

# Human Papillomavirus: Should Males be Immunized Too?



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Pharmacotherapy Conference  
January 15, 2010

## Objectives:

1. Describe the pathophysiology of human papillomavirus (HPV) infection
2. Analyze available literature regarding efficacy of HPV vaccines in females and males
3. Review the types of non-cervical cancers caused by HPV viruses
4. Understand the controversies regarding immunization of males

## Human Papillomavirus (HPV): Should Males be Immunized Too?

- I. Human Papillomavirus (HPV)
  - A. Virus characteristics<sup>1-4</sup>
    1. Double stranded, enveloped DNA virus
    2. Over 100 characterized serotypes
    3. Grouped into three categories (Table 1)
      - a. Nongenital cutaneous
      - b. Anogenital/mucosal
        - i. anogenital warts
        - ii. anogenital cancers
      - c. *Epidermodysplasia verruciformes*
    4. At least 40 serotypes infect human mucosa
    5. At least 14 serotypes are considered 'high risk' for malignancy

Table 1: Common HPV serotypes<sup>2</sup>

| Category                        | Examples                                | Common HPV Serotypes                           |
|---------------------------------|---|--|
| Nongenital Cutaneous            | common warts, flat warts, plantar warts | 1, 2, 3, 4, 7, 10, 63                          |
| Anogenital/Mucosal              | anogenital cancer: high risk            | 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 |
|                                 | anogenital cancer: probable high risk   | 26, 53, 66, 68, 73, 72                         |
|                                 | oropharyngeal cancer                    | 16, 18, 31, 33, 35                             |
| Epidermodysplasia verruciformes |   | 5, 8, 9, 10, 12, 14, 17, 20                    |

- B. Pathophysiology of infection in human host (Figure 1)<sup>2-4</sup>
  1. HPV enters epithelial tissues through microabrasions in host mucosa
  2. HPV genome amplification occurs in basal cell nuclei (50 to 100 copies per cell) followed by episomal maintenance phase
  3. Infected cell moves up from basal layer to become more differentiated, which triggers increased viral genome expression
  4. As cell moves to outer layers of squamous epithelium, viral assembly occurs. Production and assembly of virus particles can occur only in highly differentiated keratinocytes
  5. As cells are sloughed off, virions are released and may infect adjacent tissues or other hosts

