

Epidemiology of HPV Infection

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Outline

- Background
- Transmission
- Sexual Behavior
- Laboratory Methods
- Treatment
- Epidemiology of HPV
- Immunity
- Serology

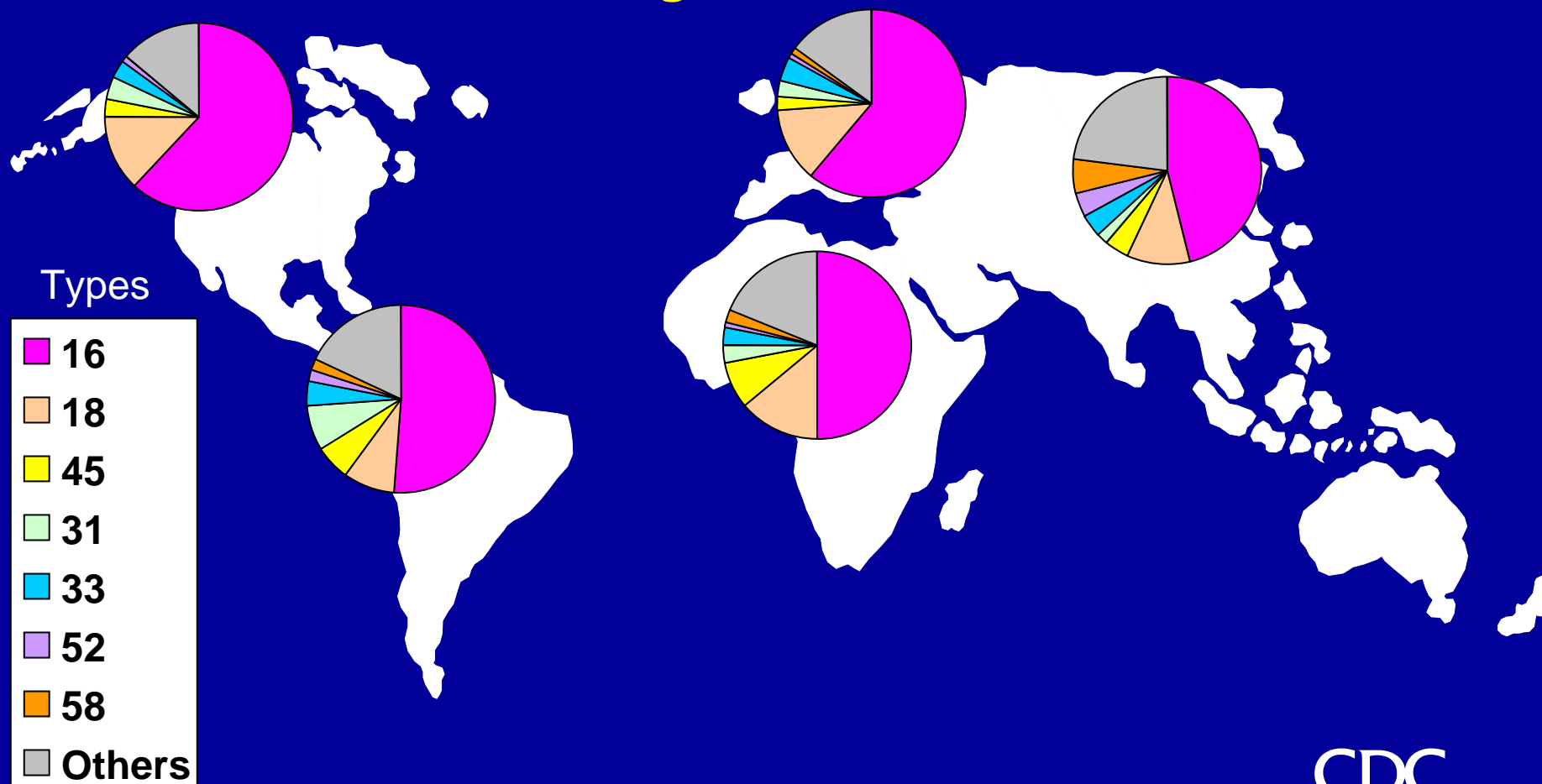
Background: HPV

- More than 100 different types
 - 40 types are mucosal
 - “High risk”, oncogenic types (**16, 18**, 31, 33, 35, 39, 45, 51, 52, 56, 58....)
 - “Low risk”, nononcogenic types (**6, 11**, 42, 43, 44...)

Munoz, NEJM 2003;348:518-27

Background: HPV Types in Cases of Cervix Cancer

Different Regions of the World



Clifford: Br J Cancer 2003

Background: HPV-associated Conditions

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% |
| – Vulvar/Vaginal/Penile | ~40% |
| – Head and neck cancers | ~10% |
| • HPV 6, 11 | |
| – Low grade cervical abnormalities | 10% |
| – Genital warts | 90% |
| – Recurrent respiratory papillomatosis (RRP) | 90% |

Clifford GM, 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

Background: Genital Warts

- Transmission: Sexual
- Burden of Disease
 - No reporting, imprecise estimates
 - Managed Care Data
 - Peak prevalence: ages 20-29 years
 - Incidence: 157/100,000 persons
 - Frequent recurrences, repeat treatments (average of 3 clinic visits)

