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Center of Excellence in
women's health

HPV Prevention and Vaccination

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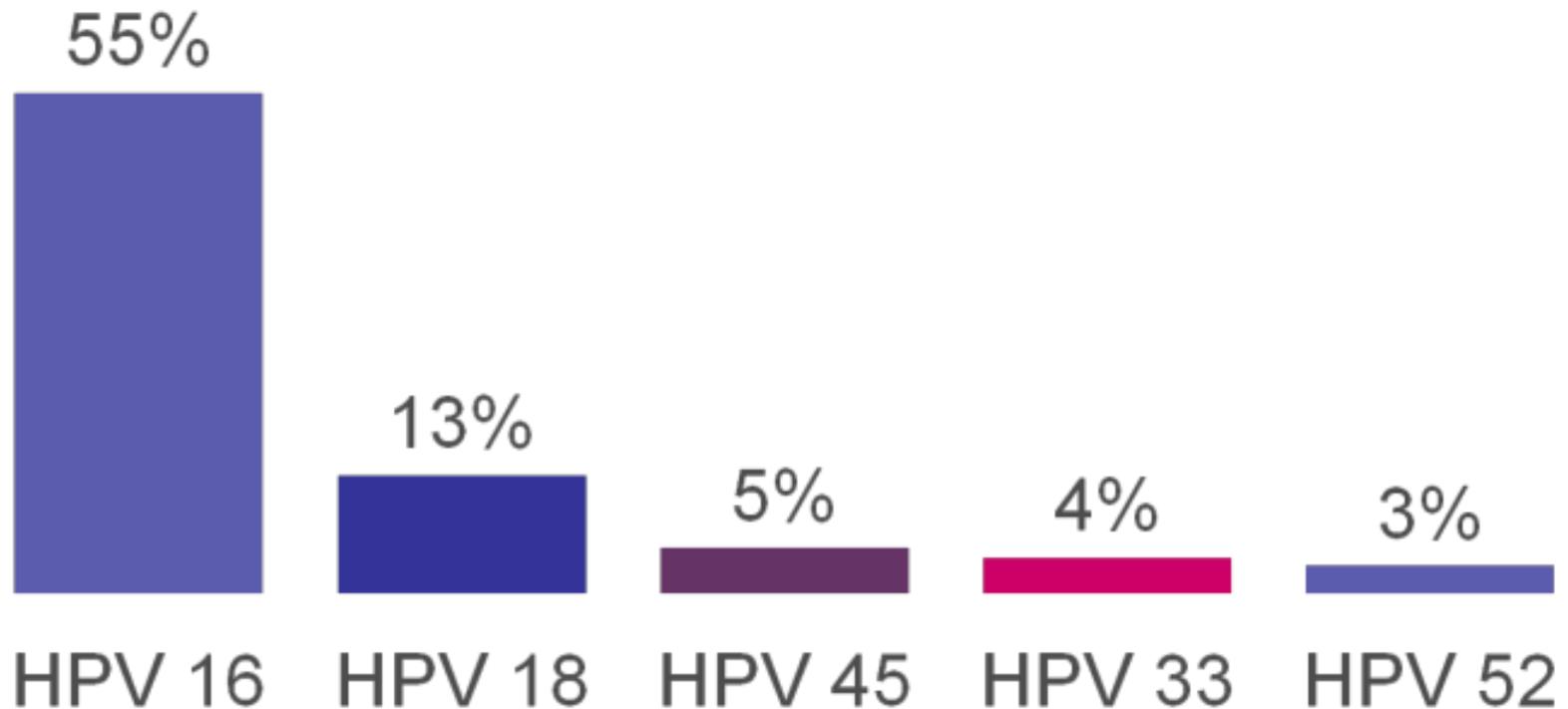
Faculty Disclosure

- Dr. Garcia has no financial interests or affiliations to disclose.

