HPV Vaccine:

One Year Later

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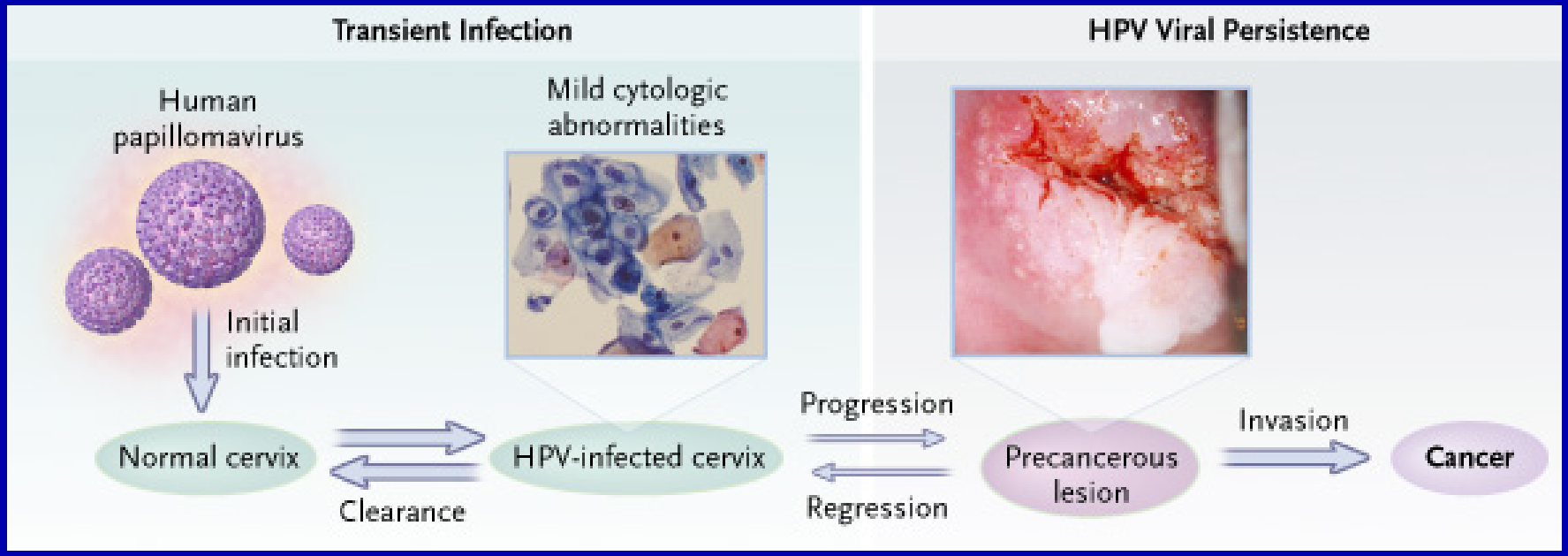
Public Health Impact of Prophylactic HPV Vaccines

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

HPV Prophylactic Vaccine

- HPV cause and cure
- Vaccine clinical data
- Vaccination recommendations
- Who pays?
- To mandate or not?
- Impact on providers
- Impact on screening
- Future vaccine developments

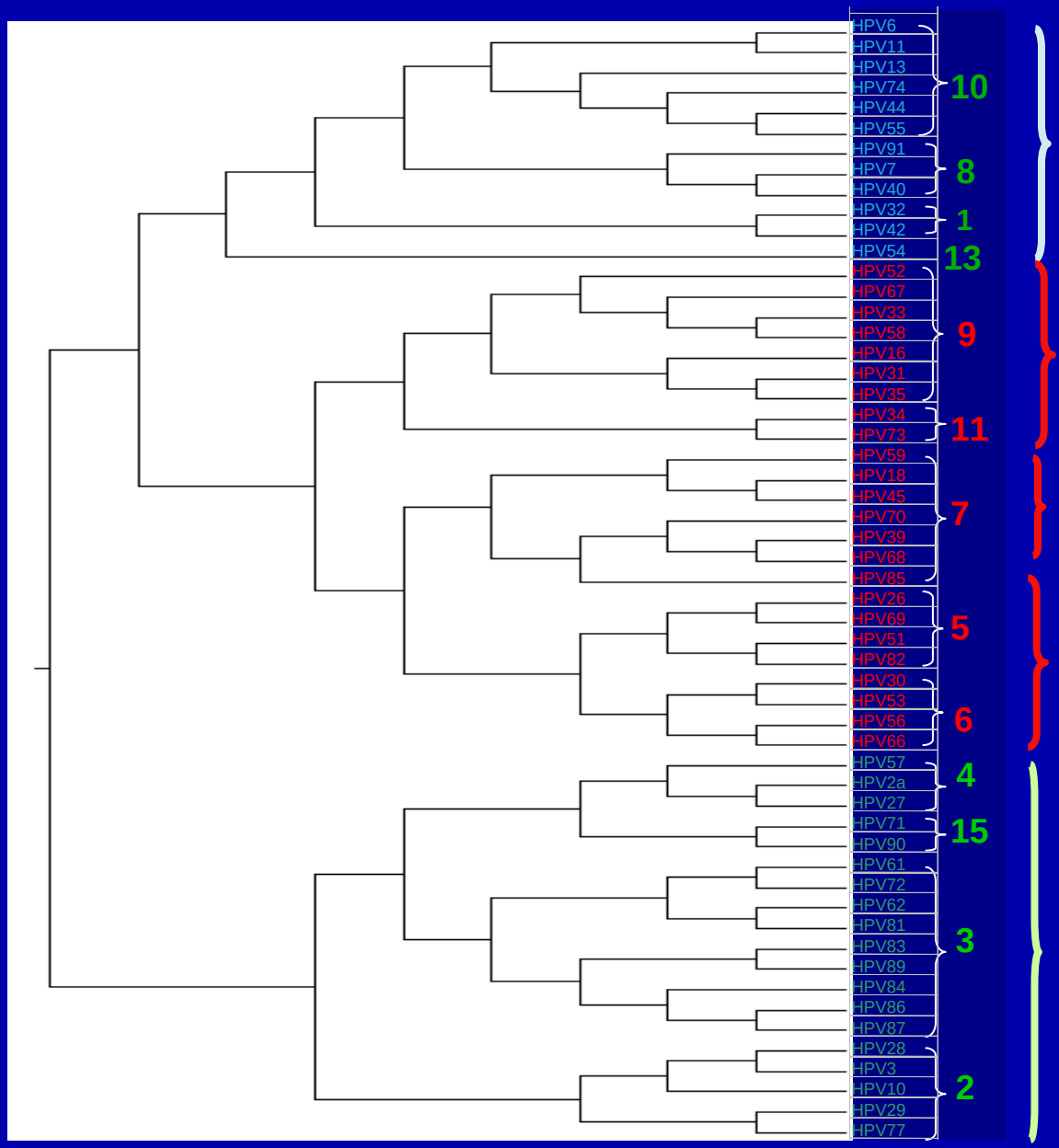
Cervical Cancer Pathogenesis



HPV: Cervical Cancer

- HPV infection
  - over 100 types of HPV
  - approximately 30 types involve genital tract
  - approximately 15 types associated with cervical cancer; most common 16, 18, 31 and 45
- Low risk HPV types:
  - condyloma acuminatum 6 & 11
  - many LR types subclinical 53