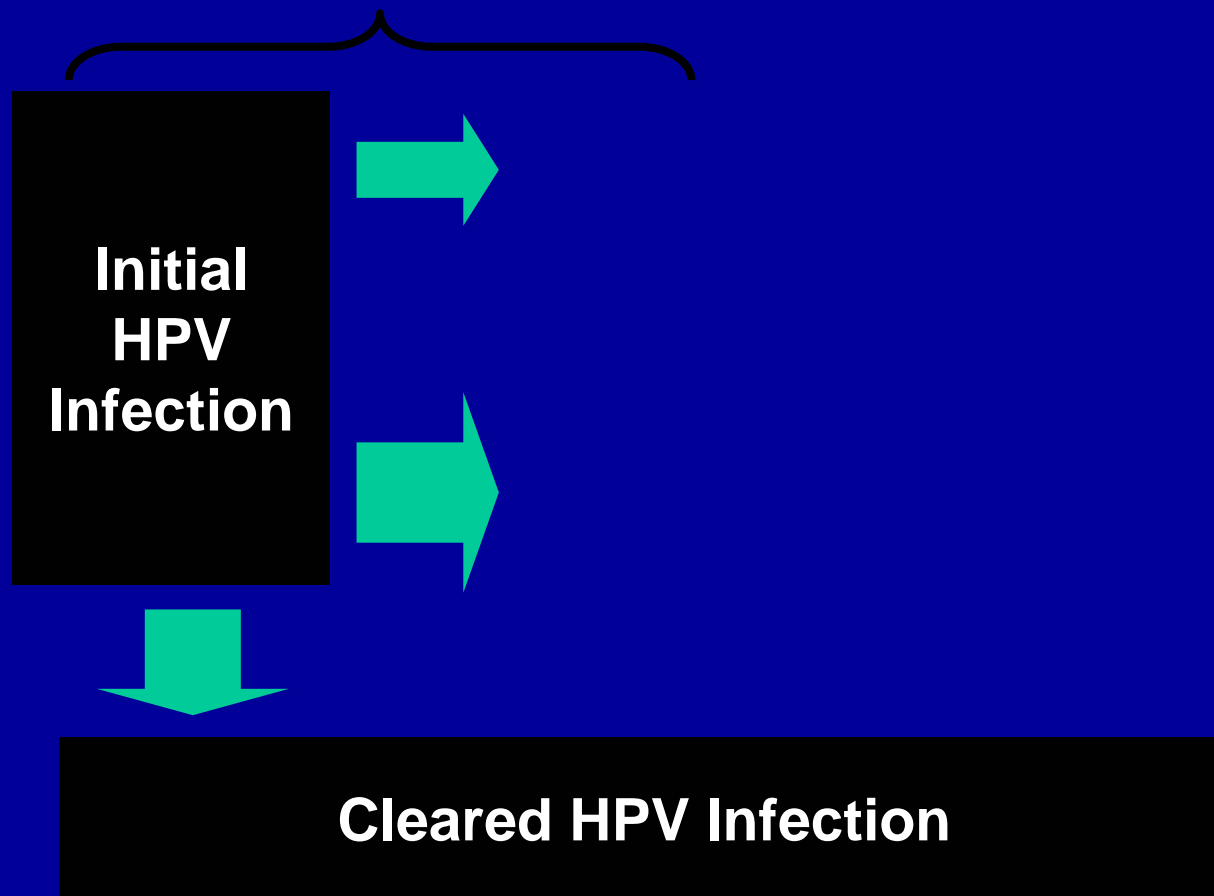
Koutsky A J Med 1997;102, R Insigna CID 2003;36,
Koshiol JE STD 2004;12

Background: Recurrent Respiratory Papillomatosis (RRP)

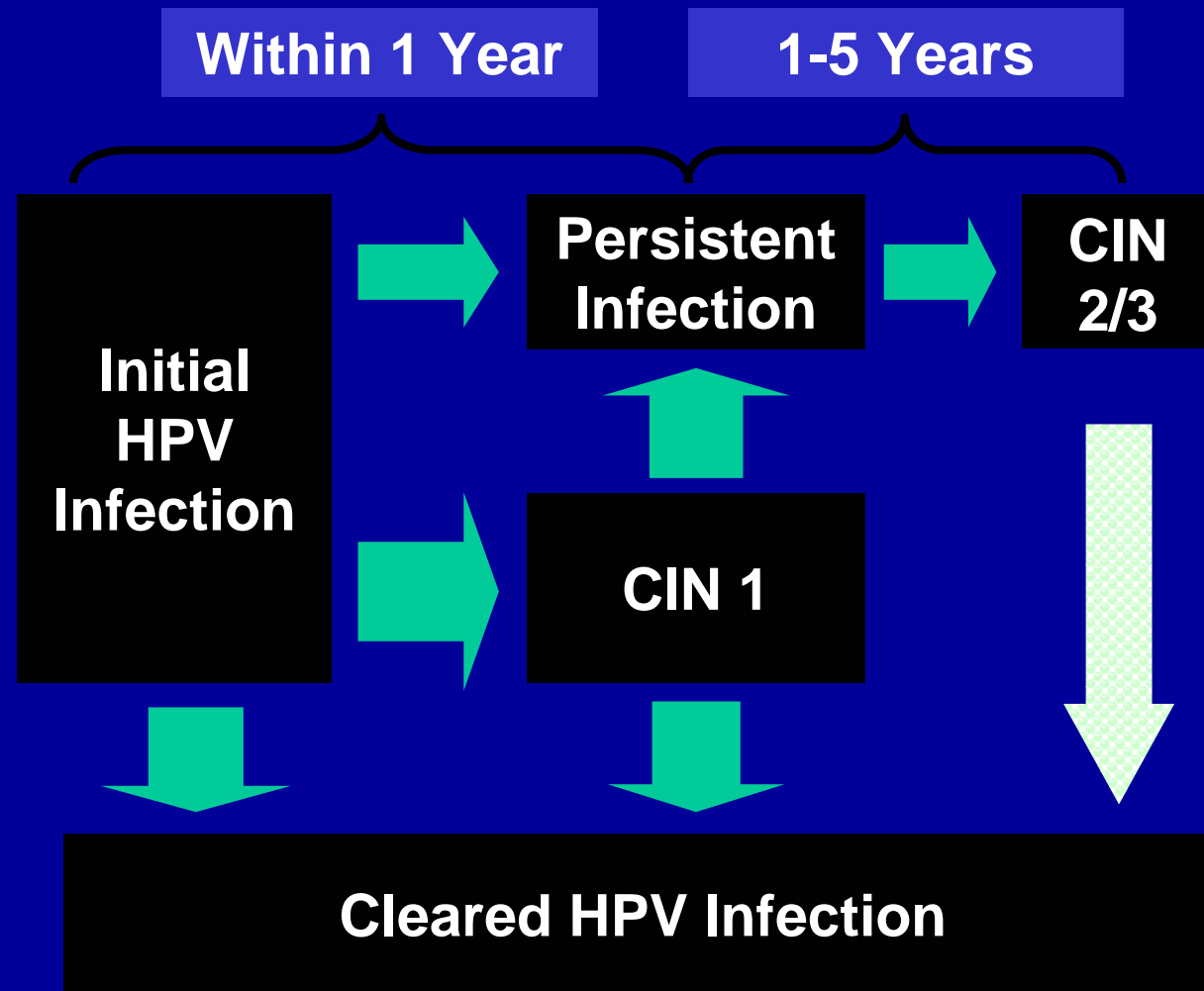
- Transmission: Vertical--Juvenile
- Burden of disease
 - No reporting, imprecise estimates
 - Registry data
 - Prevalence: 1.0 – 4.0/100,000 children
 - Incidence: 0.1 – 2.1 /100,000 children
 - Debilitating/recurrent disease requiring multiple surgeries
 - Median number of surgeries 13 (range, 2 – 179)