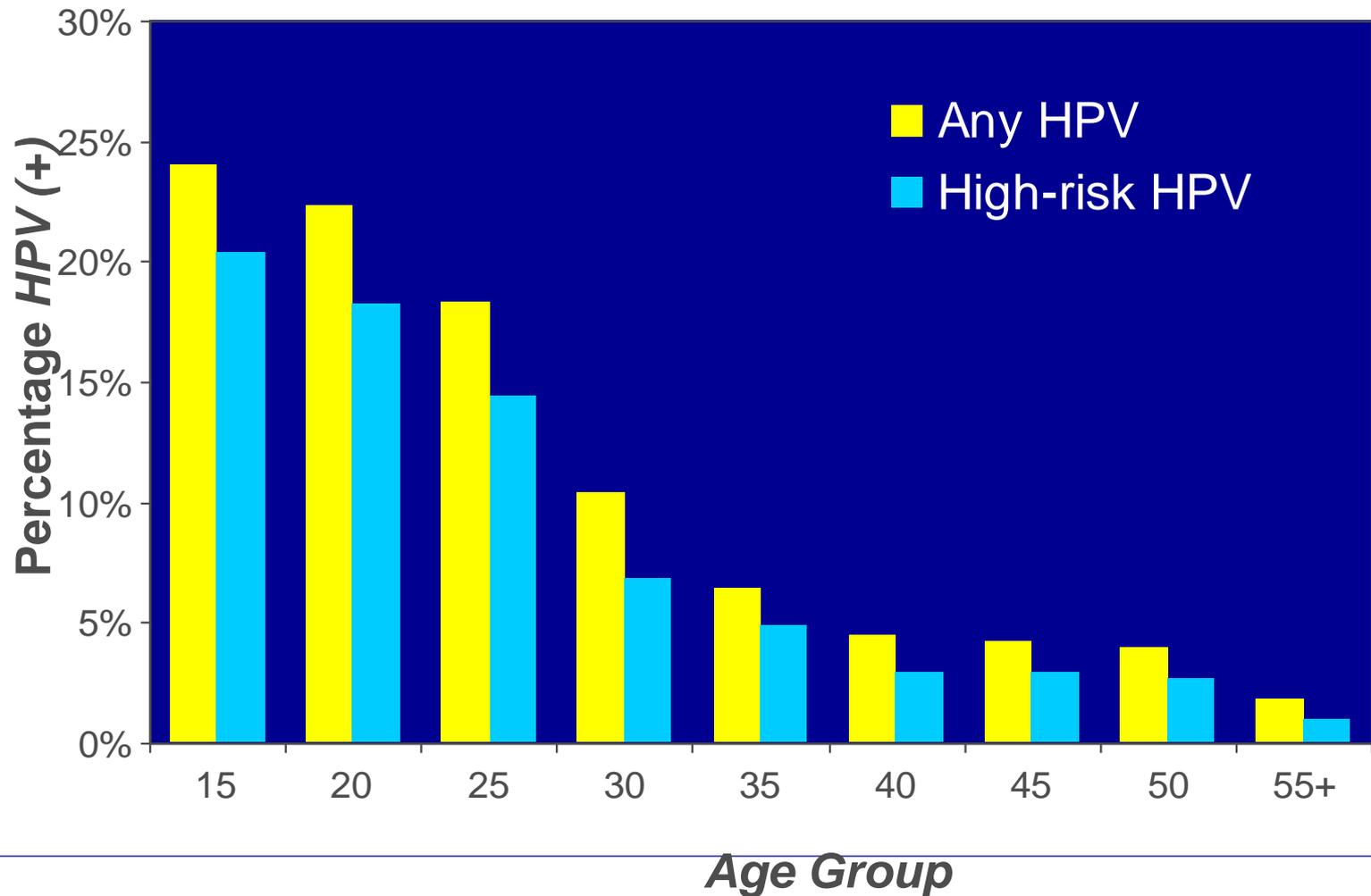
Learning Objectives

- Apply knowledge of HPV transmission and carcinogenesis to counsel patients about prevention
 - Answer questions about adverse events associated with HPV vaccination
 - Identify target populations who benefit the most from HPV vaccine
 - Explain to the need for ongoing cervical cancer screening after HPV vaccination
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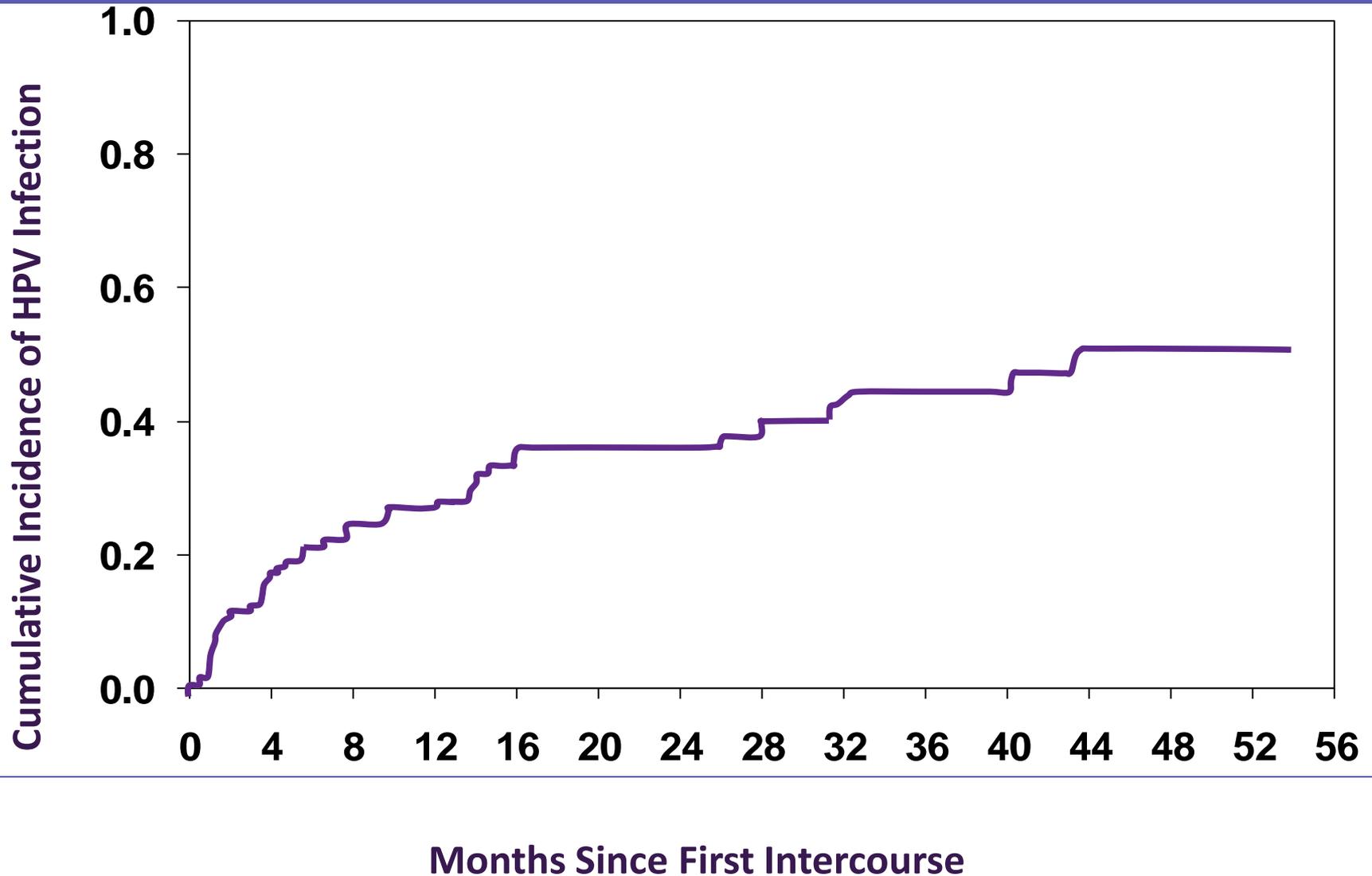
HPV in Squamous Cell Carcinoma