HPV Types and Genetic Relatedness



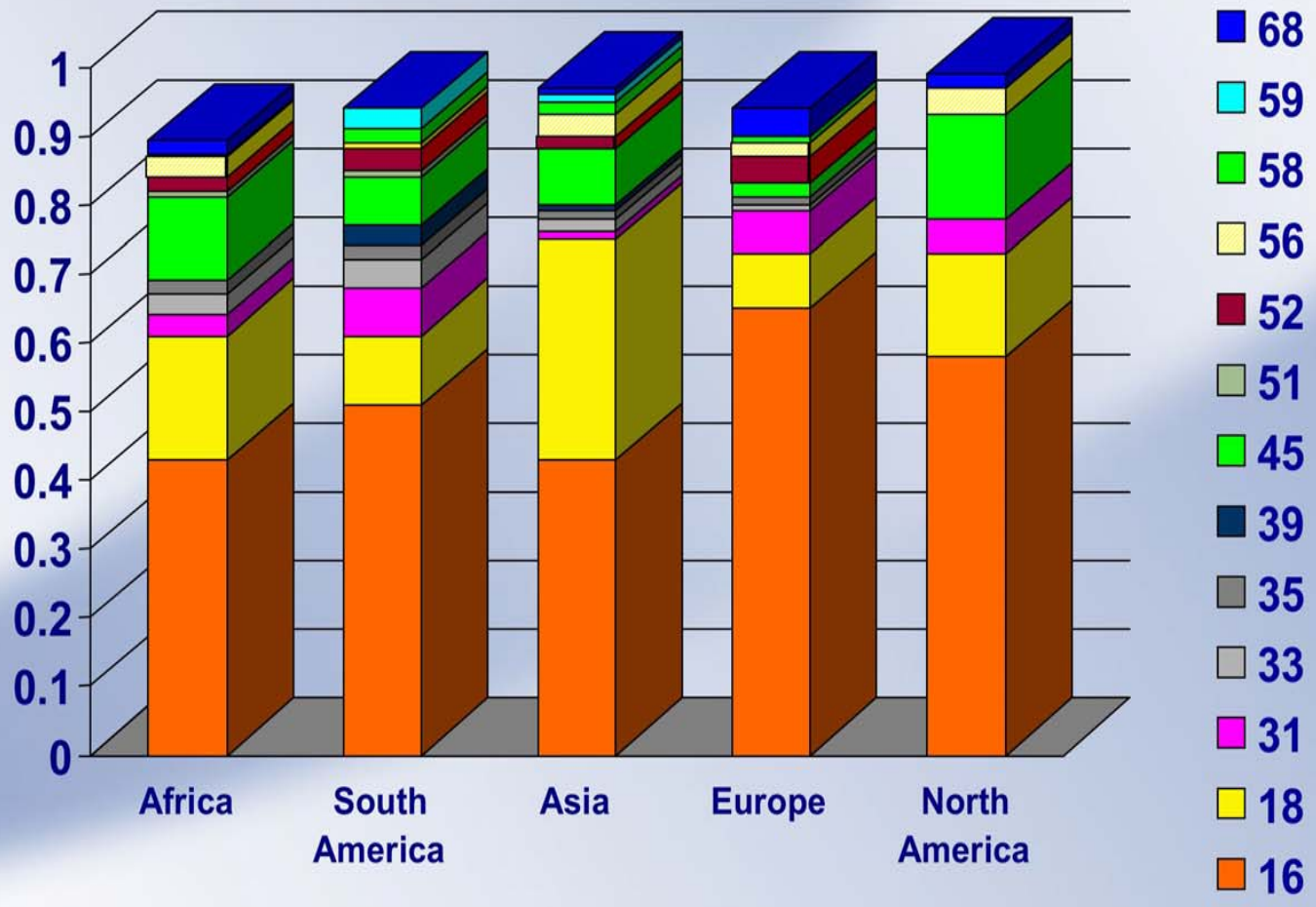
α1/α8/α10/α13
Genital Warts

α9/α11
α7
α5/α6
Squamous Cell Carcinoma & Adenocarcinoma

A3/α15
Commensal Infections

HPV Types in Cervical Cancer by Region

15 types are associated with cervical cancer



Potential Reduction in Cervical Cancer from the Addition of Multiple HPV Types to Vaccine

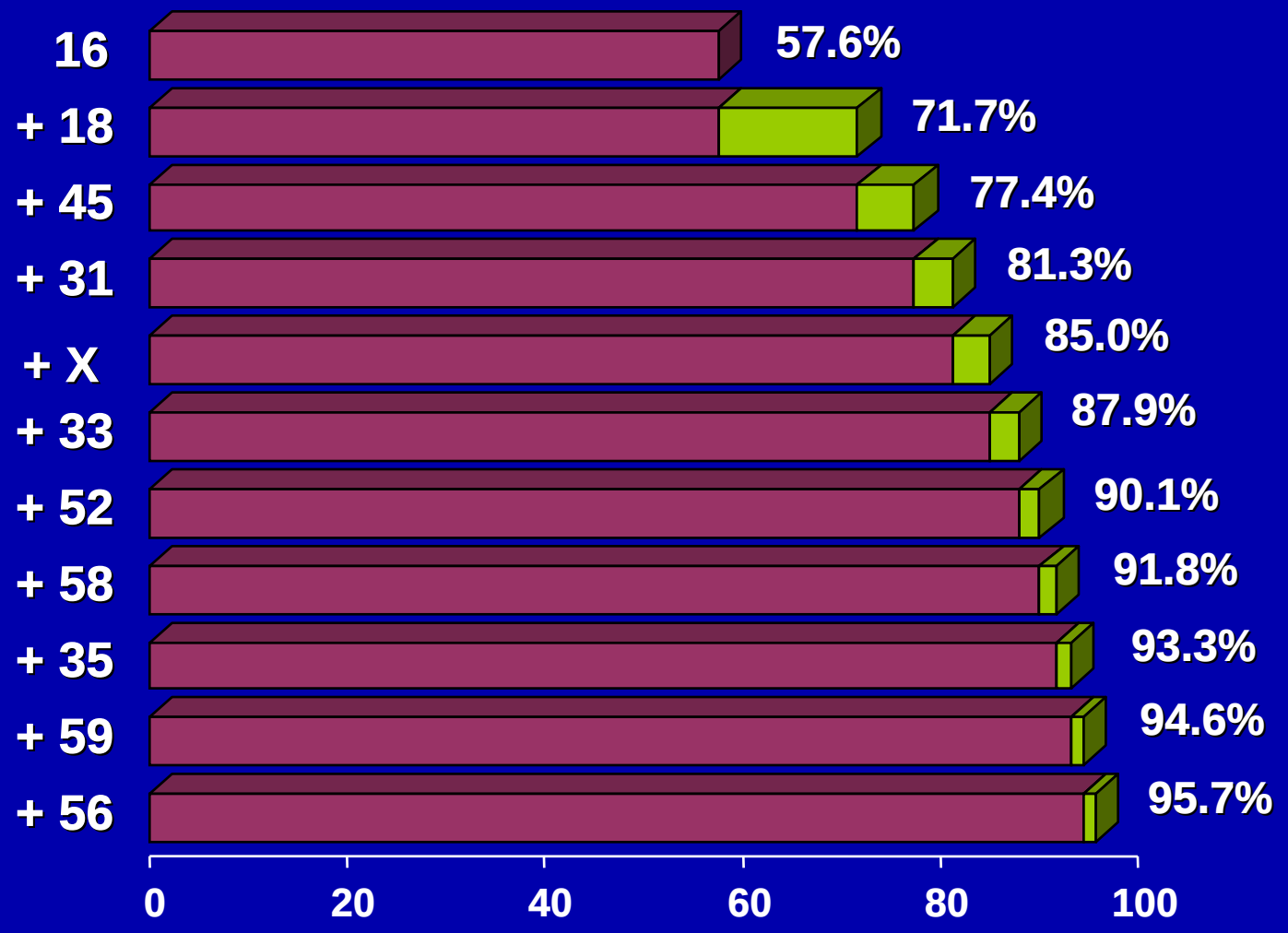


TABLE 1. Cancers associated with human papillomavirus (HPV) and percentage attributable to oncogenic HPV — United States, 2003

Cancer	Cases*	% Attributable to oncogenic HPV†
Cervix§	11,820	100
Anus¶	4,187	90
Vulva¶	3,507	40
Vagina¶	1,070	40
Penis¶	1,059	40
Oral cavity and pharynx¶	29,627	≤12

* **Source:** U.S. Cancer Statistics Working Group. United States cancer statistics: 2003. Incidence and motality. Atlanta, GA: US Department of Health and Human Services, CDC, and the National Cancer Institute; 2006. Available at http://www.cdc.gov/uscs.

† **Source:** Parkin M. The global health burden of infection-associated cancers in the year 2002. Int J Cancer 2006;118:3030–44.

§ A total of 70% attributed are HPV types 16 or 18.

¶ Majority of these cancers attributable to HPV type 16.

Prophylactic HPV Vaccines

- Merck Gardasil
  - types 6-11-16-18 with aluminum adjuvant
- GSK Cervarix
  - bivalent types 16-18 with ASO4 adjuvant
- VLP composed of HPV L1 protein
- 95% - 100% efficacy against specific viral type in naïve women
- Requires 3 IM injections over 6 months
- Requires refrigeration
- Expensive

VLP: Mechanism of Action

- Protection against new infection via neutralizing antibodies
- Measure neutralizing antibodies in serum
- No established antibody level that correlates with of immunity
- Natural infection may not result in detectable antibodies

Efficacy vs Effectiveness

Efficacy	Effectiveness
ATP	ITT
Optimal study conditions	Real World Impact
Relative % reduction in endpoint	Absolute rate reduction per 1,000 vaccinated
Similar place to place	Varies depending on: prevalence; risk factors