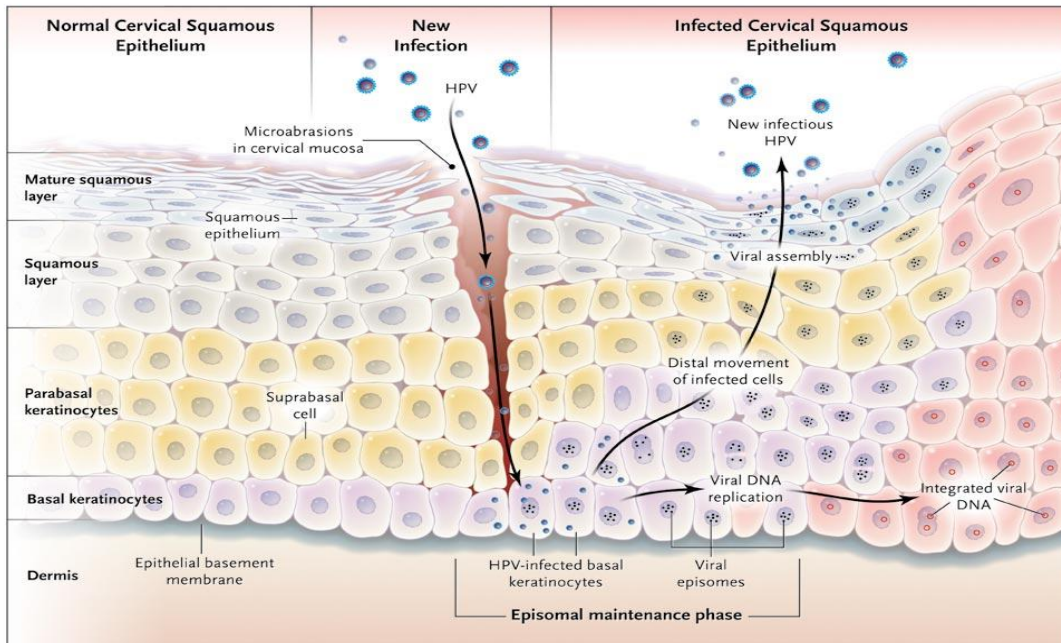


Figure 1: Human Papillomavirus life cycle in mucosal epithelium<sup>4</sup>

#### C. Host immune response

1. Viral reproduction in bloodless epithelial cells allows HPV to efficiently evade the host immune system<sup>2</sup>
2. Immune system surveillance may miss HPV infection for years<sup>4</sup>
3. However, 90% of the time the virus is eventually cleared<sup>3</sup>

#### D. Nonmalignant infection vs. malignant transformation

1. Requires persistent infection (ten years or more)<sup>4-7</sup>
2. Low risk HPV isotypes: exist as circular episomes separate from host nuclear DNA<sup>1</sup>
3. High risk HPV isotypes: become integrated into host DNA
  - a. Must contain DNA sequences for viral proteins E6 and E7<sup>2</sup>
    - i. E6: binds and inactivates P53
    - ii. E7: binds and inactivates Rb
  - b. Leads to defects in cell cycle regulation, DNA repair mechanisms and apoptosis<sup>1</sup>

#### E. Progression to cervical cancer

1. Cervical intraepithelial neoplasia (CIN) is cell dysplasia caused by HPV infection<sup>4,6,7</sup>
2. CIN is categorized by level of severity; CIN 2 and 3 are widely accepted surrogate markers for cancer (Figure 2)<sup>6,7</sup>

**SCHEMATIC OF MICRO SIMULATION NATURAL HISTORY MODEL OF CERVICAL CARCINOGENESIS**

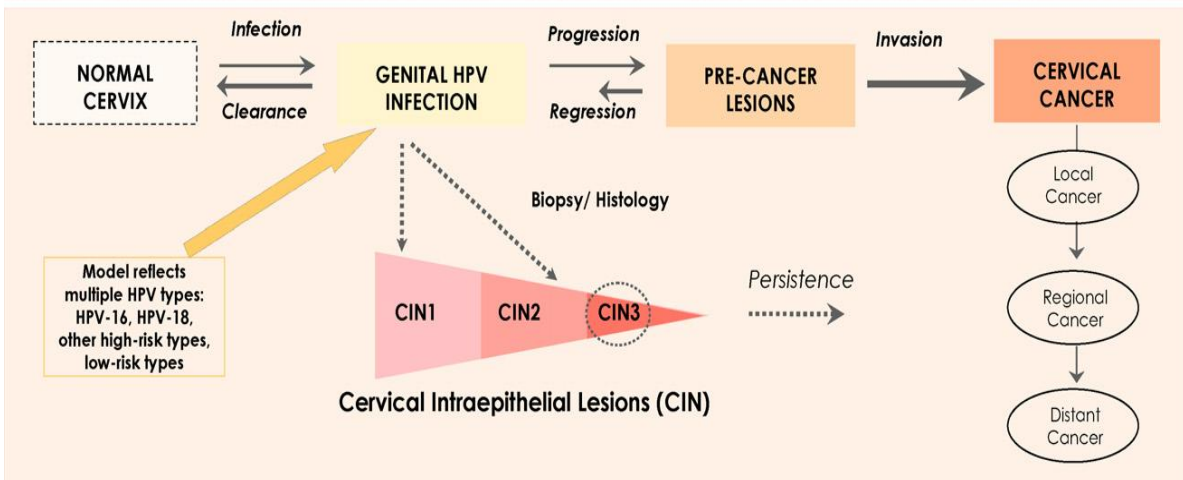


Figure 2: Schematic model of cervical cancer natural history<sup>24</sup>

3. Because using cancer as an outcome in efficacy studies would be impractical and unethical, CIN 2 and 3 are used as surrogate markers for cervical cancer (Table 2)<sup>6,7</sup>