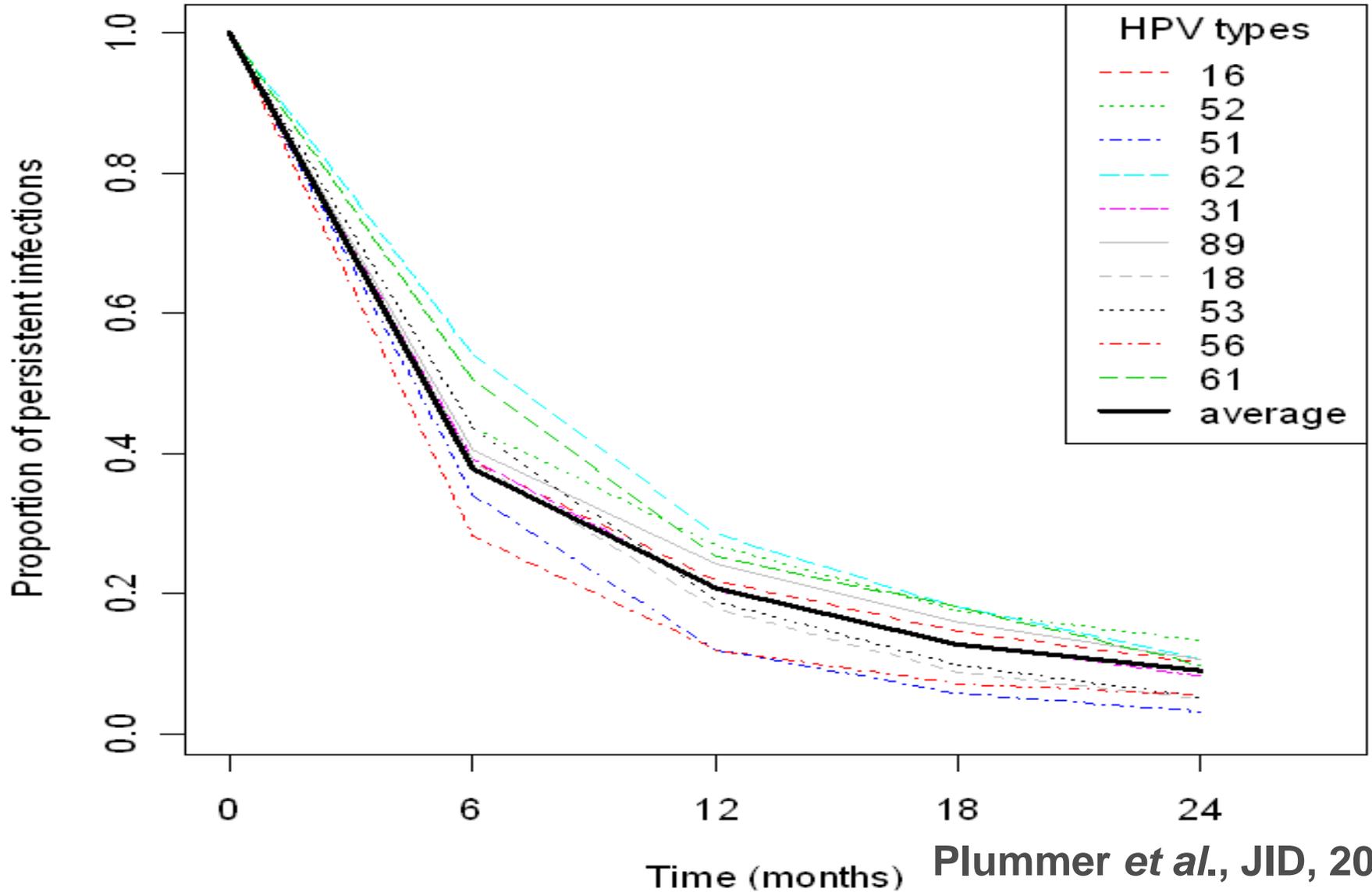
HPV Positivity by Age



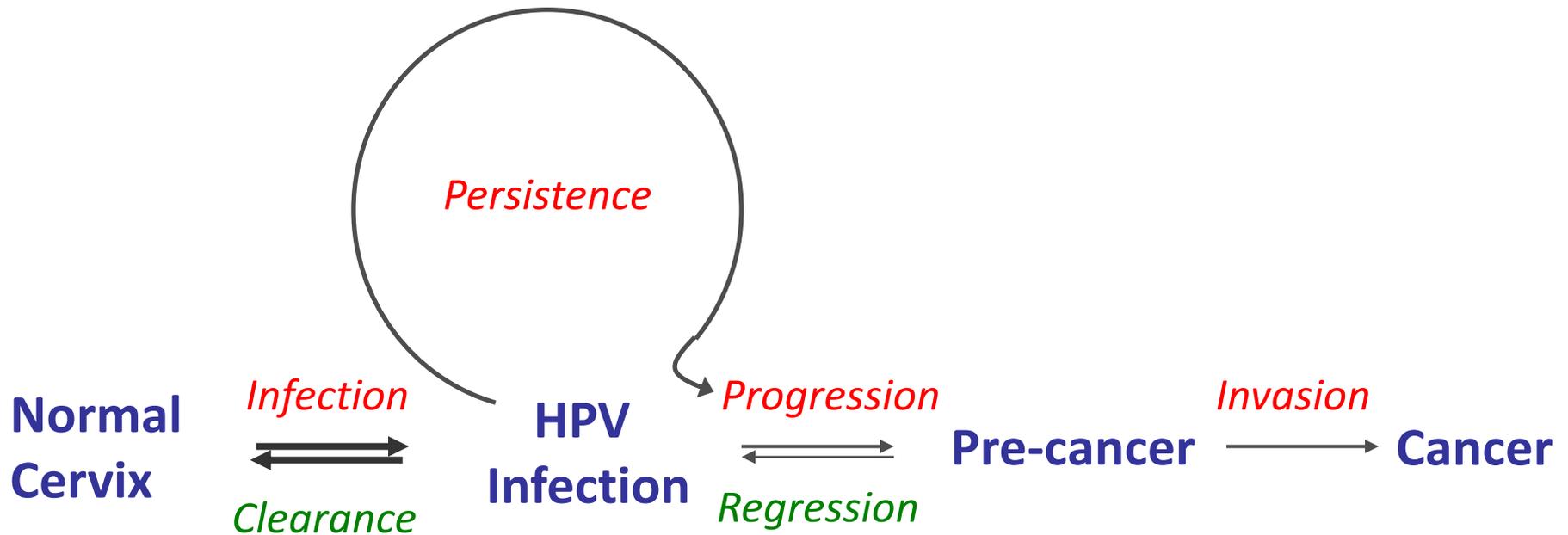
Infection From Time of First Sexual Intercourse (Winer 2003)