Gardasil

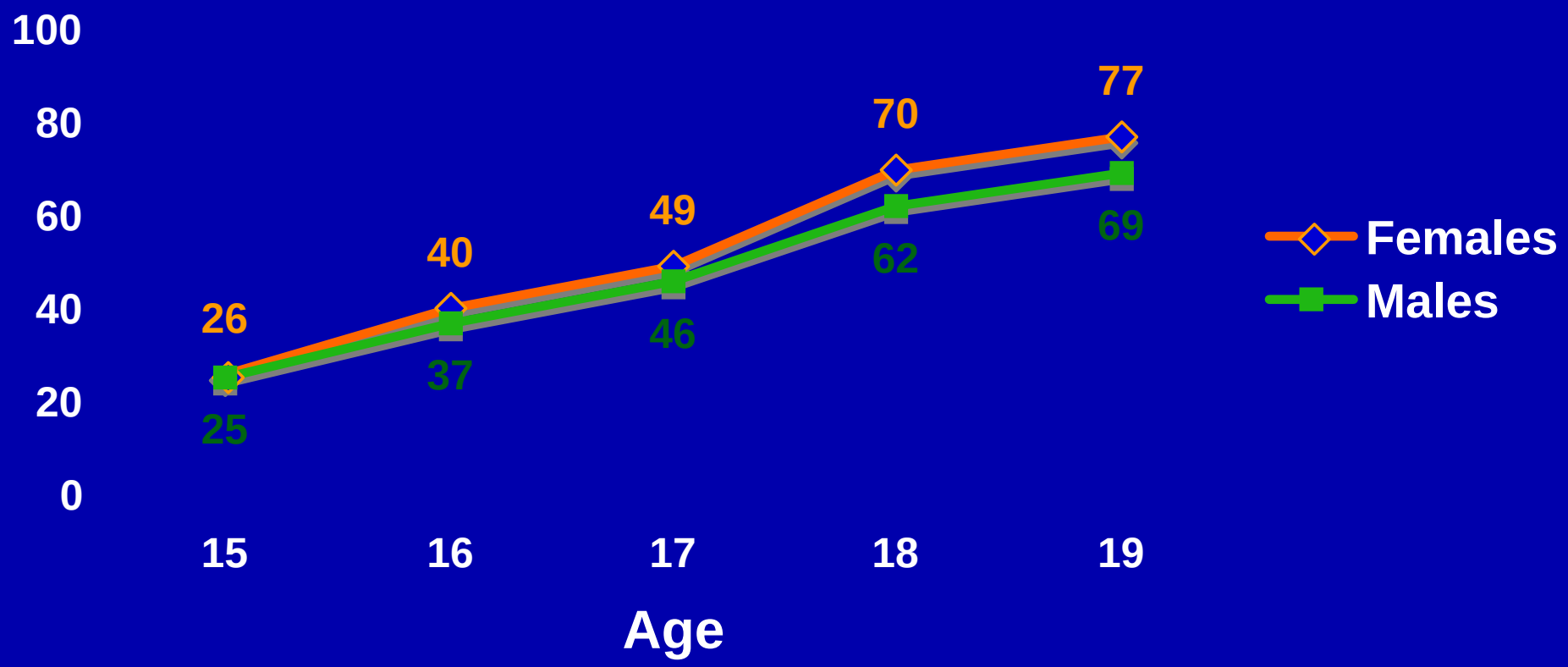
	ATP %Reduction	ITT %Reduction
CIN2+ 16/18	99%	39%
Genital Warts 6, 11, 16, 18	93%	68%
All CIN2+	35%*	12%^

* incident CIN2+ only
^Includes incident and prevalent CIN2+

GSK ASO4: Phase II

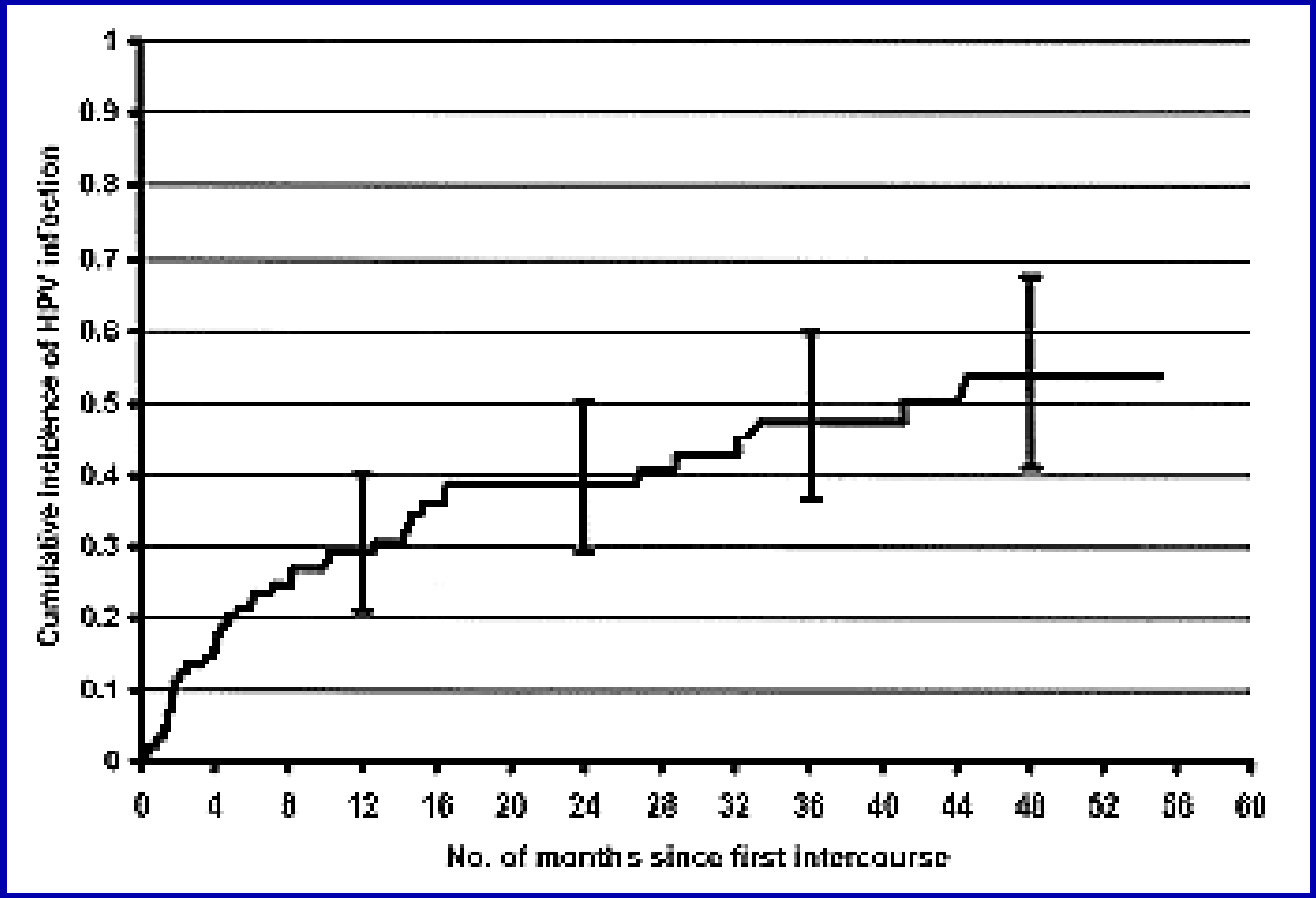
	% Reduction
Persistent HPV 16/18	96%
Incident HPV 31	55%
Incident HPV 45	94%
CIN2+ 16 *	100%

Percentage of Teenagers in USA Who Have Had Vaginal Sex



From Mosher et al., Vital and Health Statistics 362, 2005

Cumulative Incidence of HPV Infection after Sexual Debut



Winer *et al.*, AJE, 2003

Vaccination Recommendations Gardasil

ACIP and American Cancer Society

- Routine vaccination of 11 - 12 yr old girls
- May vaccinate girls as young as 9 yrs

- “Catch up” vaccination 13 to 26 yrs ACIP
- “Catch up” vaccination 13 to 18 yrs ACS

  (Insufficient data to recommend for or against vaccination for 19-26 yrs)

Benefits of Vaccination

Greatest in unexposed females

Decreased benefit in older women:

- Previously exposed, now HPV 16/18 negative (immunocompetent)
- Prevalent infection - no vaccine effect
- Lower risk of subsequent exposure