Table 2: Cervical Intraepithelial Neoplasia (CIN) grades<sup>4</sup>

| <b>Cervical Intraepithelial Neoplasia (CIN) Grade</b> | <b>Degree of Dysplasia</b>  | <b>Chance of progression to cancer</b> |
|---|---|--|
| <b>CIN grade 1</b>                                    | <b>Mild dysplasia</b> , abnormal cells occupy lowest third of cervical epithelium         | <b>10%</b>                             |
| <b>CIN grade 2</b>                                    | <b>Moderate dysplasia</b> , abnormal cells occupy lower two thirds of cervical epithelium | <b>57%</b>                             |
| <b>CIN grade 3</b>                                    | <b>Severe dysplasia</b> , abnormal cells occupy full thickness of cervical epithelium     | <b>70%</b>                             |

F. How common is HPV?

1. Most common sexually transmitted disease in the United States<sup>4,8,10,15</sup>
2. Estimated 6.2 million people infected annually<sup>10</sup>
3. 80% of women infected during their lifetime<sup>10</sup>
4. More than 50% of women are infected within first three years of sexual debut<sup>15</sup>
5. One meta-analysis found that condoms are 0 to 80% effective in preventing HPV transmission<sup>14</sup>
6. In women HPV has a bimodal distribution<sup>15</sup>
  - a. Peaks in early 20s (20 to 24)
  - b. Progressively declines
  - c. Increases sharply in late 40s and early 50s (45 to 55)
  - d. May result from re-infection or reactivation of HPV

- II. HPV vaccine and cervical cancer
  - A. Epidemiology of cervical cancer
    - 1. Global epidemiology<sup>3,5</sup>
      - a. 2<sup>nd</sup> most frequent cancer among women
      - b. 490,000 women diagnosed annually with invasive cervical cancer
      - c. 270,000 deaths annually

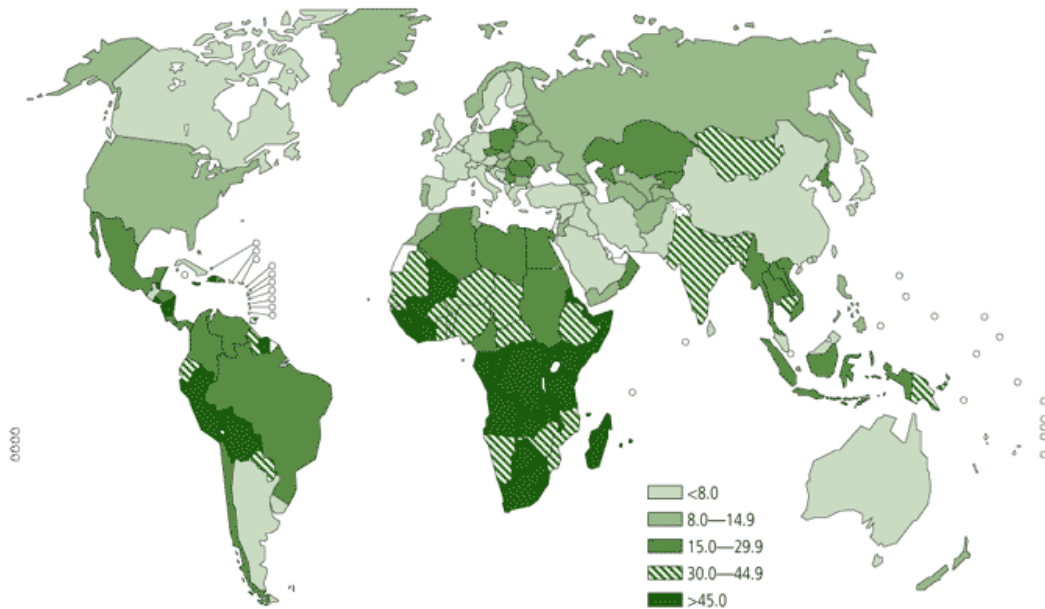


Figure 3: Worldwide incidences of cervical cancer per 100,000 females (2005)<sup>10</sup>