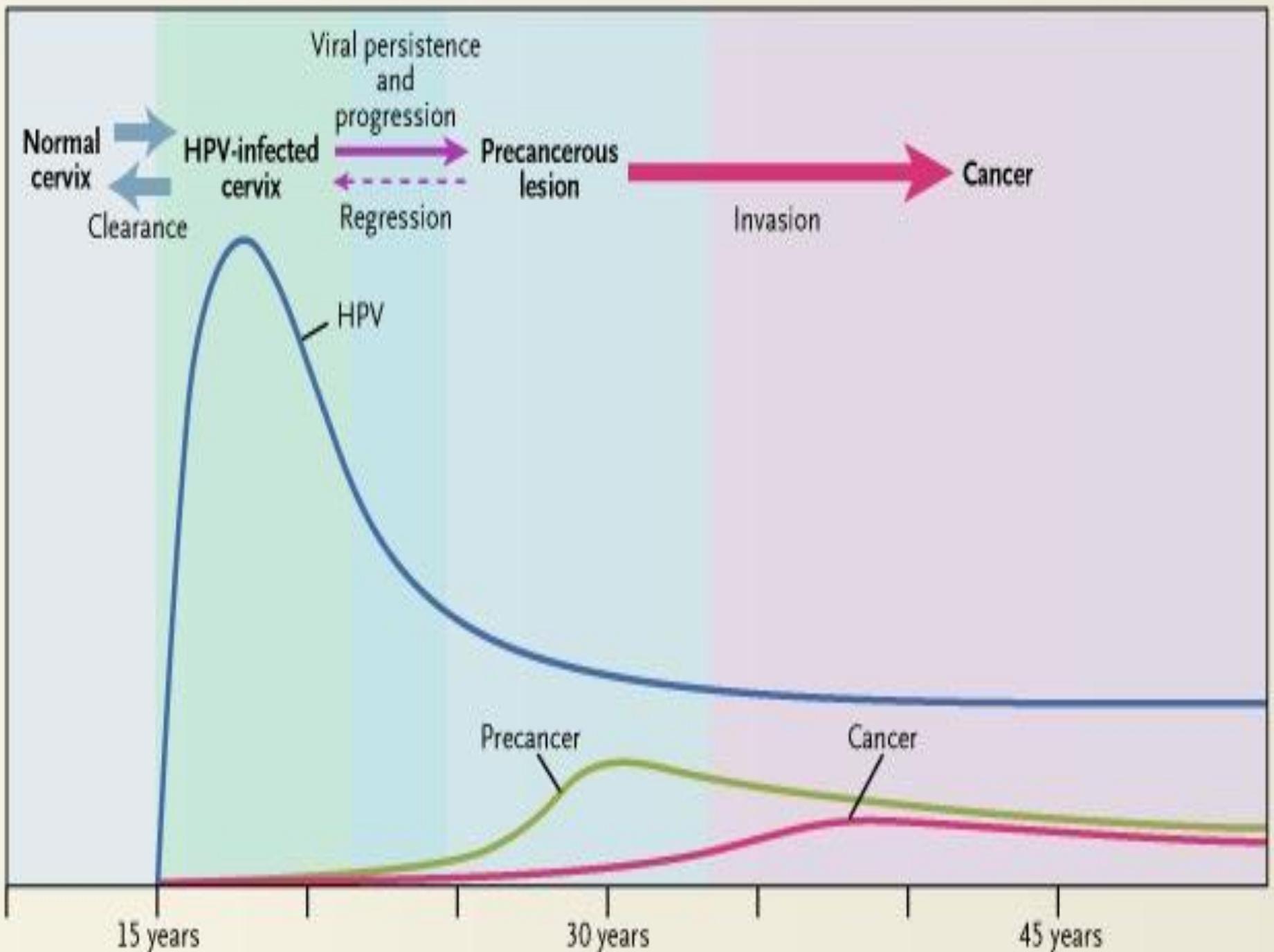


Prevalent HPV Infections Resolve Spontaneously and Rapidly in Young Women



Natural History of HPV Infection & Cervical Cancer

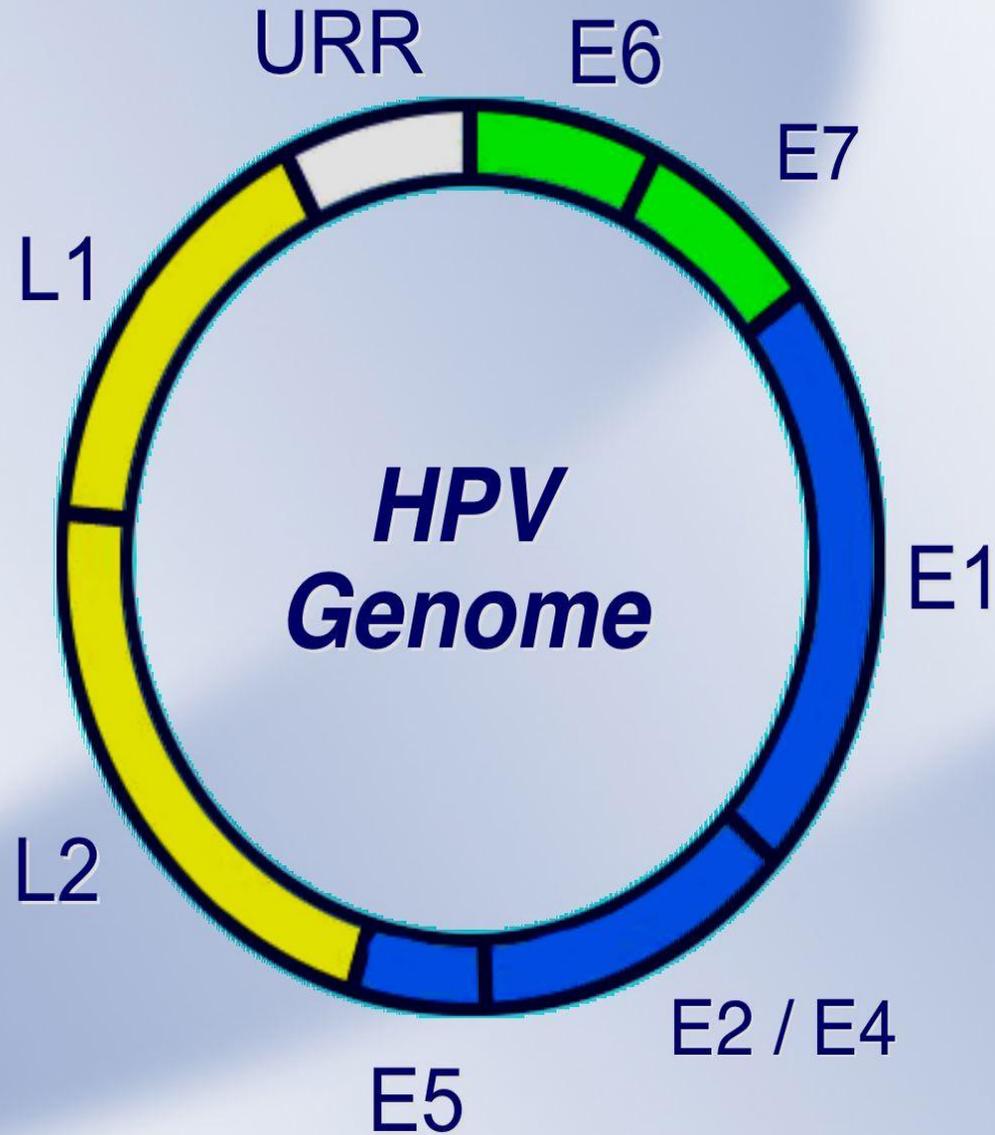




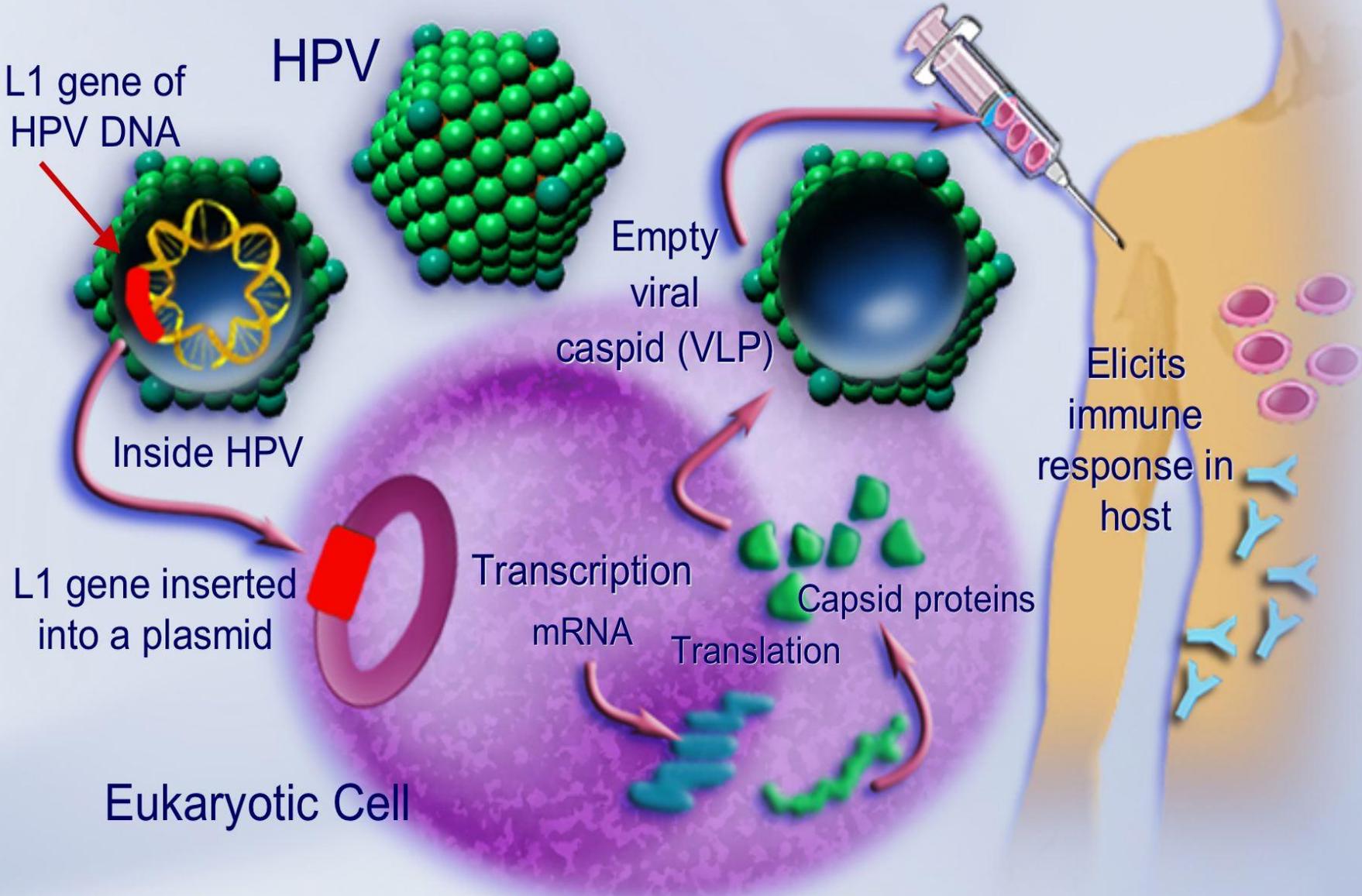
Prophylactic Vaccination

Current Status of Prophylactic Vaccines

- 2006, Merck quadrivalent HPV 6, 11, 16, 18 vaccine approved by FDA
 - Recommended for use by ACIP and included in VFC program
 - 2009, GSK bivalent HPV 16, 18 vaccine approved by FDA
 - 2010, Merck quadrivalent approved for boys
-



HPV L1 Virus-Like-Particle (VLP) Vaccine Synthesis



Summary of Phase III Studies

| Feature | Quadrivalent | Bivalent |
|-----------------|----------------|----------------|