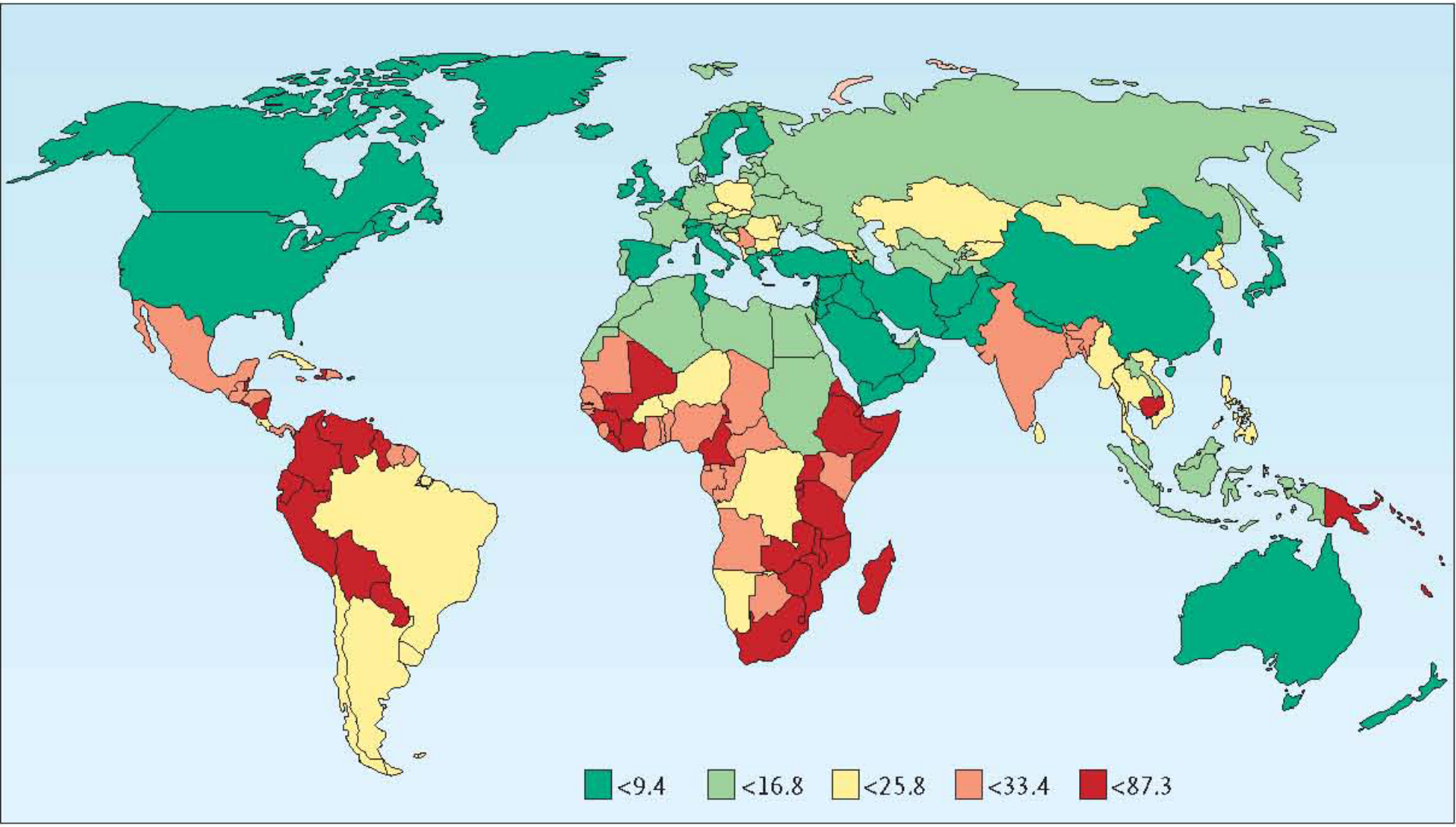
Even with high *efficacy* of vaccine, *effectiveness* may be very low

Will HPV Vaccines Decrease Cervical Cancer?

Will HPV Vaccines Decrease Cervical Cancer?

‘YES’ and ‘NO’

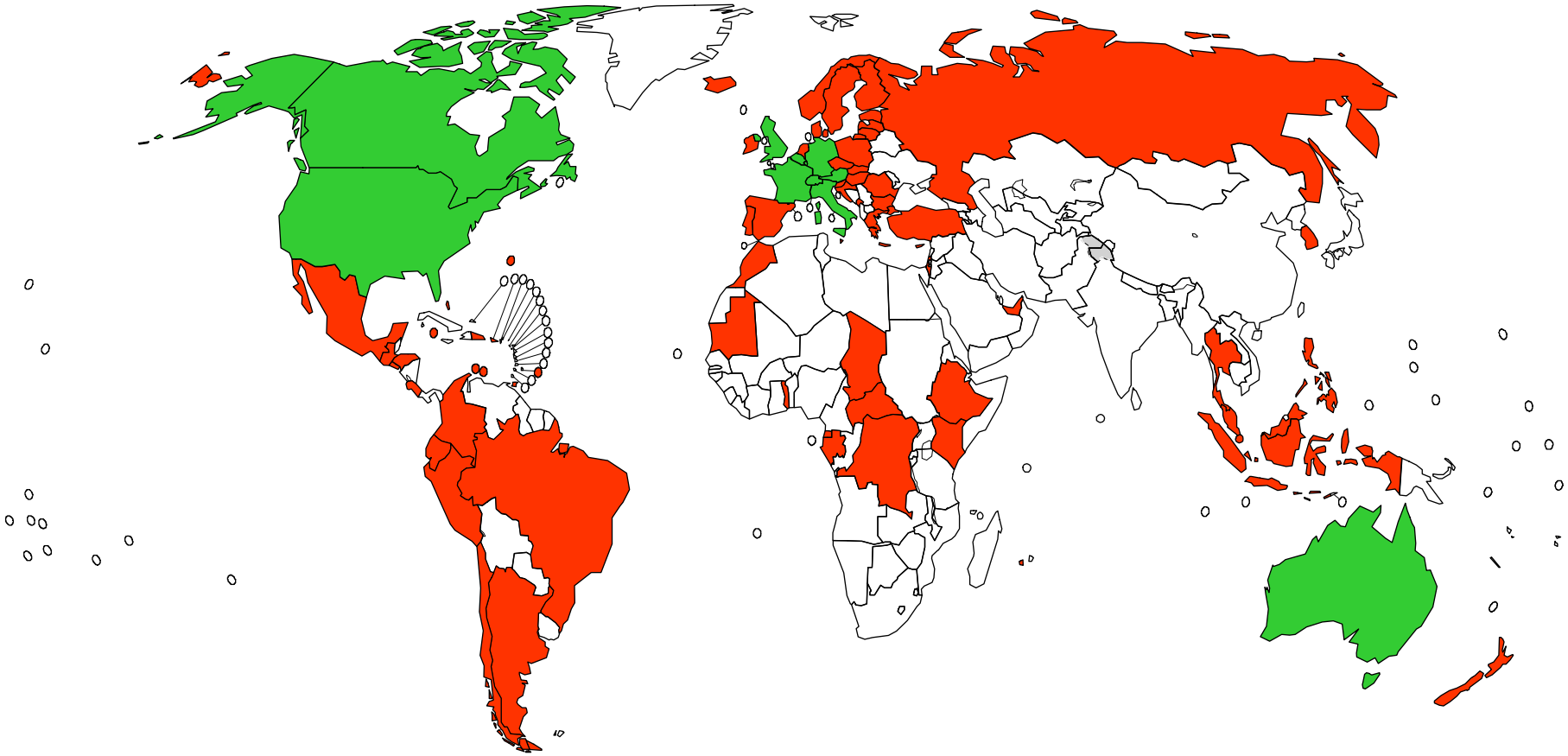
Incidence of Cervical Cancer Worldwide



Incidence of Cervical Cancer Worldwide.

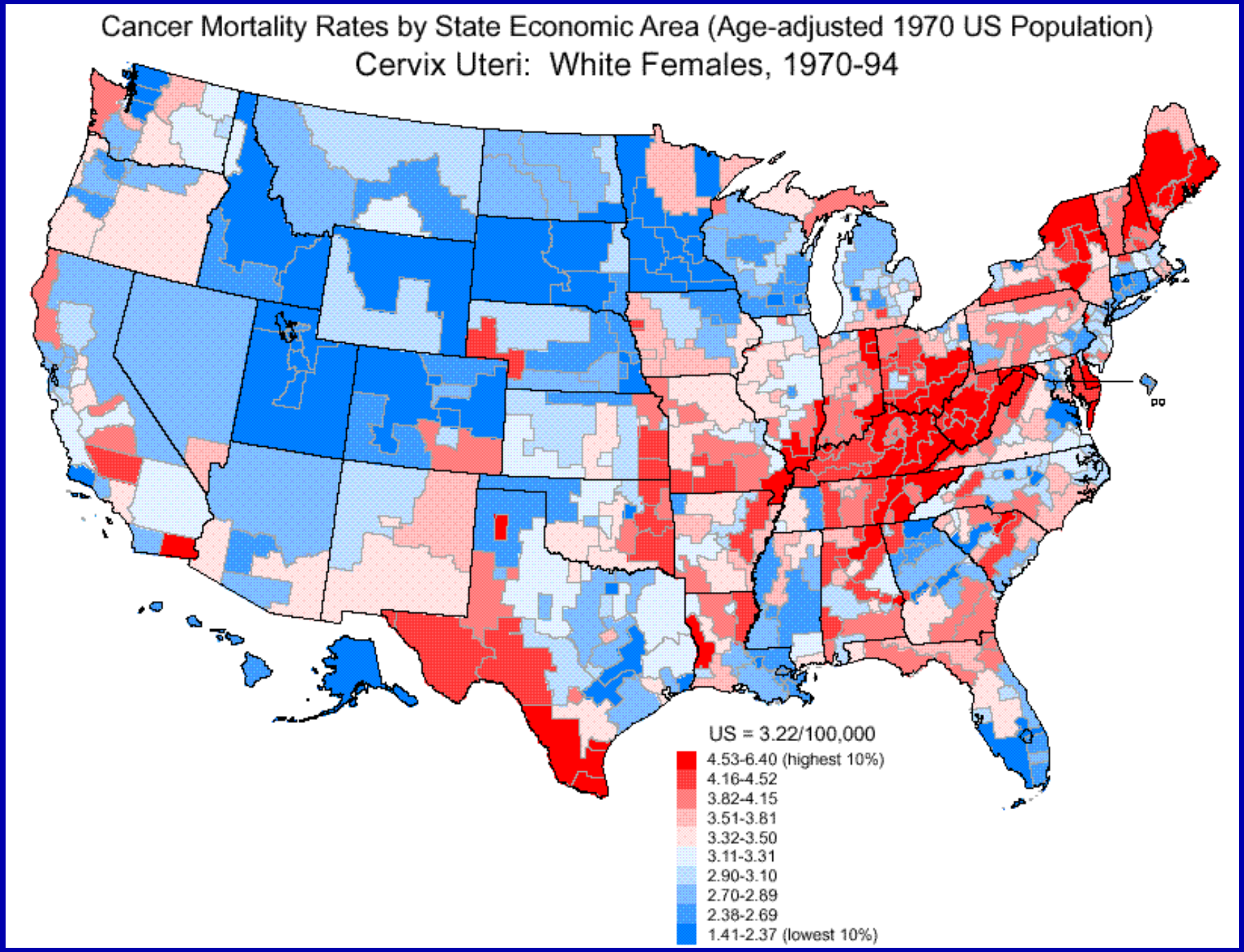
Numbers indicate cases per 100,000 population.

