

Who?

- Women 9-26
- Do not need to have pap smear before vaccination
- Testing for HPV is not recommended prior to vaccination
- Sexually active women can be vaccinated, may be less effective in women who have been previously exposed to HPV

Vaccination in the clinic

- Case: 24 year old diabetic teacher not currently in a relationship. Just finished successful treatment for condyloma.
- ? Vaccinate
- Yes: likely had only one strain, vaccination will provide protection against the remaining 3 strains

Vaccination in the clinic

- 19 year old just treated for CIN 3 with a LEEP
- Offer vaccine?
- Yes
 - Likely had only 1 strain
 - Will benefit from the other 3 strains
 - Likely to be exposed in the future

Vaccination in the clinic

- 24 yr old university student with ASCUS x 2 and HPV on biopsy
- Vaccinate?
- Yes offer the vaccine.
 - Some evidence that there is a “trend” towards earlier clearance of the present strain.
 - May benefit from vaccination against other strains

Who not to vaccinate

- Women with established CIN/AIS/Cancer etc: NOT THERAPEUTIC
- Women over 26???
 - Studies underway
 - May benefit but less so

How to vaccinate?

- Likely through GP
- Script given
- Vaccine picked up at drug store in cold pack
- GP administers IM vaccine
- **NEED TO PROTECT COLD CHAIN**

Cross protection

- Does vaccination for 16/18 provide protection against other strains?
 - Does not occur with natural infection.
- Yes!
 - Harper et al (2006)
 - Cervarix provided cross-protection against HPV 31 and 45 (54%-95%)
 - Preliminary evidence that Gardasil has similar crossprotection

Cost effectiveness

- Numerous studies done:
- Depends on:
 - Universal program
 - Age 12 +/- catch-up
 - ? Men
 - Cost of vaccine
 - Vaccine efficacy 70% vs. 90+ % with cross-protection
- Most suggest costs will not be reduced for 10-20 years unless have widespread vaccination on all women less than 26
 - Main benefit is in less colposcopy

What about men?

- HPV associated cancers, Penis, Anus, Head/Neck (~1000/yr Canada)
- Men are the vectors for female infection
- Studies not yet completed
- Australia has approved vaccination of boys 9-15
- Cost implications:
 - Tiara et al (2004)
 - 12 yr old women \$14, 583 per QALY
 - + 12 yr old men \$442, 000 per QALY

Effect on Screening/ Prevention Programs

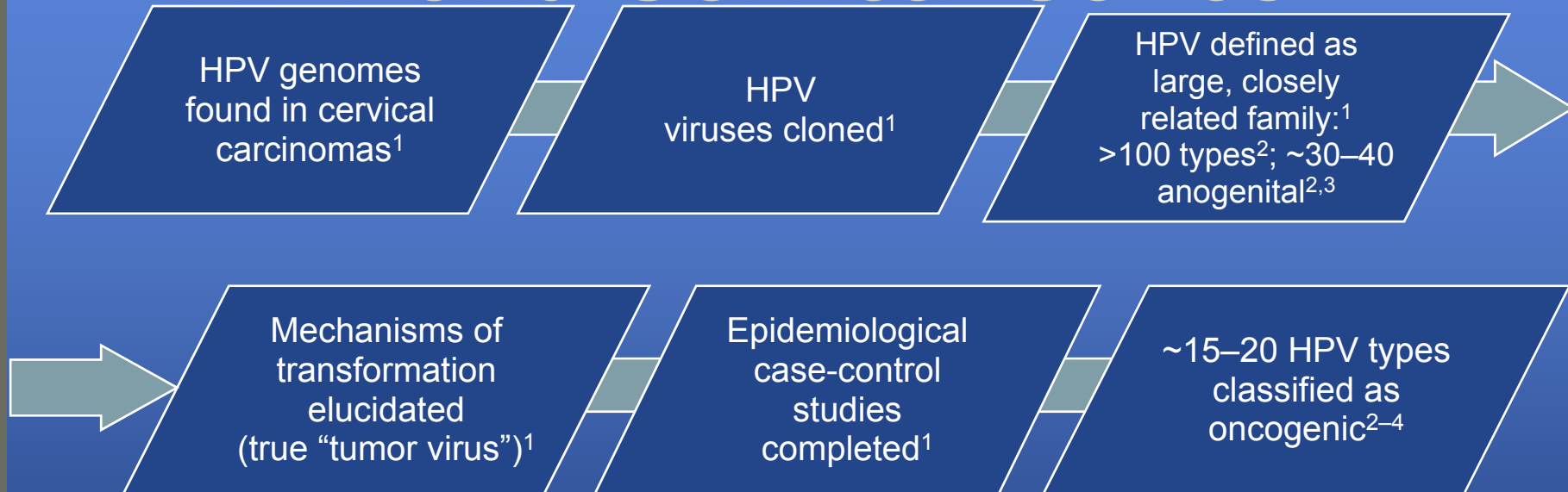
- Currently none
- Problems:
 - Need to integrate a vaccine registry with screening databases
 - Long term efficacy (need for booster?)
 - Strain migration
- Screening will be modified if vaccine is as successful as we believe.

HPV Vaccination

- PRIMARY CERVICAL CANCER PREVENTION

Discovery of the Link Between

HPV and Cervical Cancer



- Body of information developed based on advances in cellular, molecular, and immunological diagnostic technologies over the past 20 years¹