| Vaccine Type | 6, 11, 16, 18 | 16, 18 |
| Age | 16-24 years | 15-25 years |
| Schedule | 0, 2, 6 months | 0, 1, 6 months |
| Number patients | 17,633 | 18,644 |
| Mean follow-up* | ~ 30 months | 14.8 months |

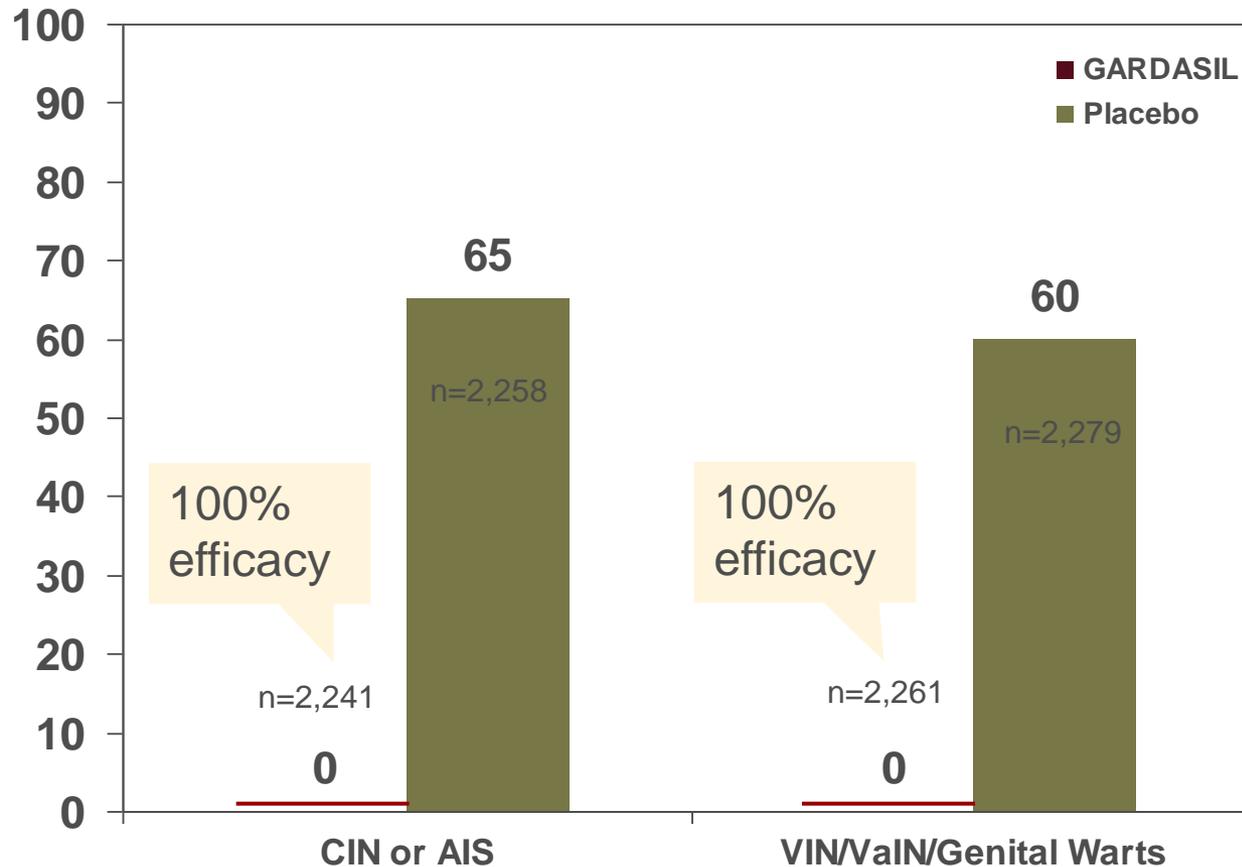
* After 1st dose of vaccine

Quadrivalent Phase III Trials: Future I Per Protocol Population

- Per-protocol population
- “Naive” to vaccine HPV types at enrollment
- Did not become infected during first 6 mos
- Received all three doses of vaccine
- Demonstrates vaccine effectiveness in uninfected women

Prophylactic Efficacy Against HPV 6/11/16/18–Related CIN or AIS, VIN/VaIN/Genital Warts in Per-Protocol Population

Subjects were free of HPV 6, 11, 16, 18 infection through 1 month Postdose 3.