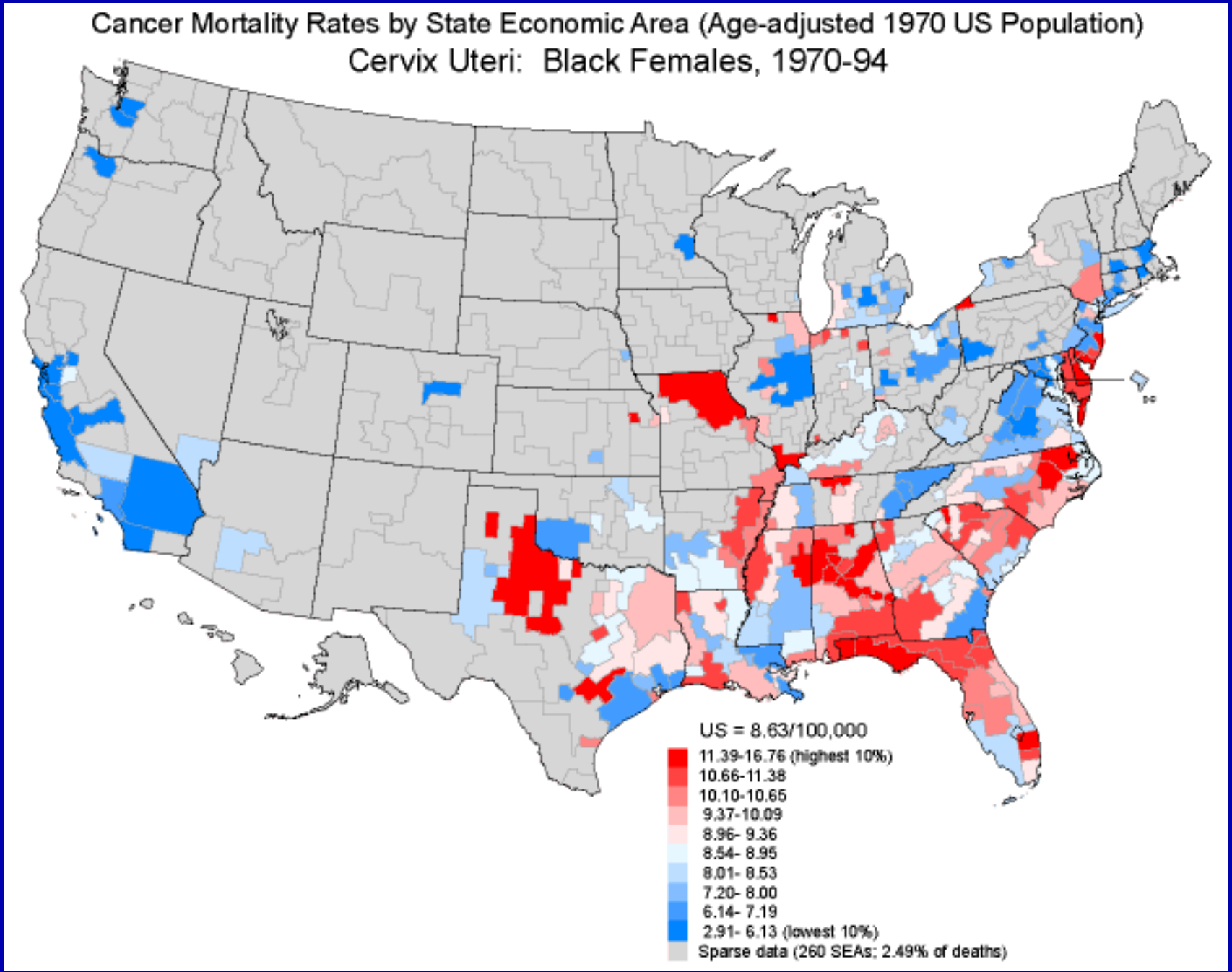
Status of cervical cancer vaccine licensure, as of 10 July 2007



Gardasil® licensed

Gardasil® licensed and introduced in public sector


Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)
Cervix Uteri: White Females, 1970-94
US = 3.22/100,000
4.53-6.40 (highest 10%)
4.16-4.52
3.82-4.15
3.51-3.81
3.32-3.50
3.11-3.31
2.90-3.10
2.70-2.89
2.38-2.69
1.41-2.37 (lowest 10%)


Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)
Cervix Uteri: Black Females, 1970-94
US = 8.63/100,000
11.39-16.76 (highest 10%)
10.66-11.38
10.10-10.65
9.37-10.09
8.96- 9.36
8.54- 8.95
8.01- 8.53
7.20- 8.00
6.14- 7.19
2.91- 6.13 (lowest 10%)
Sparse data (260 SEAs; 2.49% of deaths)

Impact on Cervical Cancer

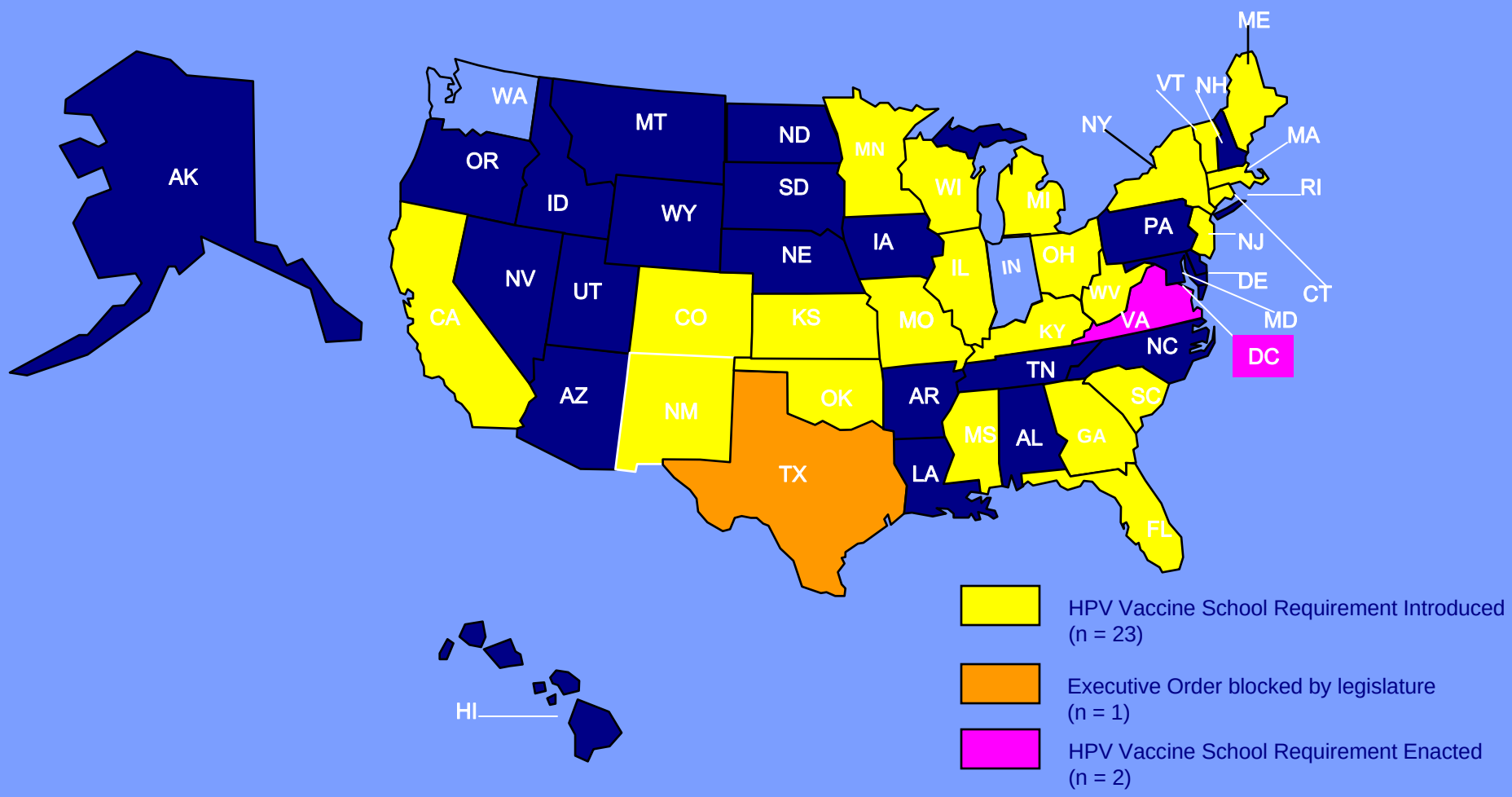
- Greatest potential impact in developing areas without widespread available screening infrastructure
- US and elsewhere with established screening programs, the vaccine may not lead to a significant decrease in mortality from cervical cancer
- Women who have not accessed screening are the same demographic groups that will be hard to vaccinate: rural, poor and immigrant women