- 2. United States (U.S.) epidemiology<sup>3-5</sup>
  - a. Reduced incidence due to well organized cytoscopic screening programs
  - b. 11,000 women diagnosed annually with invasive cervical cancer
  - c. 3,900 deaths annually
  - d. Direct medical costs: \$4.0 billion annually
  - e. Indirect medical costs: \$1.3 billion annually
- B. HPV Vaccine Characteristics<sup>2</sup>
  - 1. Composed of “virus-like particles” (VLPs) made from protein L1, the major HPV capsid protein
  - 2. Non-infectious (contains no viral DNA)
  - 3. Highly immunogenic
    - a. IgA and IgG
    - b. IL2, gamma interferon
    - c. B- and T-cell proliferative responses

C. Vaccine administration<sup>3</sup>

1. 0.5 mL administered intramuscularly (IM)
2. Contraindicated in anyone with a history of an immediate hypersensitivity to yeast
3. Can be administered at same visit as other vaccines
4. Cost (full series): Gardasil \$399, Cervarix \$386 (wholesale list price)
5. Adverse effects:
  - a. Clinical trials: pain, erythema, swelling at injection site, headache, fatigue, myalgia
  - b. CDC Vaccine Adverse Events Reporting System (VAERS)
    - i. 11,916 reports of adverse events
    - ii. 94% nonserious: dizziness, syncope, nausea, rash
    - iii. 6% serious: Guillain-Barre, venous thromboembolism, death. Do not appear to be causally linked to vaccine.

D. Quadrivalent Vaccine (Gardasil)

1. Contains HPV serotypes 6, 11, 16, 18
2. Manufactured by Merck
3. Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE II) Trial (Table 3)<sup>6</sup>
4. FDA indications: vaccination in females 9 to 26 years of age for prevention of genital warts caused by HPV types 6 and 11 and cervical cancer caused by HPV types 16 and 18
5. New FDA indication 10/18/09: vaccination in males 9 through 26 years of age for the prevention of genital warts caused by HPV types 6 and 11<sup>34</sup>

E. Bivalent Vaccine (Cervarix)

1. Contains HPV serotypes 16 and 18
2. Novel ASO4 adjuvant (consisting of aluminum hydroxide and 3-O-desacyl-4'-monophosphoryl lipid A)
3. Manufactured by Glaxo Smith Klein Biologicals
4. Papilloma Trial against Cancer In young Adults (PATRICIA) Trial (Table 4)<sup>7</sup>
5. New FDA indication 10/16/09: vaccination in females 10 to 25 years of age for prevention of cervical cancer and precancerous lesions caused by HPV types 16 and 18<sup>34</sup>