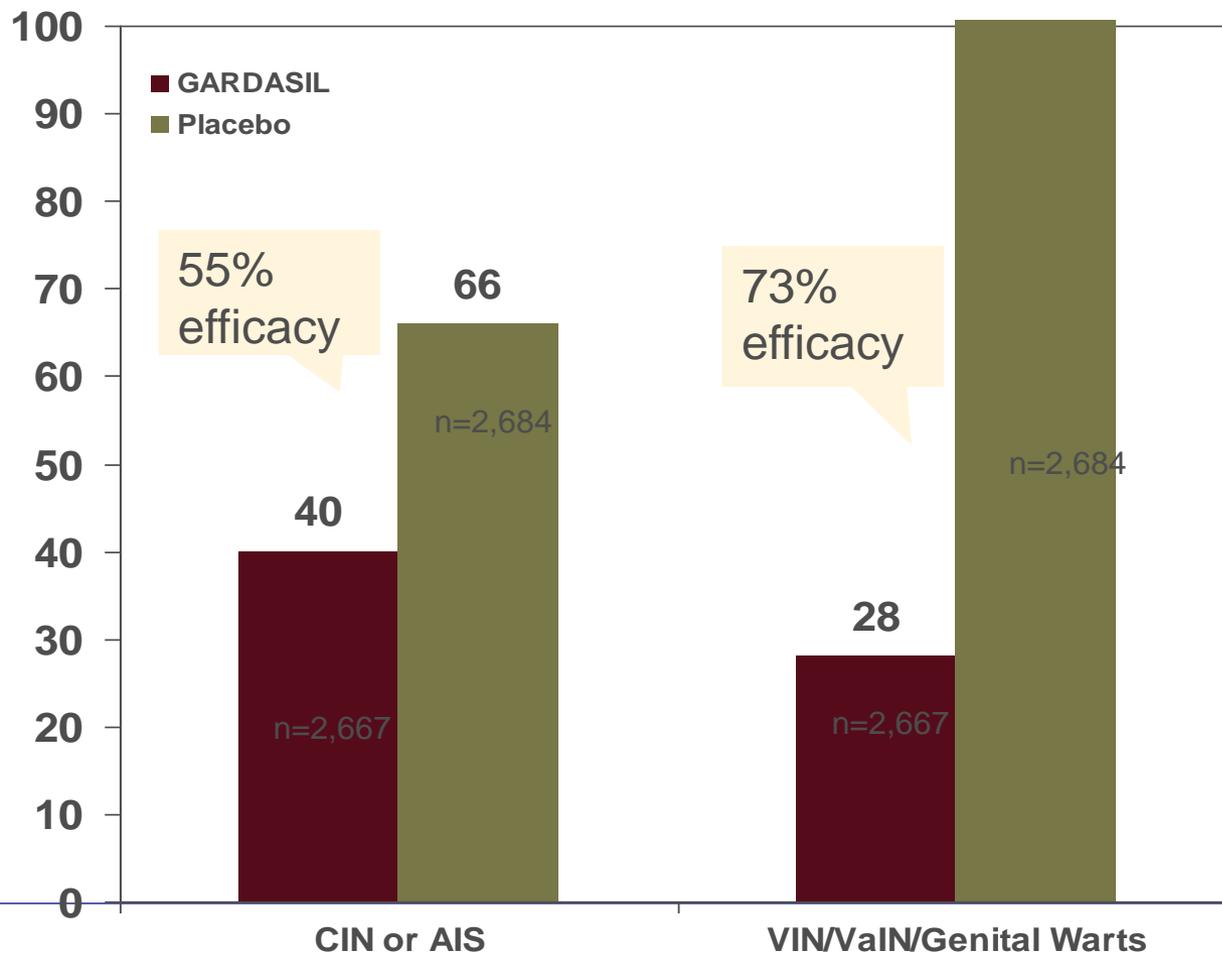
22 95% confidence interval: 94%–100%.

Quadrivalent Phase III Trials: Future I Intention-to-Treat Population

Intention-to-treat population

- Includes all women studied
- Demonstrates vaccine effectiveness in general population

Prophylactic Efficacy for HPV 6/11/16/18–Related CIN/AIS, VIN/VaIN/Genital Warts Intent to Treat Population



Bivalent Vaccine Phase III Trial: Impact on Persistent Infections

| | Number of Cases | | 6 mo efficacy | 12mo efficacy |
|--------|-----------------|---------|---------------|---------------|
| | Vaccine | Placebo | | |
| HPV 31 | 46 | 215 | 78.7% | 79.4% |
| HPV 33 | 67 | 123 | 45.7% | 38% |
| HPV 45 | 23 | 94 | 75.7% | 63% |
| HPV 52 | 314 | 339 | ns | ns |
| HPV 58 | 144 | 147 | ns | ns |

Bivalent Vaccine Phase III Trial: Impact on CIN2+

| | Number of Cases | | |
|--------|-----------------|---------|---------------|
| | Vaccine | Placebo | 6 mo efficacy |
| HPV 31 | 2 | 25 | 92% |
| HPV 33 | 12 | 25 | 51.9% |
| HPV 45 | 0 | 4 | 75.7% |
| HPV 52 | 12 | 14 | ns |
| HPV 58 | 6 | 17 | 64.5% |

Quadrivalent Cross-Protection: ITT Data (Wheeler JID)

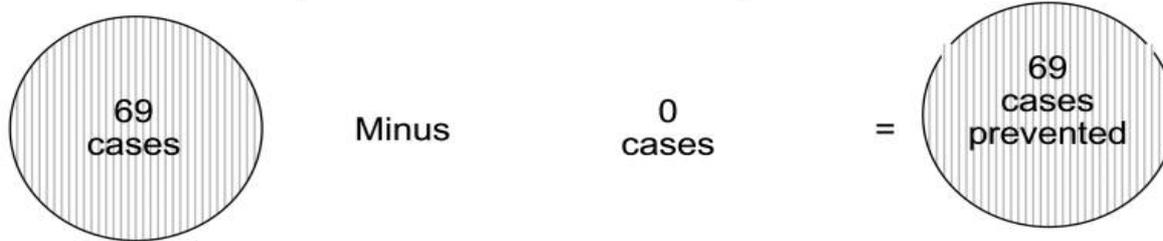
Table 2. Prespecified analysis of cross-protection for human papillomavirus (HPV) infection of ≥ 6 months' duration in the intention-to-treat (ITT) population.

| HPV type | Vaccine (<i>n</i> = 1732 ^a) | | Placebo (<i>n</i> = 1727 ^a) | | Efficacy, % (95% CI) |
|--|--|-------------------|--|-------------------|----------------------|
| | Cases, no. | Rate ^b | Cases, no. | Rate ^b | |
| HPV-31 or -45 | 152 | 2.7 | 217 | 4.0 | 31.6 (15.4 to 44.7) |
| HPV-31, -33, -45, -52, or -58 | 359 | 7.0 | 424 | 8.5 | 17.7 (5.1 to 28.7) |
| Nonvaccine A9 species (HPV-31, -33, -35, -52, and -58) | 355 | 6.9 | 408 | 8.2 | 15.1 (1.8 to 26.5) |
| HPV-31  | 107 | 1.9 | 158 | 2.9 | 33.6 (14.6 to 48.5) |
| HPV-33 | 43 | 0.7 | 55 | 1.0 | 22.5 (-17.6 to 49.3) |
| HPV-35 | 45 | 0.8 | 43 | 0.8 | -3.7 (-61.4 to 33.2) |
| HPV-52 | 158 | 2.8 | 161 | 2.9 | 2.3 (-22.4 to 22.1) |
| HPV-58 | 91 | 1.6 | 103 | 1.8 | 12.8 (-16.7 to 35.0) |
| Nonvaccine A7 species (HPV-45 and -59) | 153 | 2.7 | 194 | 3.6 | 22.9 (4.2 to 38.1) |
| HPV-45 | 59 | 1.0 | 73 | 1.3 | 20.1 (-14.2 to 44.3) |
| HPV-59  | 104 | 1.8 | 135 | 2.4 | 24.6 (1.9 to 42.2) |

Impact of Cross Protection (Brown JID)

Number of cases Placebo Group Minus **Number of Cases Vaccine Group** = **Total number of cases of CIN2/3 or AIS prevented by vaccination:**