Background: Natural History

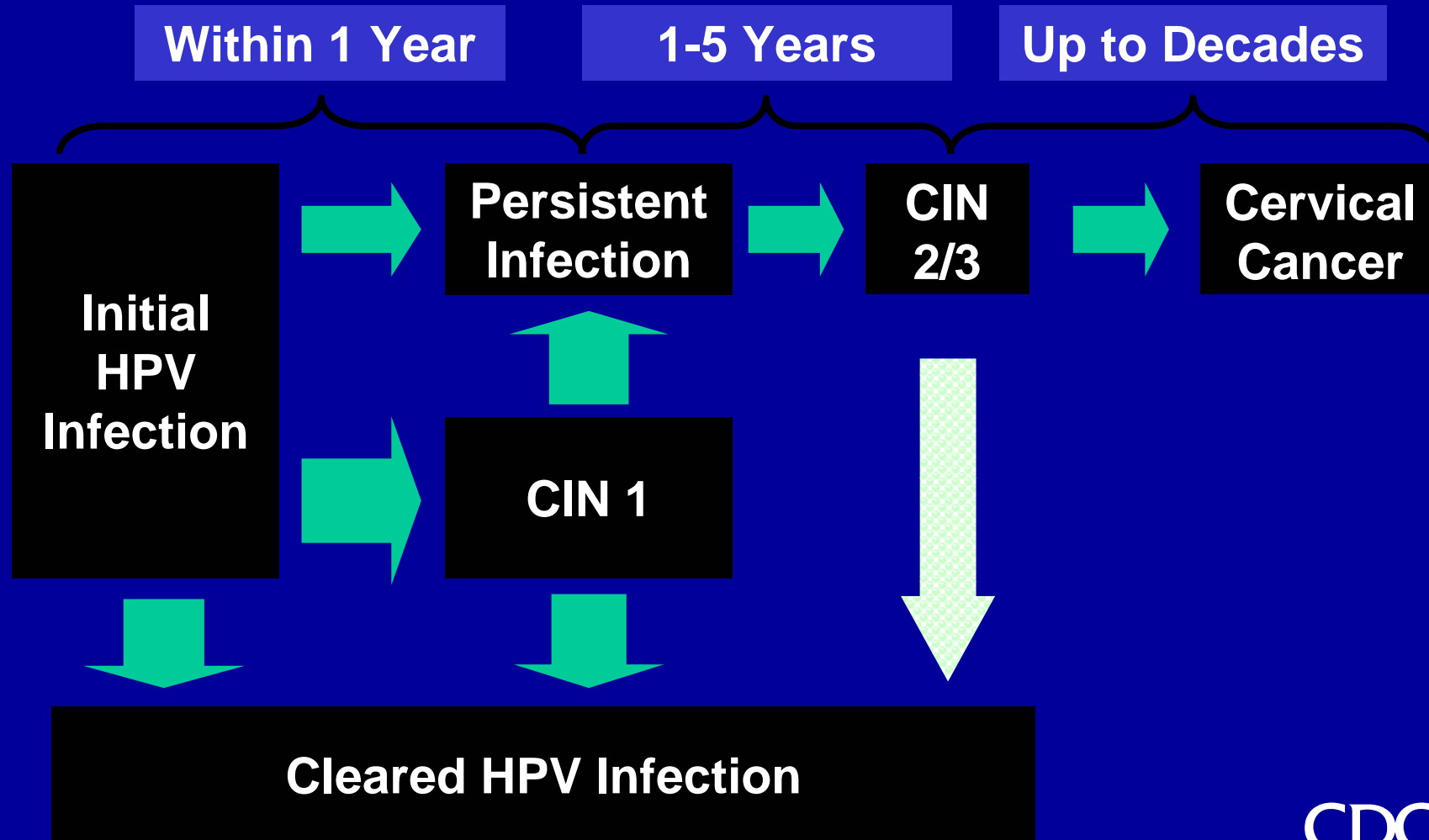
Within 1 Year



Background: Natural History



Background: Natural History



HPV Transmission

- Transmission by sexual contact
 - sexual intercourse
 - other types sexual contact—transmission much less common
- Transmission determined by: per partner transmission probability, infectiousness, and average number of partnerships formed per unit time
- No epidemiologic data on HPV transmission probability per sex-act or partnership
 - Modeling estimates:
 - 0.4, 0.6

HPV Laboratory Methods

- HPV DNA Detection
 - No culture methods: detection of DNA used to measure infection
 - Detection of DNA:
 - PCR: Type specific/consensus assays
 - Hybridization assay: Digene® HC II: clinical indications for use in cervical cancer screening and management. Detects any of 13 high risk HPV types.
- HPV Serology
 - ELISA-based detection of type-specific antibodies against L1 virus like particles (outer antigens)
 - Serum or mucosal: IgG or IgA
 - Poor standardization of methods

Treatment

- No treatment for infection
- Treatment directed to HPV-associated conditions (genital warts, cervical cell changes)
- Unknown if treatment results in decrease transmission

HPV Epidemiology: Challenges

- No culture methods: detection of DNA used to measure infection
 - Transmission studies difficult
- No routine testing for HPV infection
 - Limited HPV prevalence/incidence data
- No reporting of HPV infection or HPV-associated conditions
 - Limited surveillance data to assess impact of interventions
- HPV infection or HPV-associated conditions not always associated with antibody detection
 - No reliable marker of past or current infection among individuals

HPV Prevalence: Population Estimates, U.S.

- 20 million people are infected
- 15% of persons age 15-49 currently infected
- 6.2 million new infections each year
- > 50% of sexually active men & women acquire genital HPV infection