PRO & CON for Mandatory Vaccination of 11-12 year old girls

- Mandatory vaccination will reach underserved areas
- Good safety profile to date
- Protection for at least 5 years; boosting feasible
- Delay will exclude cohorts of girls who would benefit from vaccination

- Screening is a good alternative; no need to mandate
- Rare effects cannot be ruled out
- Peak risk of sexual exposure lasts for >10 years
- “Go slow” accumulate more data and public acceptance based on voluntary vaccinations

2007 Legislative Consideration of HPV Mandates (n=26)



Source: WomeninGovernment.org/prevention As of 09/27/07

Safety Issues

- Vaccine Adverse Event Reporting System
- Local injection site reactions
- Syncope (15 min post vaccination waiting period)
- Guillain-Barre Syndrome (n=13 as of June 07)

Public Funding of Vaccines

VACCINES FOR CHILDREN (VFC)

- Free vaccines to age19 who are: Un/underinsured, Medicaid eligible, American Indian, Alaska native

MEDICAID EARLY, PERIODIC SCREENING, DIAGNOSIS & TREATMENT(EPSDT)

- Covers ACIP-recommended vaccines until enrollee is 21
- After 21 must establish adult eligibility. Each state has different criterion based on income, parental status, disability, gender

STATE CHILDREN'S HEALTH INSURANCE PROGRAM (SCHIP)

- Covers ACIP-recommended vaccines for children in families with incomes that are too high for Medicaid, but have no insurance. States set age limitations for program eligibility.

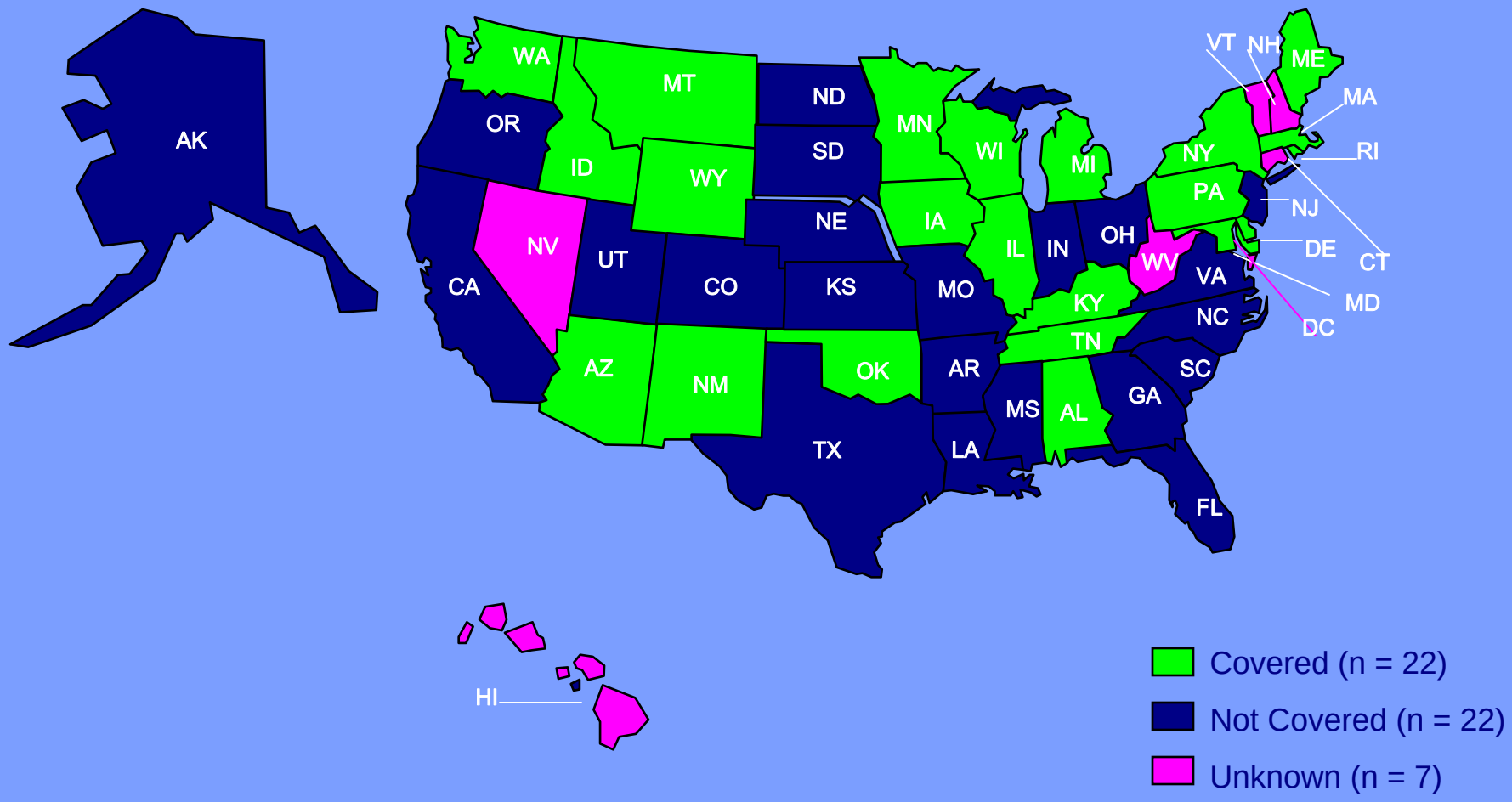
SECTION 317

- Awards grants to state, local, & territorial public health agencies for program operations and vaccine purchases. Limited funds available for vaccine purchase

PUBLIC HEALTH CLINICS

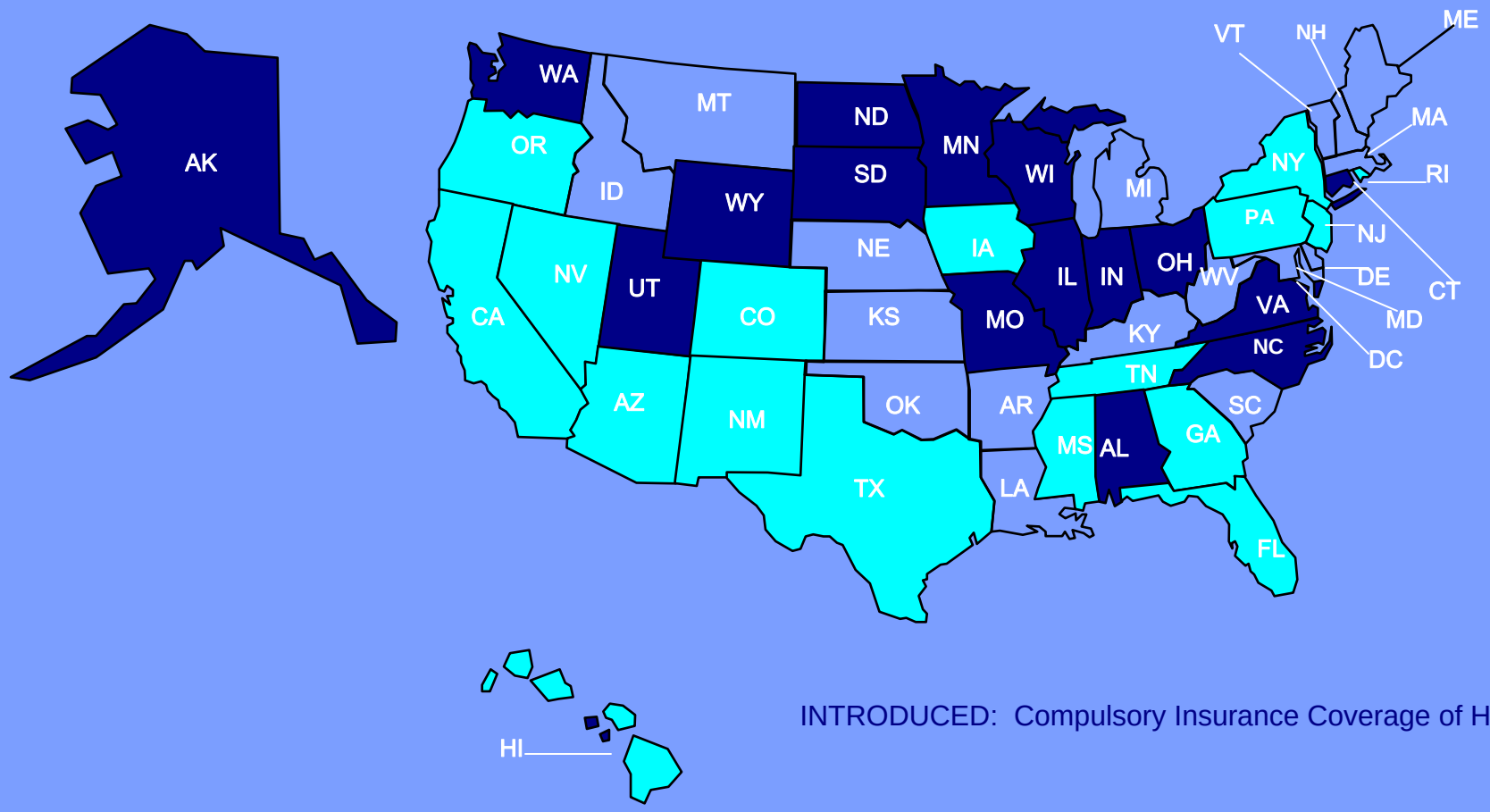
- Some states provide free or low-cost vaccines to the uninsured (children/adults)