Table 3: FUTURE II trial

| The FUTURE II Study Group. <b>Quadrivalent Vaccine against Human Papillomavirus to Prevent High-Grade Cervical Lesions.</b> NEJM, 2007. 356(19): 1915-27. |   |
|---|---|
| <b>Study Methods</b>  | <ul style="list-style-type: none"> <li>• Multi-center, randomized, double-blind, placebo-controlled trial</li> <li>• 12,167 women between the ages of 15 and 26 years old</li> <li>• Inclusion criteria: not pregnant at time of enrollment, no previous abnormal Papanicolaou smears, &lt;4 lifetime sexual partners</li> <li>• Subjects received three doses of vaccine or placebo administered at day 1, month 2 and month 6 and were asked to use effective contraception during vaccination period</li> <li>• Follow-up visits at months 7, 13, 24, 36, 48 for Papanicolaou smear (and colposcopy if necessary) based on a standardized treatment algorithm</li> </ul> <p><u>Two study cohorts:</u></p> <ul style="list-style-type: none"> <li>• Per protocol group: women receiving all doses of vaccine who had no virologic evidence of infection with HPV 16/18 through 1 month after third dose of vaccine (represent girls before sexual debut)</li> <li>• Intention-to-treat group: all women including those who had virologic evidence of HPV 16 or 18 at day 1 given at least 1 dose of vaccine (represent the general population of young women)</li> </ul> |
| <b>Outcomes</b>   | <ul style="list-style-type: none"> <li>• Primary composite endpoint: CIN grade 2 or 3, adenocarcinoma in situ, or cervical cancer related to HPV 16/18</li> </ul>   |
| <b>Results</b>  | <ul style="list-style-type: none"> <li>• Participants were followed for an average of three years after receiving first dose</li> <li>• Seroconversion at 24 months: HPV-6 96%, HPV-11 99%, HPV-16 99%, HPV-18 68%</li> <li>• Vaccine efficacy for preventing primary composite endpoint:<br/>per-protocol population: 98% (CI, 86 to 100%)<br/>intention-to-treat population: 44% (CI, 26 to 58%)</li> </ul>   |
| <b>Conclusions</b>  | <ul style="list-style-type: none"> <li>• Quadrivalent HPV vaccine significantly lowers incidence of high-grade CIN related to HPV 16/18 in women without previous HPV 16/18 infection</li> <li>• Vaccine does not appear to alter the course of HPV 16/18 infection or lesions already present</li> </ul>   |
| <b>Comments</b>   | <ul style="list-style-type: none"> <li>• CIN 2/3 is not an exact surrogate marker for cervical cancer<sup>3</sup></li> <li>• Infection with more than one oncogenic strain of HPV increases chance of progression to cancer</li> <li>• ITT group may have had increased selection toward CIN 2/3 as lesions tend to persist in that cohort</li> </ul>   |

Table 4: PATRICIA trial

|  |   |
|--|---|
| <p>Paavonen J, Naud P, Salmeron J, et al. <b>Efficacy of human papillomavirus (HPV)-16/18 ASO4 –adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomized study in young women.</b> Lancet, 2009. 25;374(9686):301-14</p> |   |
| <p><b>Study Methods</b></p>  | <ul style="list-style-type: none"> <li>• Multi-center, randomized, double-blind, placebo-controlled trial</li> <li>• 18,644 women aged 15 to 25 years</li> <li>• Inclusion criteria: not pregnant at time of enrollment, &lt; 6 lifetime sexual partners, no previous colposcopy, no autoimmune disease or immunodeficiency</li> <li>• Subjects received HPV 16/18 vaccine or hepatitis A control vaccine at 0, 1, and 6 months and were asked to use effective birth control during vaccination period</li> <li>• Cervical biopsy samples taken every 6 months for HPV DNA typing of 14 oncogenic HPV strains</li> <li>• Follow-up visits every 12 months for Papanicolaou smear (and colposcopy if necessary) based on a standardized treatment algorithm</li> <li>• Blood samples gathered at months 0, 7, and 24 for HPV 16/18 antibodies</li> </ul> <p><u>Two study cohorts:</u></p> <ul style="list-style-type: none"> <li>• Total vaccinated- naive cohort (TVC-N): women receiving all doses of vaccine who had no virologic evidence of infection with HPV 16/18 through 1 month after third dose of vaccine (represent girls before sexual debut)</li> <li>• Total vaccinated cohort (TVC): all women including those who had evidence of HPV 16 or 18 infection (represent the general population of young women)</li> </ul> |
| <p><b>Outcomes Primary</b></p>   | <ul style="list-style-type: none"> <li>• CIN grade 2 or 3, adenocarcinoma in situ, or invasive cancer associated with HPV 16/18</li> </ul>  |
| <p><b>Secondary</b></p>  | <ul style="list-style-type: none"> <li>• CIN associated with other oncogenic HPV types</li> </ul>   |
| <p><b>Results</b></p>  | <ul style="list-style-type: none"> <li>• Mean follow-up time was 34.9 months after third dose</li> <li>• Seroconversion at 36 months: HPV-16 100%, HPV-18 100%</li> <li>• Vaccine efficacy in preventing CIN 2+ lesions caused by HPV 16/18:<br/>TVC-naïve cohort: 98.1% (CI, 88.4 to 100%)<br/>TVC cohort: 30%: (CI, 21.5 to 38%)</li> <li>• Significant cross-protection against HPV 31, 33, 45, 52 and 58</li> <li>• Vaccine efficacy in preventing CIN 2+ lesions caused by <b>any</b> HPV type<br/>TVC-N: 68.2% (CI, 54 to 80.9%)</li> </ul>   |
| <p><b>Conclusions</b></p>  | <ul style="list-style-type: none"> <li>• Bivalent HPV vaccine significantly lowers incidence of high-grade CIN related to HPV 16/18 in women without previous HPV 16/18 infection</li> <li>• Vaccine does not appear to alter the course of HPV 16/18 infection or lesions already present</li> <li>• Vaccine provides cross protection against HPV 31, 33, 45, 52, 58</li> </ul>   |