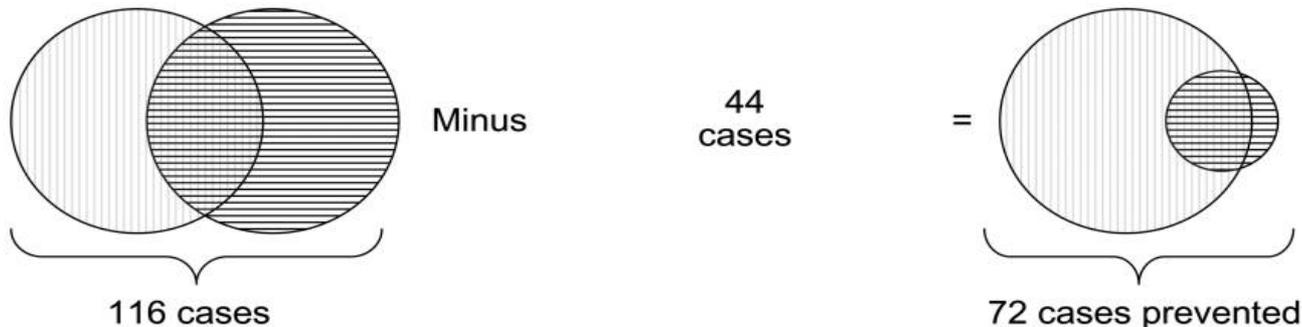
A. HPV 16 or 18 cases (with or without coinfections):



B. HPV 31, 33, 35, 52, or 58 cases (with or without coinfections):



C. HPV 16, 18, 31, 33, 35, 52, or 58 cases (with or without coinfections):



Net Benefit =
3 Additional
Cases
Prevented;
Increment of
4.3%

Quadrivalent Vaccine Efficacy Among 24-45 yo Women

- International, multicenter, randomized, double blind, placebo controlled trial
 - Women 24-45 years & no history of EGW or cvx dz
 - Outcome persistent (>6 m) infection & any related CIN/VIN/VAIN/EGW
 - n=3819, mean age=34.3
 - Evidence of prior infection by serology (30%), HPV DNA PCR (8%)
-

Quadrivalent Vaccine Efficacy 24-45 yo, Per Protocol

| Endpoint | Number of Cases | | |
|--|-----------------|---------|------------------|
| | Vaccine | Placebo | % efficacy (CI) |
| Persistent HPV 16/18/6/11 & CIN/VIN/VAIN/EGW | 4 | 41 | 90.5% (73-97) |
| Persistent Infection | 3 | 40 | 92.6% (77-98) |
| CIN/VIN/VAIN/EGW | 1 | 13 | 92.4% (49-99) |

Quadrivalent Vaccine Efficacy 24-45 yo, Intent to Treat

| Persistent HPV Infection | Number of Cases | | % efficacy (CI) |
|--------------------------|-----------------|---------|------------------|
| | Vaccine | Placebo | |
| 16/18/6/11 | 108 | 154 | 30.9% (11-46) |
| 16/18 | 90 | 115 | ns |
| 6/11 | 24 | 45 | 47.1% (11-69) |

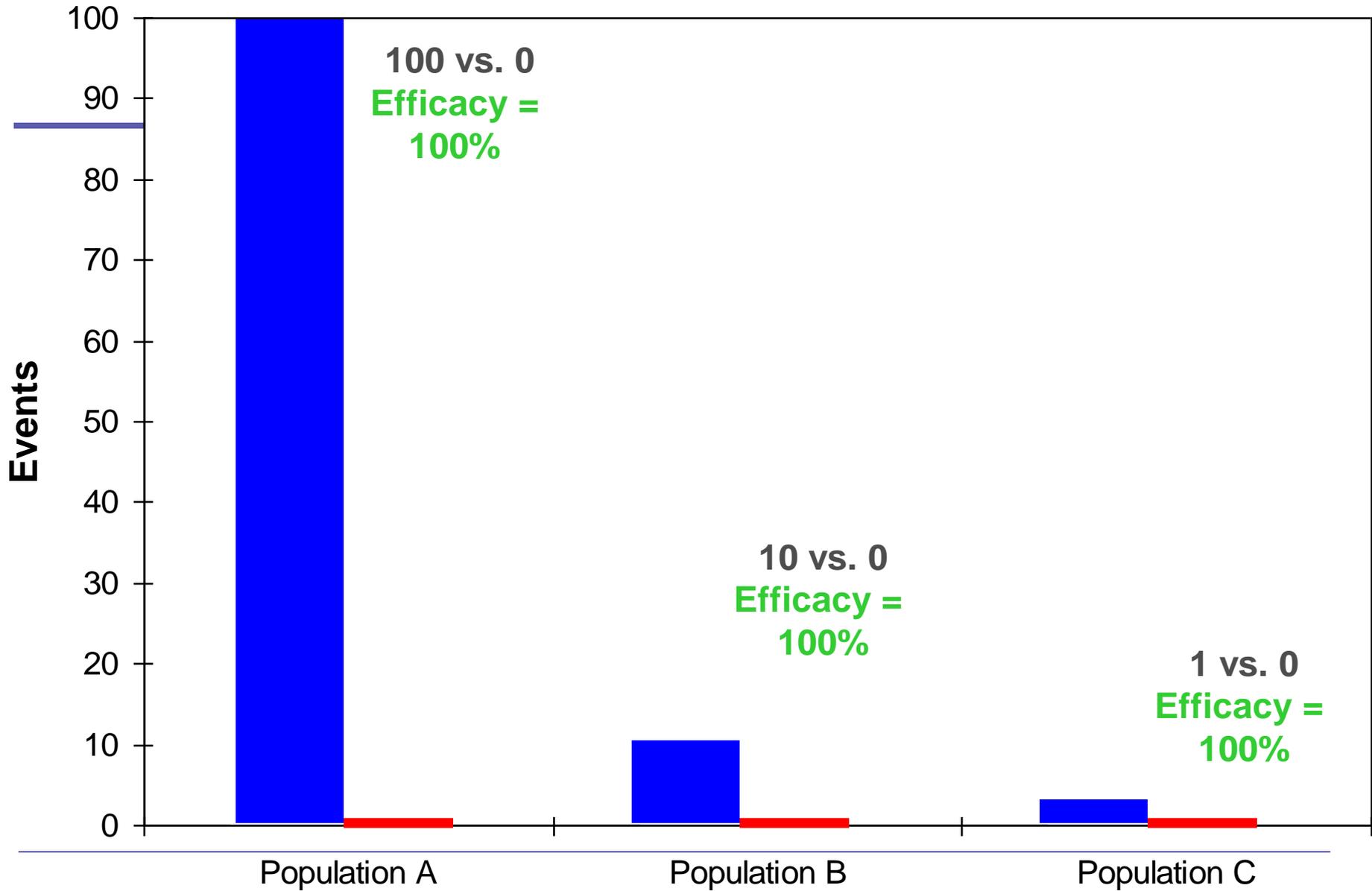
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So now what?