W. Cates, STD April 1999, Weinstock, Perspectives on Sexual and Reproductive Health 2004, Koutsky Am J Med 1997

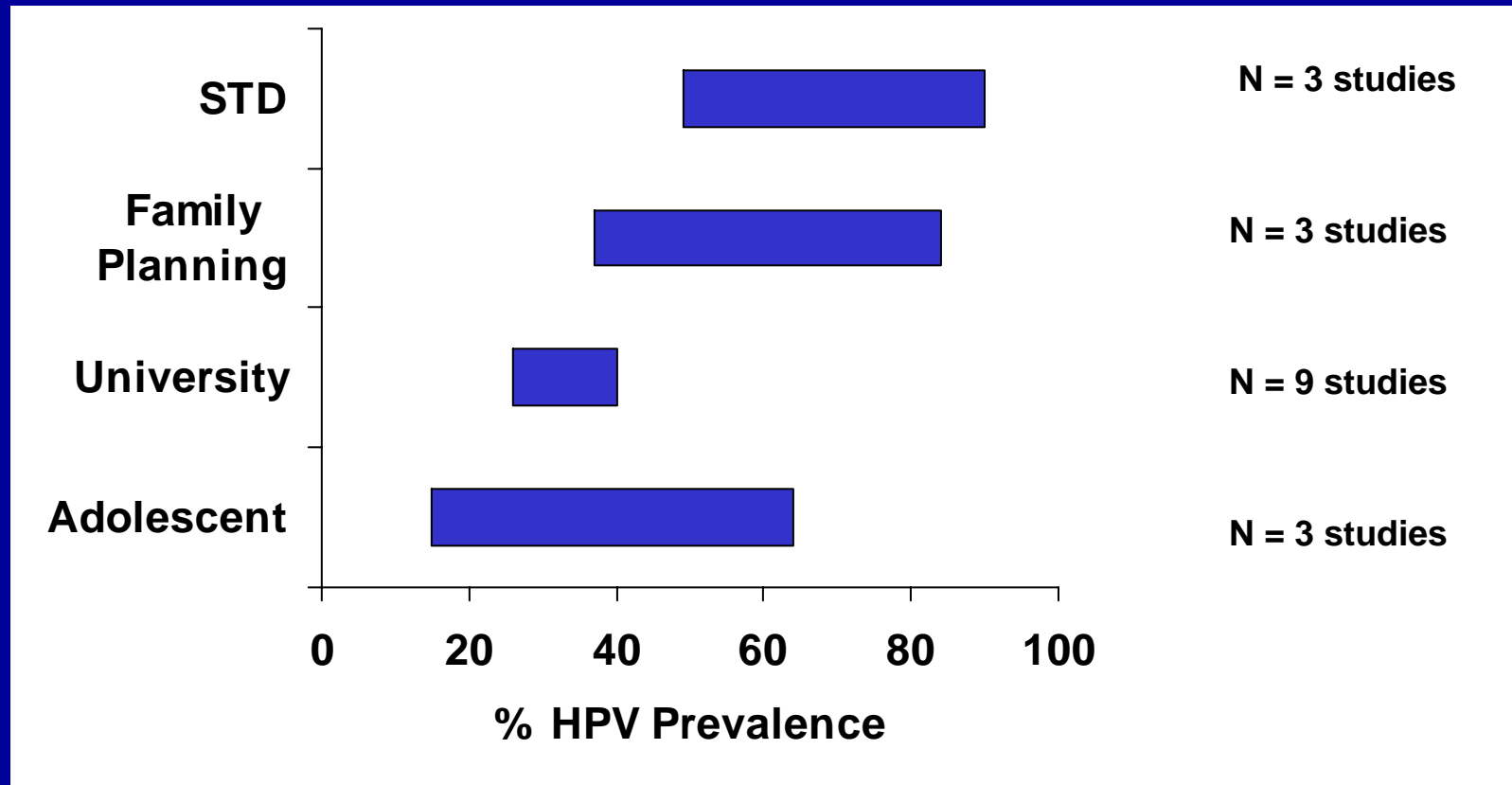
Sexual Behavior, U.S.

- Sexual Initiation
 - 7% before 13
 - 25% by 15
 - 48% by 17
- 2+ partners in the past 12 months, 15-19 year olds
 - 14% females
 - 18% males

HPV DNA Prevalence in Women, U.S.

- Systematic review of HPV in women
- CDC Sentinel Surveillance for HPV
- National Longitudinal Study of Adolescent Health (Wave III)

Prevalence HPV Infection by Clinic Type, U.S.

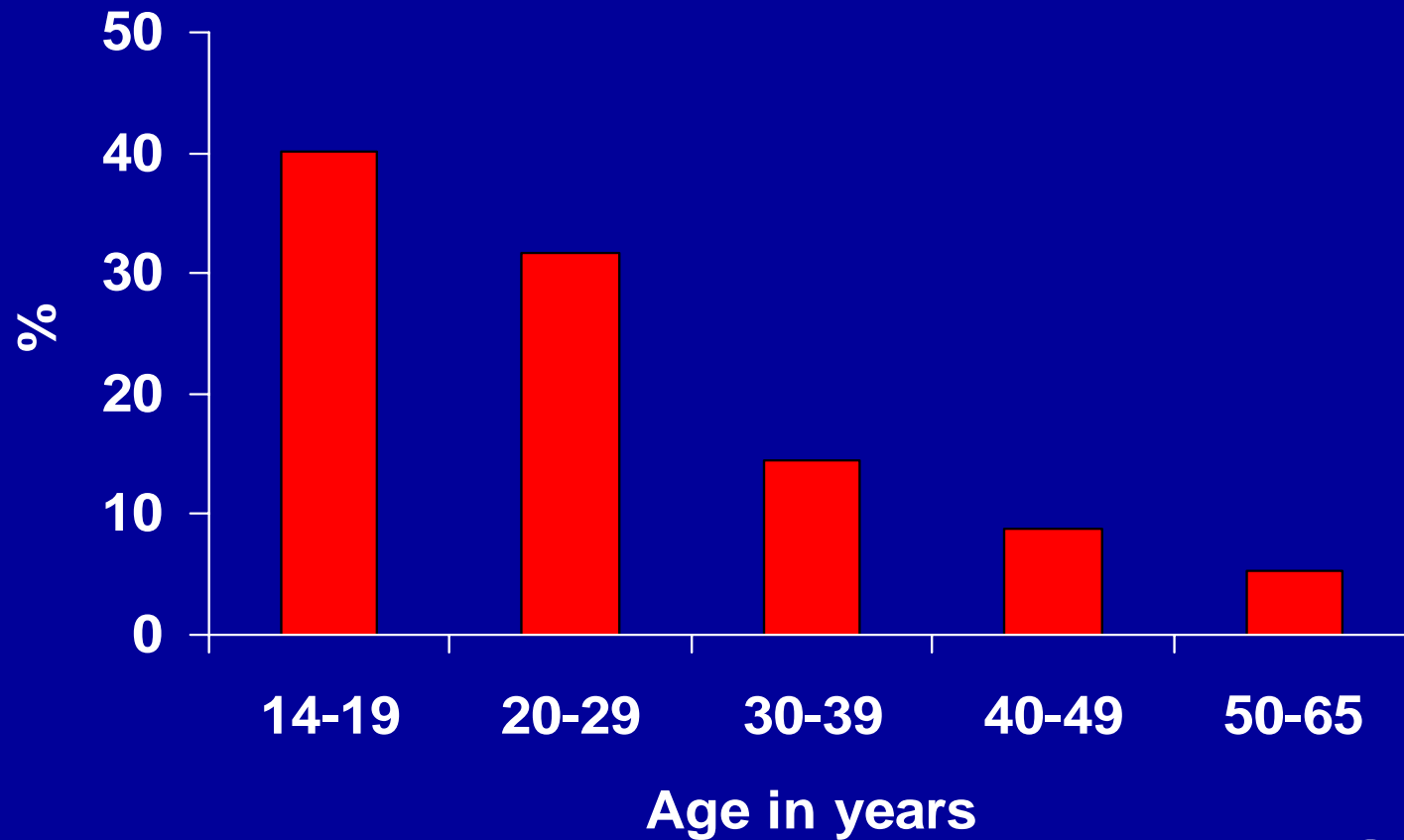


Adapted from Revzina NV Int J STD/AIDS 2005

Sentinel Surveillance for HPV in Women, U.S.