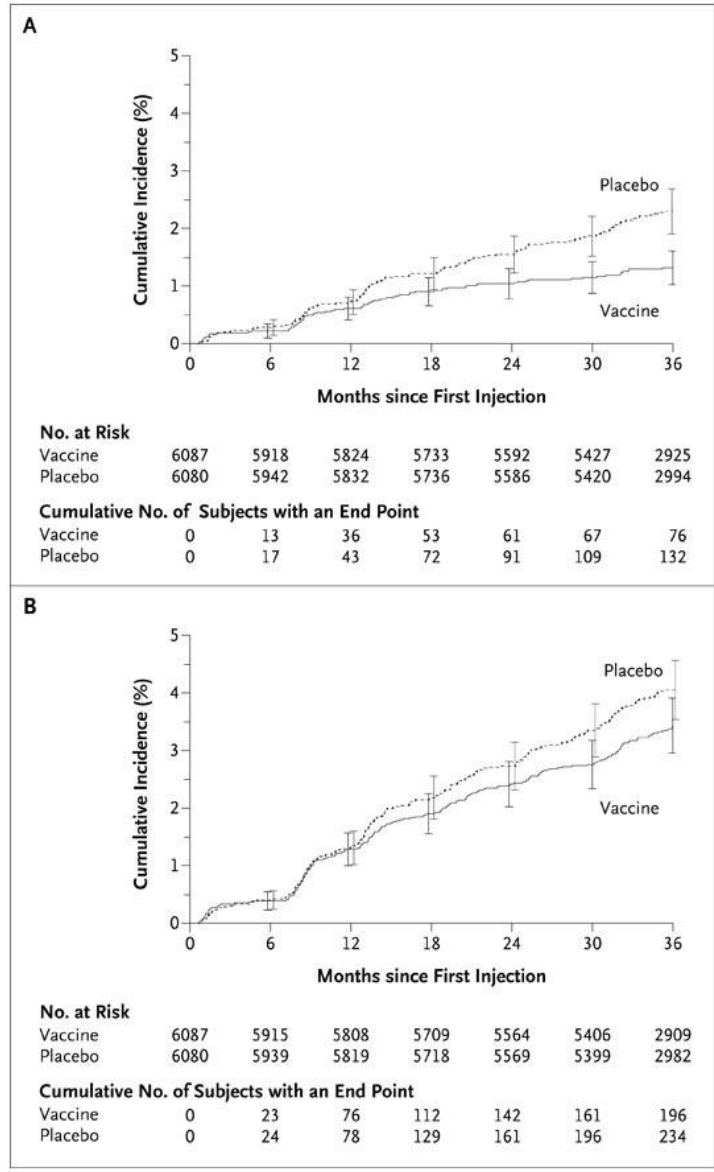


Figure 4: FUTURE II Study. Panel A: cumulative incidence of CIN 2/3 associated with HPV 16/18. Panel B: cumulative incidence of CIN 2/3 associated with any HPV type<sup>6</sup>