Efficacy vs. Public Health Benefit



CDC/ACIP Recommendations: HPV Vaccine

- Target: girls 11-12 years old (as young as 9 years old)
- Catch-up recommended: 13-26 years old
- HPV DNA testing and Pap tests are not required or recommended prior to vaccine
- Okay if:
 - Abnormal Pap results,
 - Previously tested positive for HPV
 - Lactating
 - Immunocompromised
 - Minor illness
- Not recommended if pregnant or moderate to severe acute illness

ACS Recommendations for HPV Vaccine Use to Prevent Cervical Cancer

- *Routine HPV vaccination for females age 11-12*
 - Can begin as young as 9 years
 - Catch up for females 13 to 18
 - *Insufficient data to recommend for or against universal vaccination of 19-26 yo women.* (decision should be based on informed discussion btwn woman and provider)
-

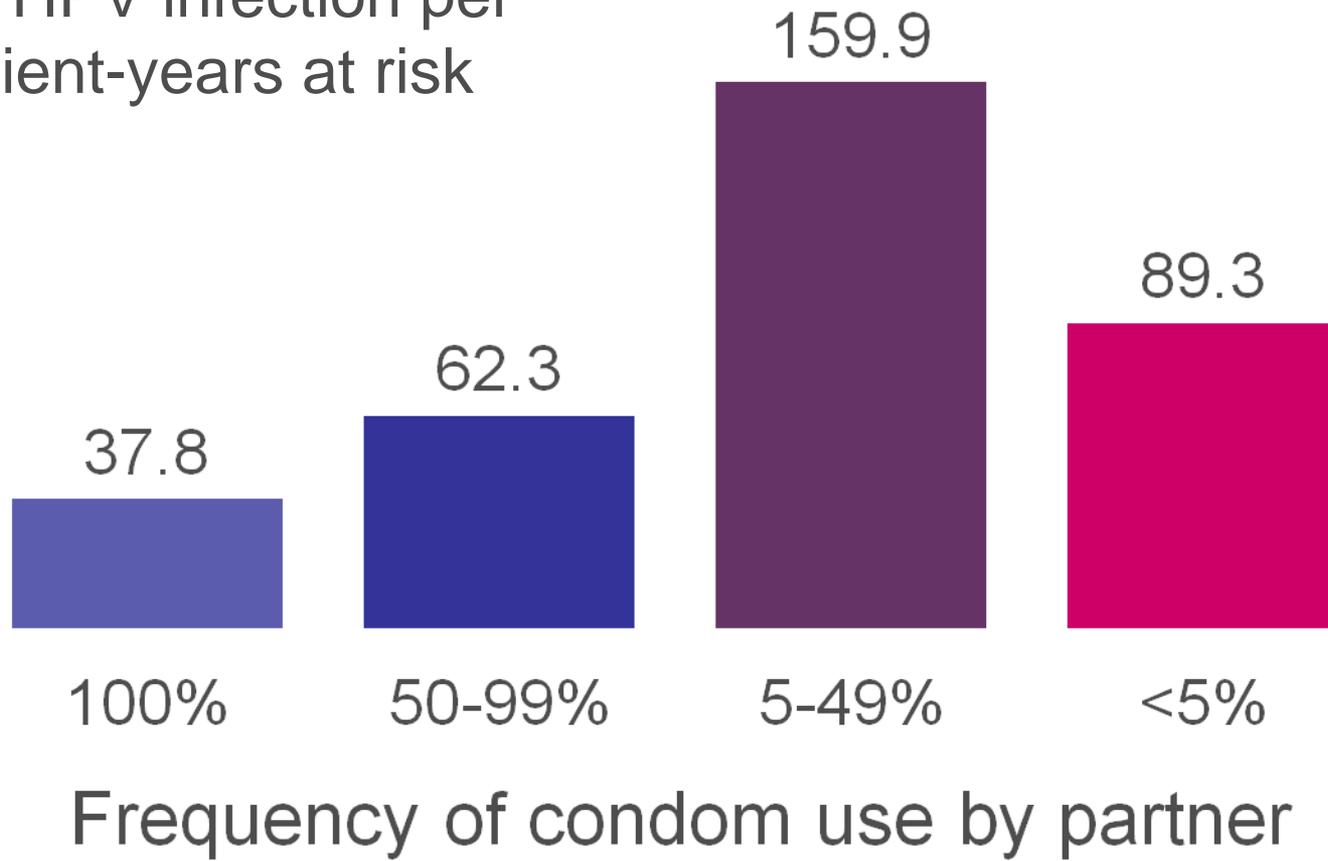
HPV Vaccination: Other Issues

- Pap/HPV testing prior to vaccination
 - Don't do it
- Screening after vaccination
 - Do it
- Secondary prevention with condoms
 - Do it



Condom Use and HPV Prevention

Rate of HPV infection per
100 patient-years at risk



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How are we doing?

HPV Vaccination

What age should be targeted?

- Vaccine is most effective when administered before HPV exposure
- Over 80% of sexually active adolescents become exposed to HPV within 3 years of sexual activity
- Best to administer prior to sexual activity

HPV Vaccine Coverage: Adolescents

- National Immunization Survey-Teen collects a national estimate of coverage for 13 to 17yo
 - Random-digit--dialed sample of households
 - Surveys mailed to vaccination providers
 - Response rate 58.7%
 - 17,835 adolescents with provider-verified vaccination records
-

HPV Adolescent Vaccine Coverage: 2007 & 2008

| Dose | 2007 n=2947 | 2008 n=17,835 | 2009 n=20,066 | 2010 n=19,257 |
|-------------|-----------------------|-------------------------|-------------------------|-------------------------|
| ≥1 | 25.1% | 37.2% | 44.3% | 48% |
| 3 | -- | 17.9% | 26.7% | 32% |

Stokely 2009, Dorrel 2011 & 2011

Adolescent HPV Vaccine Coverage by Race/Ethnicity & FPL-2010

| HPV Vaccine Dose(s) | Race/Ethnicity | | | | | | Federal Poverty Level | |
|---------------------|----------------|--------|----------|-------|-------|-------|-----------------------|-------------|
| | White | Black | Hispanic | AI/AN | API | Other | Below | At or Above |
| | n=13223 | n=1982 | n=2469 | n=253 | n=516 | n=814 | n=2,506 | n=16,781 |
| ≥1 | 46% | 49% | 56%* | 65%* | 50% | 52% | 52% | 48% |
| ≥3 | 32% | 30% | 30% | 41% | 40% | 37% | 28%* | 33% |

Dorrel MMWR 2011

Predictors of Impact of Quadrivalent Prophylactic HPV vaccination

- Young women (<19 years) are likely to experience the greatest benefit
 - Women from communities of color and those living in poverty have the greatest risk of non participation in screening and should be targeted
 - CDC's VFC program has benefitted uninsured, Medicaid eligible, IHS eligible adolescents
 - Other non-financial barriers also important
-

Adverse Events: Quadrivalent Vaccine Surveillance

- September 2009
 - 26 million distributed in US
 - 15,037 reports after vaccination
 - 93% were non-serious (brief soreness, fainting, & headache)
 - 7% were serious
 - Include severe allergic reaction, anaphylaxis, Guillain-Barre syndrome, DVT, death (44, 27 confirmed)
 - No common pattern identified after medical review
-

Conclusion

- Cervical cancer prevention efforts must balance safety and potential benefit
 - New guidelines based on improved understanding of the disease process and limitations of screening and vaccine
 - Policy decisions should be made from a societal perspective, while personal choices must reflect individual preferences and perception of risk
 - *Primum non nocere*
-

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