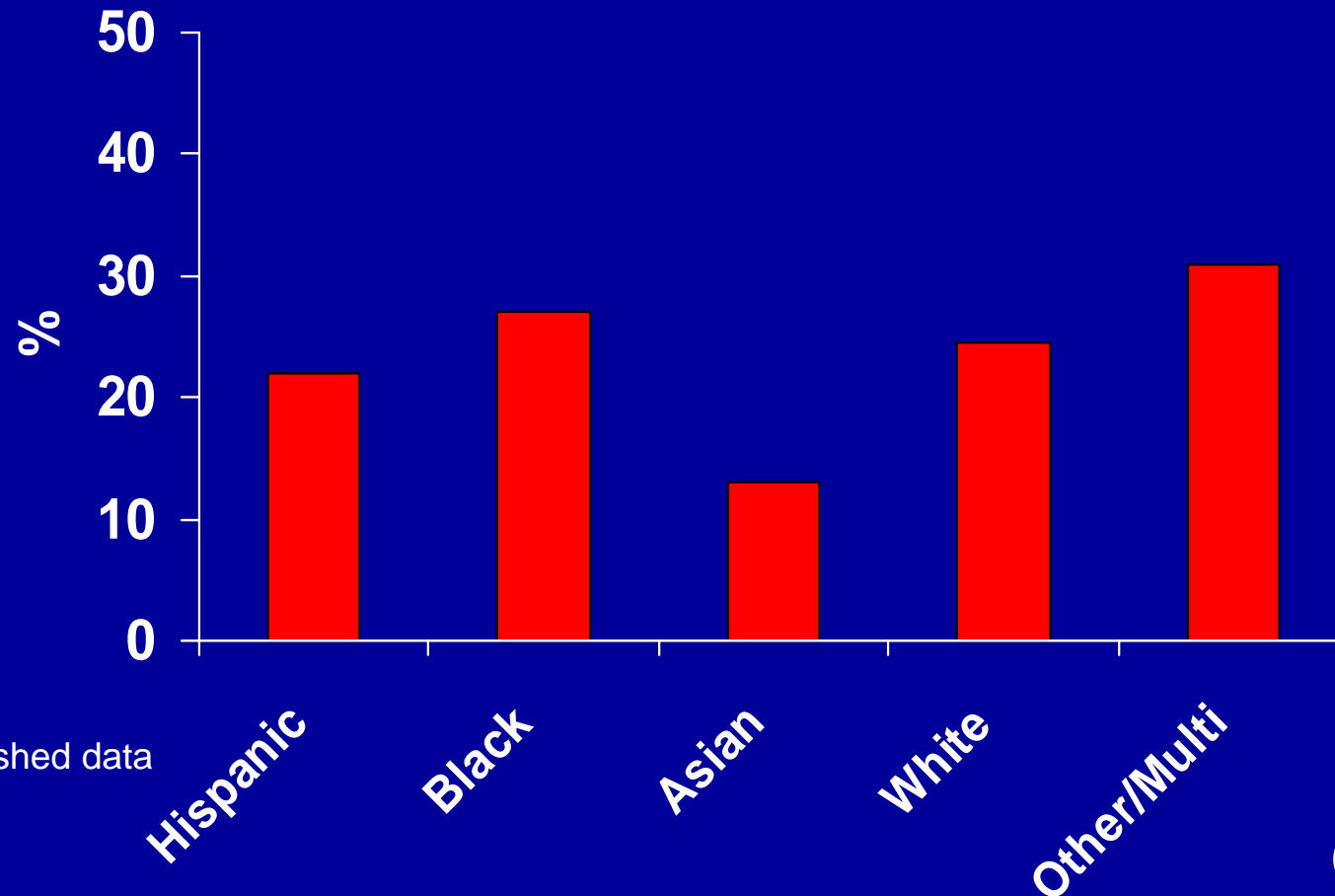
- CDC cross-sectional study of women attending a variety of clinics for Pap testing
- 6 U.S. cities
- Ages 14-65 years
- Cervical samples

High Risk HPV Prevalence by Age, Sentinel Surveillance, U.S. 2003-2004 (N=5555)