- III. Current Immunization Guidelines
  - A. CDC Advisory Council on Immunization Practices (ACIP) recommendations<sup>10</sup>
    1. Routine vaccination of girls 11 to 12 years of age
    2. Catch-up vaccination of girls 13 to 26 years of age
    3. Can be administered to girls as young as 9 years

- B. American Academy of Obstetricians and Gynecologists<sup>11</sup>
  - 1. Routine vaccination of females age 9 to 26 years
- C. American Academy of Pediatrics<sup>12</sup>
  - 1. Routine vaccination of females 11 to 12 years
  - 2. Catch-up vaccination of females age 13 to 26 years
  - 3. Can be administered to girls as young as 9 years
- D. American Cancer Society<sup>13</sup>
  - 1. Routine vaccination of females age 11 to 12 years
  - 2. Catch up programs for females age 13 to 18
  - 3. Insufficient data to recommend vaccination of young women 19 to 26 years, this decision should be made based on a discussion between patient and physician
- E. World Health Organization<sup>5</sup>
  - 1. HPV vaccination should be included in national vaccination programs provided that:
    - a. Prevention of cervical cancer and other HPV related diseases constitutes a public health priority
    - b. Vaccine introduction is programmatically feasible
    - c. Sustainable financing can be secured
    - d. Cost effectiveness of vaccination strategies is considered

IV. Reasons to vaccinate males against HPV 16/18

- A. Head and neck cancers caused by HPV 16/18
  - 1. Historically, the majority of oral cancers were associated with chronic alcohol and tobacco use
  - 2. Many studies over the past decade have found significant prevalence of HPV in certain oral cancers<sup>14-18</sup>
  - 3. Physiologic site of HPV infection<sup>14</sup>
    - a. Occur most frequently in epithelium which lines the oral cavity and pharynx
    - b. Many morphological similarities between oropharyngeal and genital epithelia
    - c. Squamous-columnar junction at tonsillar crypts and base of the tongue
      - i. greatest susceptibility to HPV
      - ii. easy exposure to basal cells
  - 4. HPV associated oral cancers have different risk factors than other oral cancers (Table 5)<sup>35</sup>

Table 5: Distinct differences between HPV negative and positive HNSCC<sup>35</sup>

| Type of HNSCC                  | HPV negative   | HPV positive  |
|--------------------------------|--|---|
| <b>Molecular factors</b>       | P53 mutational loss common<br>Rb up-regulated<br>P16 underexpression<br>D cyclin overexpression<br>No HPV DNA/RNA  | P53 wild-type present<br>Rb down-regulated<br>P16 overexpression<br>D cyclin underexpressed<br>HPV DNA (type 16 in >85% of cases)<br>HPV E6 and E7 RNA                    |
| <b>Epidemiological factors</b> | Heavy smoking<br><br>Heavy alcohol<br>Low marijuana exposure<br>Poor dentition<br>Low oral sex exposure<br>Older age (>50 years)<br>Lower socioeconomic status | Never smokers<br><br>Mild/mod. Alcohol<br>High marijuana exposure<br>Intact dentition<br>High oral sex exposure<br>Younger age (<45 years)<br>Higher socioeconomic status |
| <b>Clinical factors</b>        | Decreasing incidence<br>All head and neck sites<br><br>Worse survival<br>Radiation response unpredictable  | Increasing incidence<br>Predominantly oropharynx (tonsil and tongue base)<br><br>Better survival<br>More radiosensitive   |