Medicaid Coverage of HPV Vaccine for ages 21-26



Source: GWU/SPHHS Medicaid Coverage and HPV Vaccine for Adult Beneficiaries – April 2007

Proposed Legislation to Require Private Insurance Coverage of HPV Vaccine (n = 16)



INTRODUCED: Compulsory Insurance Coverage of HPV Vaccine

Source: Womeningovernment.org/prevention As of 09/27/07

Vaccine Headlines

“Breakthrough in cancer prevention”

“Will lead to promiscuity..”

“Emotions run high over vaccine”

Barriers to Public Acceptance of HPV Vaccine

- Discussion of genital warts = sex = parental discomfort
- Parental distrust of new vaccines in general
- Prevention of 70% of cervical cancer is not strong reason for vaccination
- 3 recommended age ranges causes confusion and encourages delay
- Lack of school mandate suggests to some that HPV vaccine is “less important” than a required vaccine

Barriers for Clinicians to Provide HPV Vaccine

COST IS PRIMARY CONCERN

- HPV vaccination highlights long-standing concerns regarding reimbursement levels for immunizations
- Pediatricians have vaccine “infrastructure”; not so for gynecologists
- Some providers refuse to buy the vaccine; some restrict access to patients with insurance reimbursement at “reasonable levels” (per Alexandra Stewart)

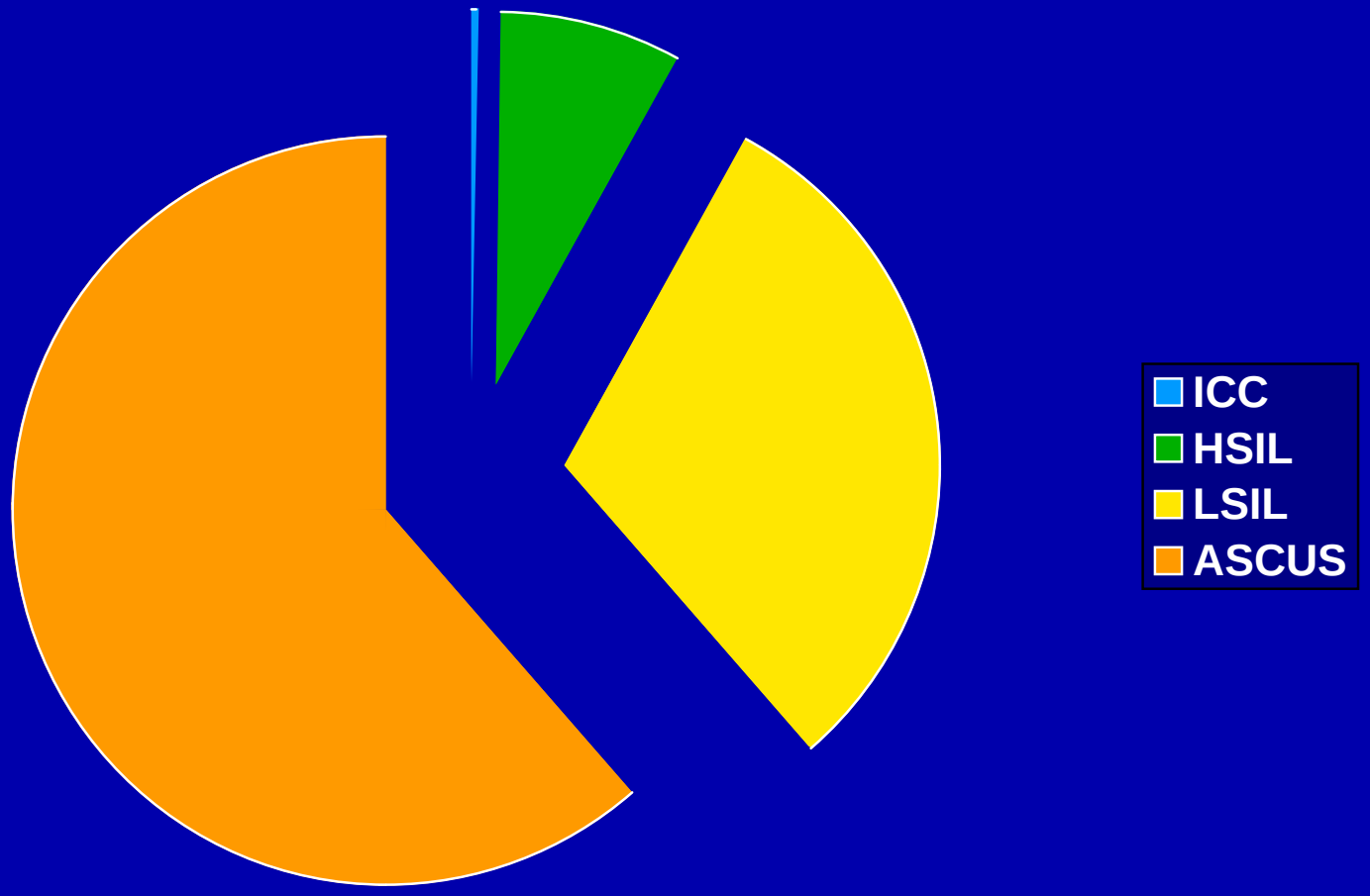
Implementation of HPV Vaccines: Public Health

- Develop/support efforts to determine to best integrate vaccines and screening
  - Avoid another layer of prevention efforts that are duplicative of coverage; save millions of $
  - Impact of vaccination on disease reduction; HPV ecology
  - Link vaccine registries, cytology and histology pathology results, HPV testing