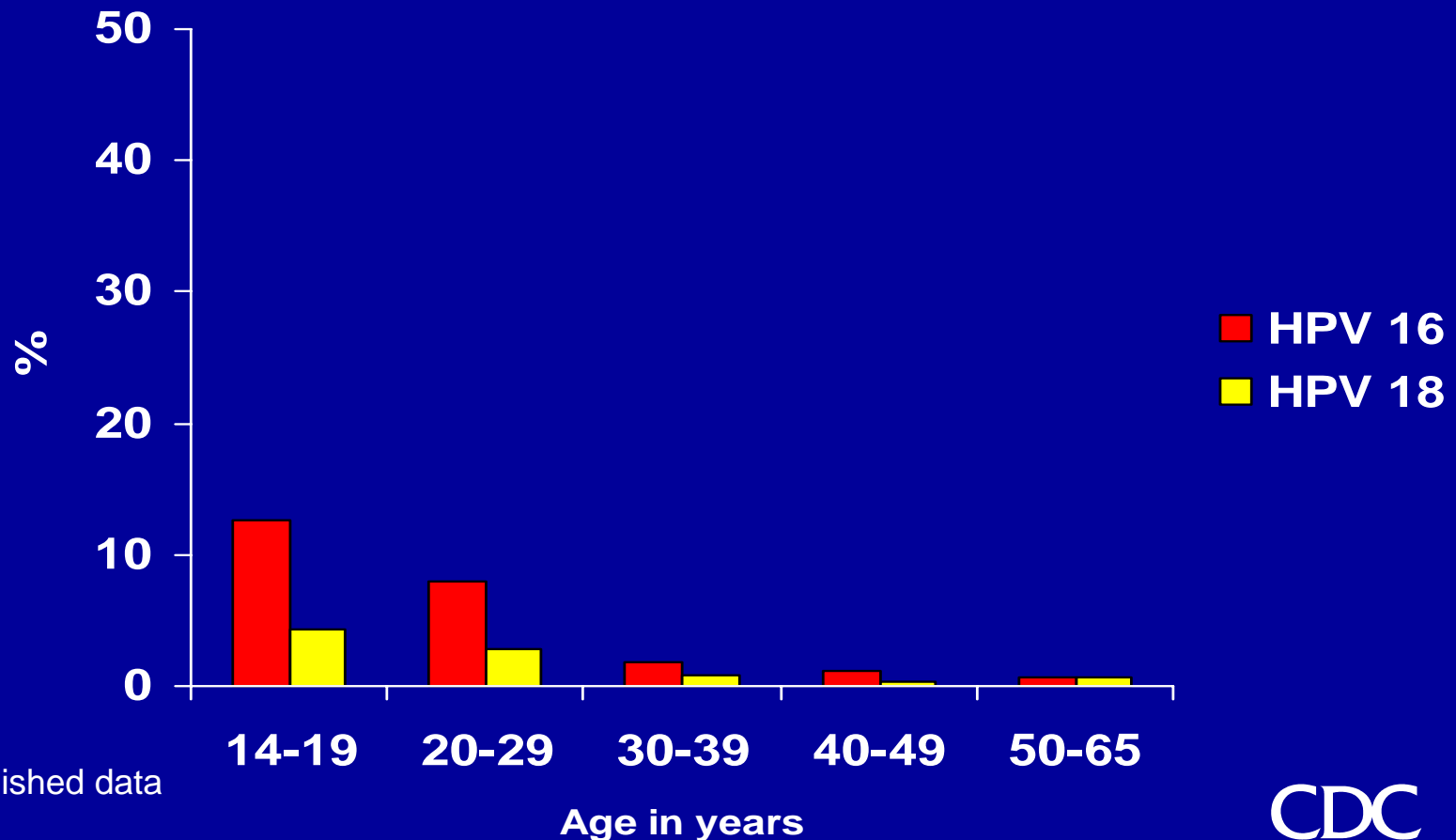
CDC, unpublished data

High Risk HPV Prevalence by Race/Ethnicity, Sentinel Surveillance, US 2003-2004 (N=5555)



CDC, unpublished data

HPV 16, 18 Prevalence by Age, Sentinel Surveillance, U.S. 2003-2004 (N=5555)



CDC, unpublished data

National Longitudinal Study of Adolescent Health

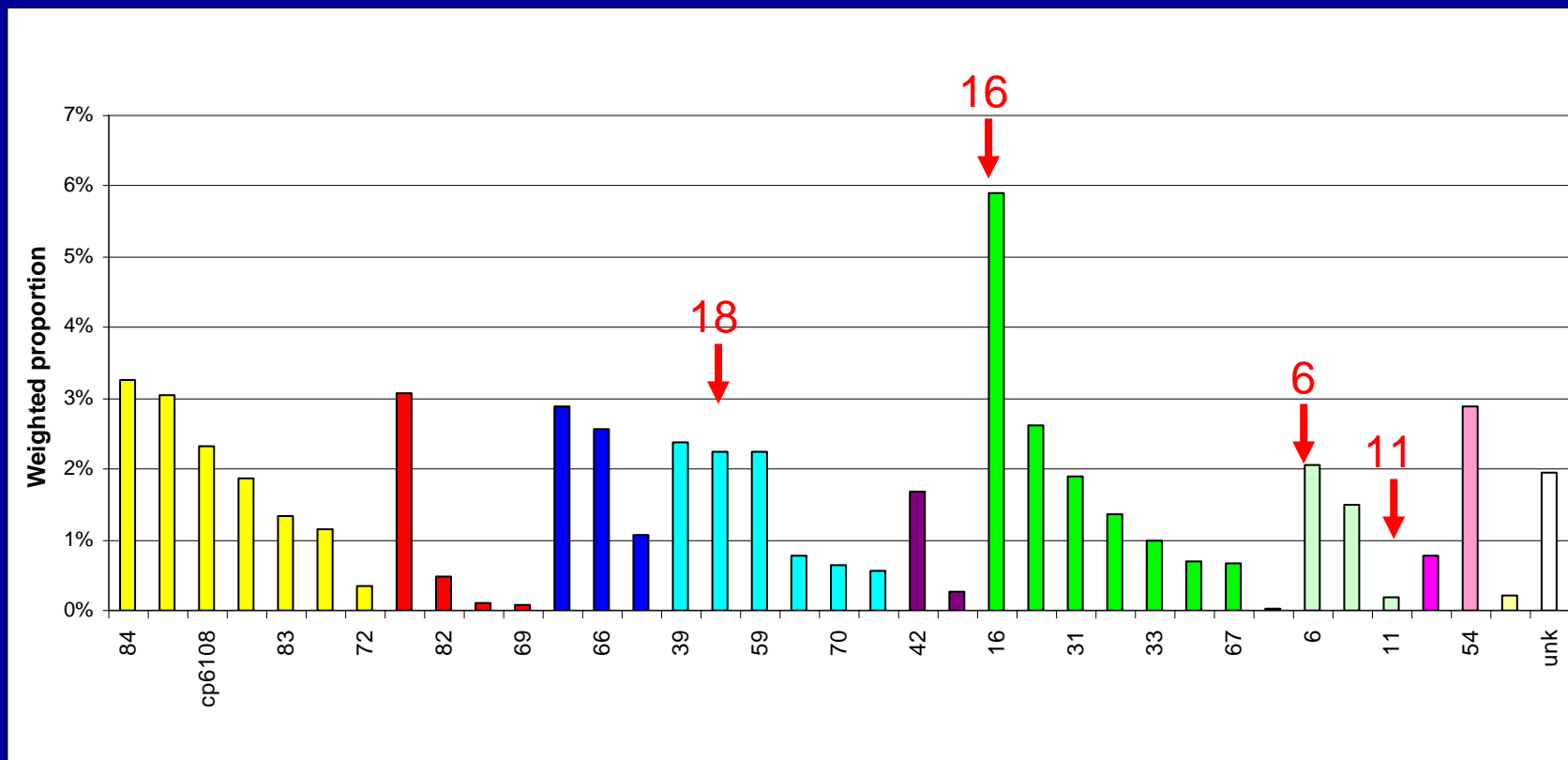
- Representative sample of sexually active females
- Longitudinal study: cross-sectional evaluation of Wave III
- Ages 18-25 years
- Urine samples

HPV Prevalence, National Longitudinal Study of Adolescent Health, 18-25 yr olds (N=3262)

| HPV type | Weighted prevalence % |
|----------|-----------------------|
| Any | 26.9 |
| 6 | 2.0 |
| 11 | 0.2 |
| 16 | 5.8 |
| 18 | 2.2 |

Manhart L, STD, in press

Distribution of HPV Types, National Longitudinal Study of Adolescent Health, 18-25 yr olds

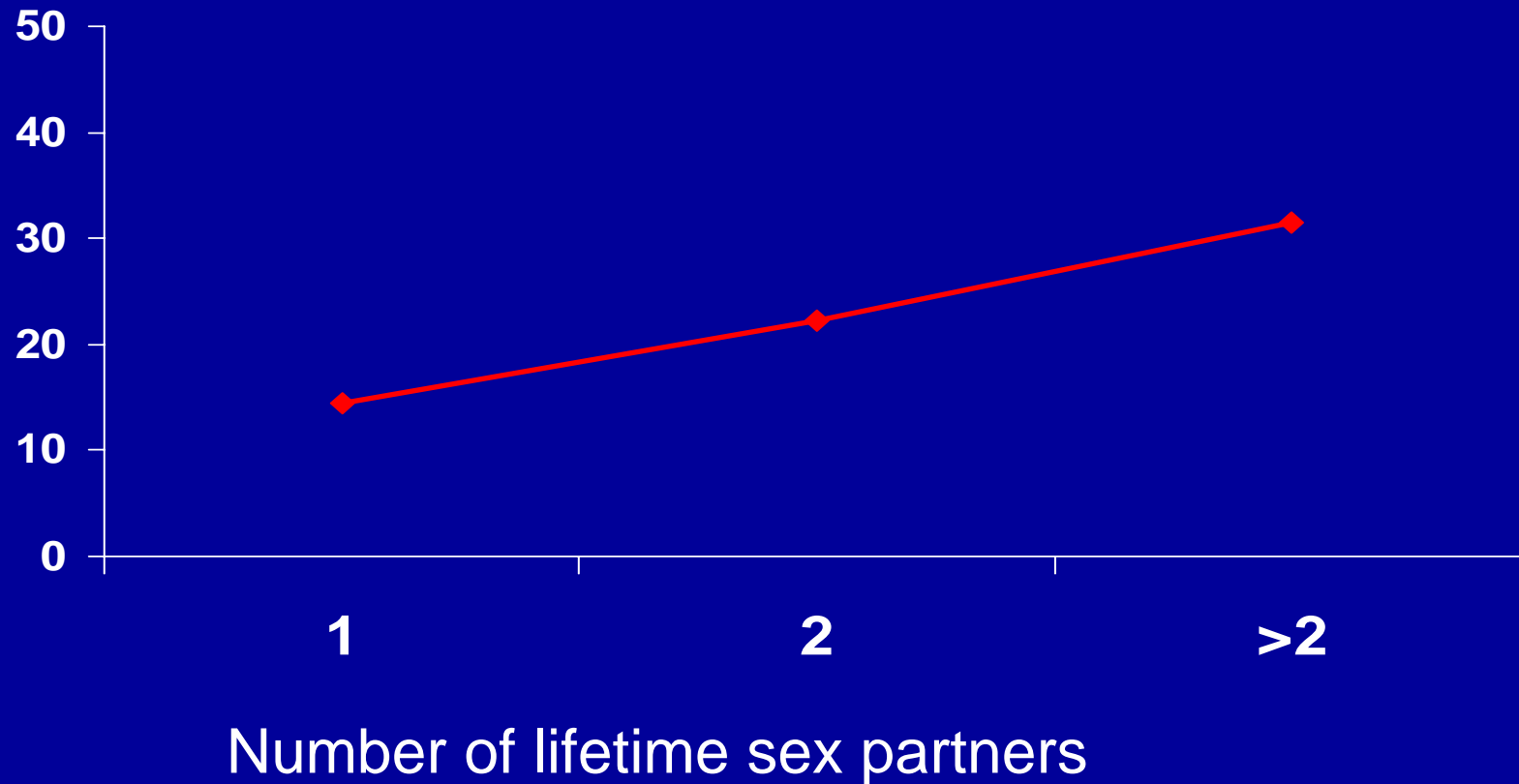


HPV type

Manhart L, STD, in press



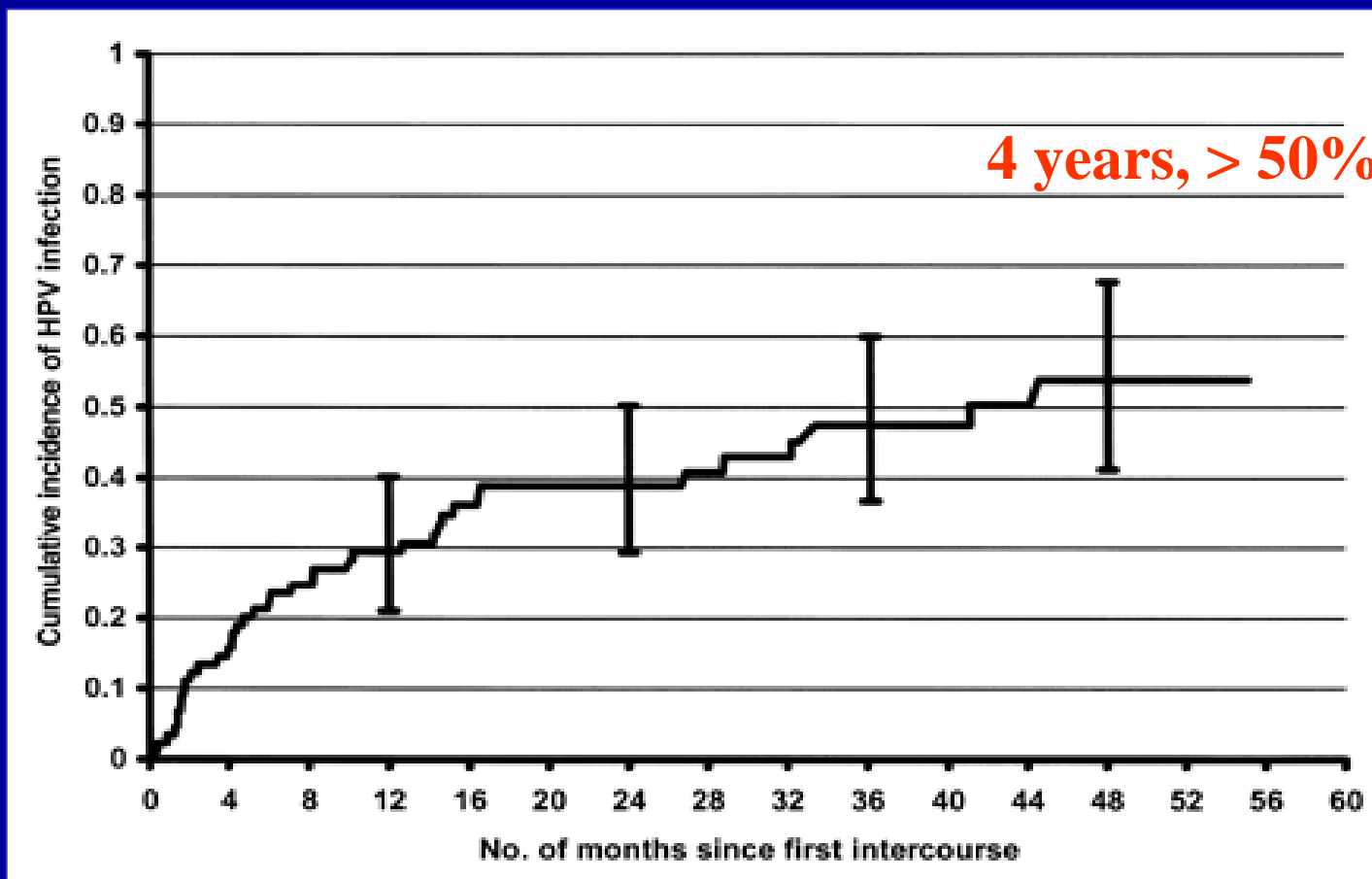
HPV Prevalence by Number of Sex Partners, National Longitudinal Study of Adolescent Health, 18-25 yr olds