Impact of Vaccines on Screening

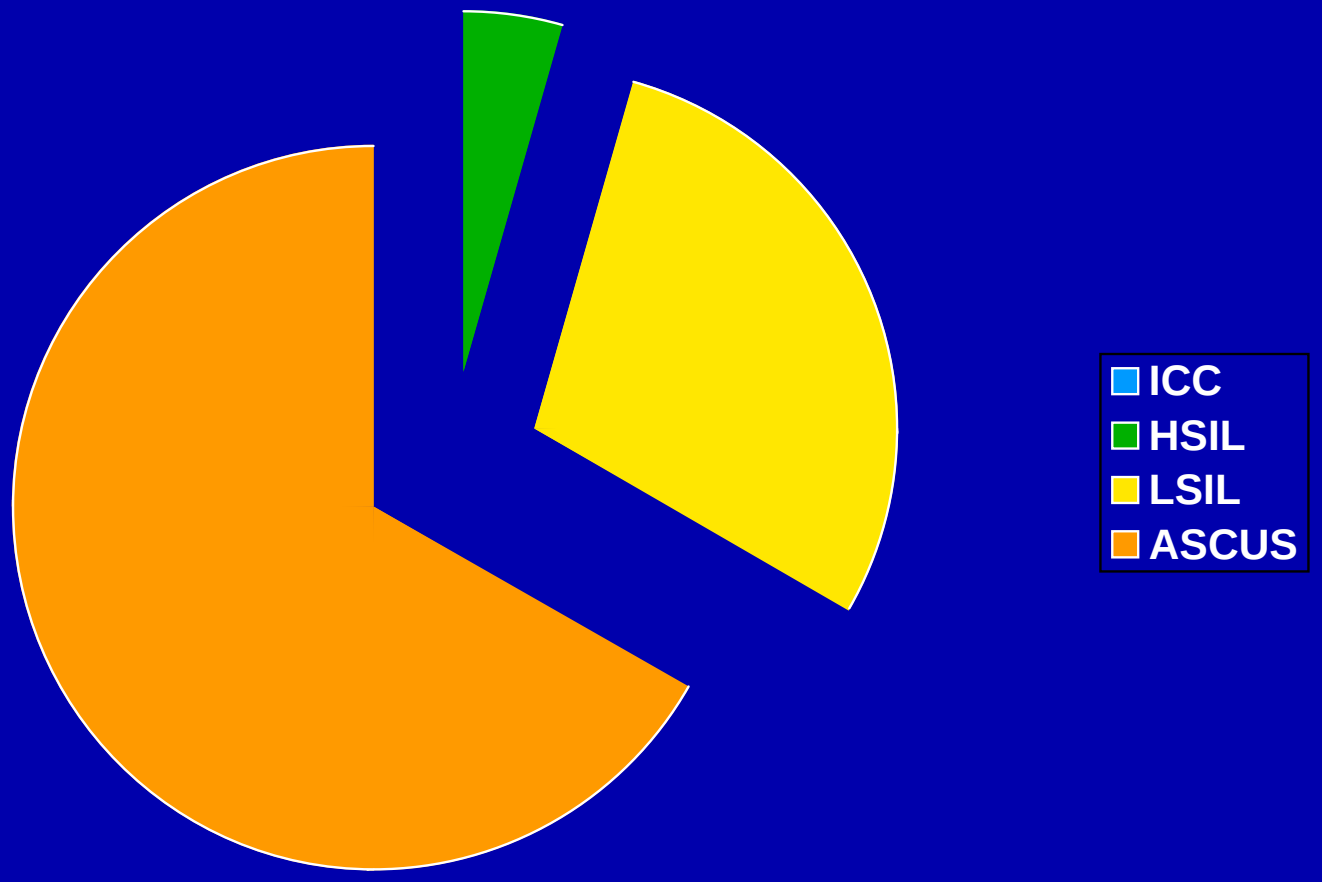
- Gradual emergence of protection
- Decline in prevalence of targeted types
  - Lower prevalence of HPV
  - Remaining HPV less carcinogenic
- Fewer cytologic abnormalities
  - Cytologic abnormalities will confer less risk
- PPV of **<u>any</u>** test based on identification of risk for CIN3 will decline dramatically

Current Distribution of Cytologic Severity



6.5% abnormalities total (CAP, Davey)

Projected Distribution Without HPV16/18



5.4% abnormalities

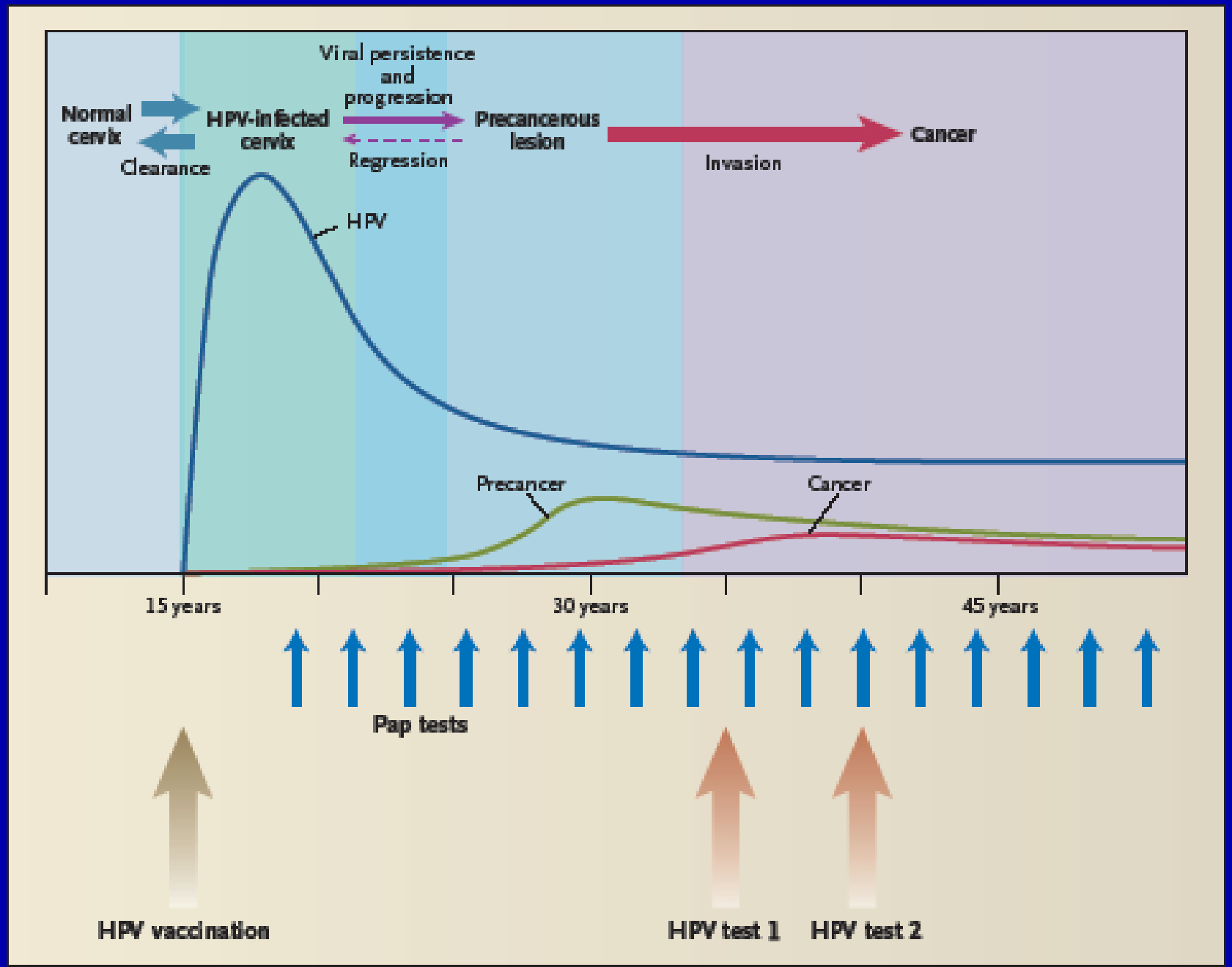
Reduction in Cytologic Abnormalities, if no HPV16 or HPV18, Guanacaste

- 17% reduction overall in LBC abnormalities
- 8% reduction in ASCUS
- 23% reduction in LSIL
- 45% reduction in HSIL
- 72% reduction in ICC

Will we need cervical screening?

- Prophylactic vaccines are not effective for women already infected
- Right now vaccine only includes 16/18 oncogenic types
- Cost will be an obstacle to widespread use
- Will still need screening for the next decade at least
- Eventually, start screening later and at extended intervals

Integration of HPV Vaccination and Screening



Screening in the Future

- Where cytology is currently performed, HPV/molecular test will be the initial screening test with cytology as the “triage” second test

- Where there is no cytology infrastructure, likely only HPV/molecular testing a few times in a woman’s life

Additional Issues

- Duration of protection
- Vaccinate males
  - Data
  - Cost effectiveness (better to first vaccinate all girls)
- Older women
- Protection against other cancers

Ongoing Efforts to Improve HPV Vaccine

- Protect against more HPV types
- Develop needle-less vaccine without need for refrigeration
- Add a therapeutic component; induce regression of prevalent infection/lesions

Cytologic Abnormalities by HPV Species

HPV Type	≥ASC (95 CI)	% ASC	% LSIL	% ≥HSIL
Single Infections	24.8 (22.4 - 27.3)	44.2%	32.0%	23.8%
α9/α11	34.3 (29.4 - 39.4)	29.0%	26.6%	44.4%
α7	25.7 (20.0 - 32.0)	51.8%	37.5%	10.7%
α5/α6	30.5 (24.3 - 37.4)	43.6%	43.6%	12.9%
α3/α15	13.1 (9.8 - 17.0)	68.8%	25.0%	6.3%
α1/α8/α10/α13	18.1 (10.0 - 28.9)	69.2%	30.8%	0.0%
HPV16	38.5 (30.8 - 46.6)	21.7%	18.3%	60.0%
HPV18	30.8 (17.0 - 47.6)	58.3%	25.0%	16.7%
HPV negative	8.0 (7.4 - 8.8)*	86.1%	10.9%	2.9%

Butsch Kovacic, Cancer Research, in press

Efficacy vs Effectiveness

Efficacy: Relative Risk Reduction

1.0% - .1% = .9/1.0 = 90%

10% - 1% = 9/10 = 90%

50% - 5% = 45/50 = 90%

Effectiveness: Absolute risk reduction per 1,000 women

10 - 1 = 9/1000 = 0.9%

100 - 10 = 90/1000 = 9%

500 - 50 = 450/1000 = 45%

Impact of Vaccination

- Decrease HPV 16/18 infections and associated cell abnormalities
- Other HPV types still cause cytologic abnormalities, many transient
- The PPV of an abnormal cytology for CIN3 will go down
- Type specific HPV testing for persistence better risk stratifier because can distinguish *persistence* from sequential new infections