Manhart L, STD, in press

Cumulative Incidence of Any HPV Infection

Months after sexual initiation, Women



Winer: Am J Epidemiol, 2003;157

Cumulative Incidence of HPV type 6, 11, 16, 18 Infection 24 months after sexual initiation, Women

| HPV Type | Cumulative Incidence at 24 months | |
|----------|-----------------------------------|-------------|
| | % | (95% CI) |
| 6 | 7.5 | (7.0, 12.6) |
| 11 | 0.9 | (0.3, 2.3) |
| 16 | 10.4 | (7.8, 13.8) |
| 18 | 4.1 | (2.6, 6.4) |

HPV Acquisition Women

- HPV acquisition usually occurs within first several years of sexual initiation
- Most sexually active adolescents acquire HPV infection
- HPV acquisition high at 24 mos (40%); 10% acquire HPV 16
- Lifetime cumulative incidence: >80% by age 50

Winer et al., Am J Epidemiol 2003;157, ER Myers Am J Epidemiol 2000; 1511.

Risk Factors for HPV Women

Consistent:

- Sexual behavior
 - Young age of sexual initiation
 - Number sex partners
 - Partner's sex partners
- Immune status
- Age (<25 years)

Less Consistent:

- Smoking
- Diet
- Hormonal Contraceptives
- Inconsistent condom use

Bauer, JAMA 1991;265:4:472-477;
Winer A J Epi 2003;157:218-226, Baken JID 1995; 171:429-432,

HPV Clearance

- Approximately 70% of new infections clear within one year, 91% within 2 years
- Most clearance in first 6 months

HPV Persistence

- Infection detected at more than one visit (usually 4-6 months apart)
 - Most important predictor of high grade cervical cancer precursors

Ho et al., NEJM 1998; Moscicki et al., J Pediatr 1998; Franco et al., JID 1999; Molano et al., Am J Epidemiol 2003

HPV Persistence (High Risk Types)

| | Definition of Persistence | High Grade Cervical Cancer Precursors RR (95% CI) |
|------------------------------------|-------------------------------|--|
| Schlecht et al., JAMA 2001 | 2 positive 4-6 month apart | 10.2 (5.9, 17.6) |
| Moscicki et al., J Pediatr 1998 | 3 positive 4 month apart | 14.1 (2.3, 84.5) |

Factors Associated with Persistent High Risk HPV Infection

- Type 16
- Immune status
- Smoking
- Multiple HPV types
- Older age
- STIs

Ho NCI 1995;87:1365-1371;

Sellors CMAJ 2003;168:421-425; Woodman Lancet 2001;357:1831-1836;,

HPV Immunity

- Type specific immunity
 - Few acquire same HPV type when that type infection cleared
 - No longitudinal cohorts to assess lifetime immunity
- Cross-protection between types
 - No evidence in cohort studies that cross-protection occurs

Franco J Infect Dis 1999;180:1415-1423.

HPV Infection in Men

- Difficult to determine the best method to sample
 - Different studies evaluate different sites/specimens
- Equally prevalent among males as females, dependant on site/sample collected
- Natural history data limited

HPV DNA Prevalence in Men, U.S.

| | Population, location | Age, yrs | % any | % high-risk | % low-risk | Site/Specimen |
|------------------|------------------------------------|-------------|----------|----------------|---------------|-----------------------------------|
| Weaver, 2004 | 318 University students, WA | 18-25 | 35.0 | UNK | UNK | glans, shaft, prepuce, scrotum |
| Baldwin, 2003 | 443 STD clinic attendees, AZ | 18-70 | 28.2 | 12.0 | 14.8 | glans, corona, urethra |

Risk Factors for HPV Men

Consistent:

- Sexual behavior
- Immune status
- Lack of Circumcision

Less Consistent:

- History STD
- Inconsistent condom use

Baldwin STD 2004;31:601-7, Lajous Cancer Epi Bio Prev 2005;14:1710,
Castellsague NEJM 2002;346:1105-12,

HPV-associated Diseases and Cancers Men

- HPV types 16,18:
 - Anal cancer
 - Penile cancer
 - Head and neck cancers
- HPV types 6, 11:
 - Anogenital warts
 - Recurrent respiratory papillomatosis (RRP)

HPV Serology

- Many persons with current/past HPV infection or associated conditions *do not* develop antibodies
 - <70% with HPV infection seropositive to that type
 - 30-70% with HPV-associated cancers seropositive

HPV 16 Serology

National Health and Nutrition Examination Survey (NHANES 1991-1994), U.S.

| | N | Overall Prevalence (95% CI) |
|------------------|------|--------------------------------|
| Ages, yrs | | |
| 6-11 | 1316 | 2.4 (1.6, 3.7) |
| 12-59 | 7218 | 13.0 (11.5, 14.7) |

Summary

- HPV infection highly prevalent in males and females
- HPV acquisition occurs soon after sexual initiation and most HPV infection clears quickly
- Lifetime cumulative incidence is >80% to any HPV infection
- HPV 16 is the most common HPV type; cumulative incidence after sexual initiation is 10% at 2 years
- HPV persistence is associated with increased risk of cervical cancer precursors
- Natural history studies of HPV infection in men are ongoing
- Serologic tests underestimate past or current HPV infection

Acknowledgments

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HPV16 Seroprevalence National Health and Nutrition Examination Survey (NHANES), U.S.