5. Epidemiology (U.S.)<sup>19</sup>
  - a. Based on 1998 to 2003 data from 39 population-based cancer registries that participate in the National Program of Cancer Registries (NCPR) and/or the Surveillance, Epidemiology and End-Results (SEER) program
  - b. 7,360 cases of oropharyngeal cancer annually
  - c. 63% of cases associated with HPV infection (95% CI, 47 to 72)
  - d. 95% of HPV associated cancers attributable to HPV 16/18
  - e. 4,416 cases HPV 16/18 associated cases per year (95% CI, 3,673 to 5,549)
  - f. While the majority of oral cancers have decreased since the 1970s, HPV site-related cancers have increased significantly<sup>20</sup>
6. Screening programs for HPV associated oral cancer<sup>14</sup>
  - a. HPV virus is rarely found routinely in oral mucosa, most likely due to saliva clearance
  - b. HPV DNA screening not feasible
  - c. p16 recently proposed as a surrogate marker of HPV DNA infection of oropharyngeal cancers
7. Prognosis<sup>18</sup>
  - a. HPV associated tumor is a positive prognostic factor in patients with oropharyngeal cancer
  - b. 60 to 80% reduction in the risk of death

- c. May be due to absence of field cancerization or enhanced radiation sensitivity

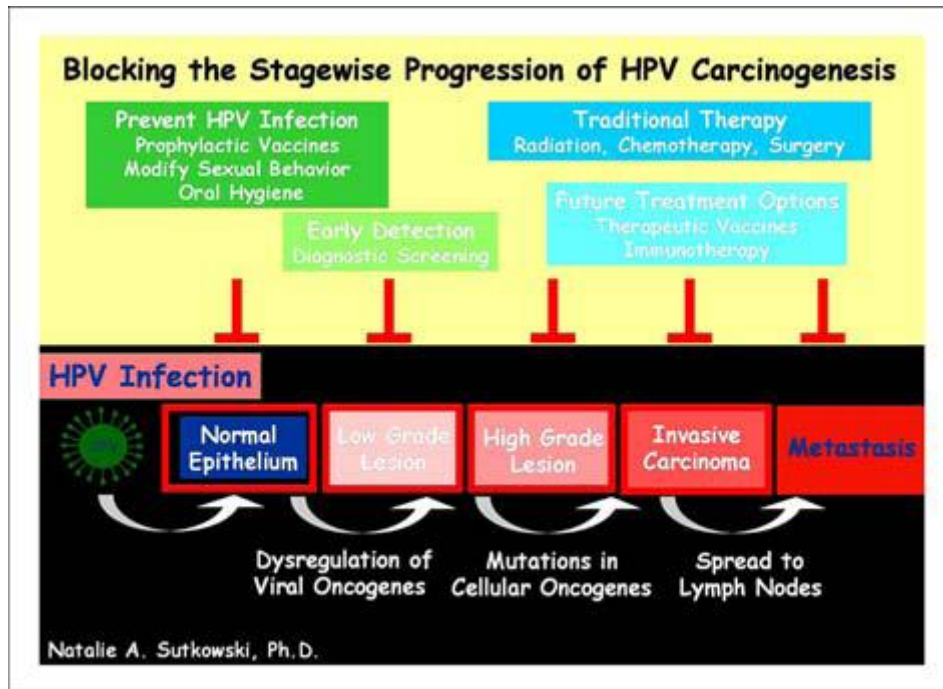


Figure 5: Multidimensional approach to HPV-positive HNSCC intervention<sup>22</sup>

## B. Anogenital cancers caused by HPV 16/18

### 1. Etiology and pathophysiology<sup>22</sup>

- a. Historically, anal cancer was believed to be the result of chronic irritation from benign conditions including hemorrhoids, fissures, and irritable bowel disease (IBD)
- b. Several studies over the last decade have found this is not the case and have identified other risk factors:
  - i. persistent HPV infection
  - ii. infection with multiple HPV genotypes
  - iii. cervical dysplasia or cancer
  - iv. HIV seropositivity
  - v. low CD4 count
  - vi. immunosuppression
  - vii. smoking
- c. Squamocolumnar junction of the anal canal is anatomically similar to squamocolumnar junction of the cervix and is a likely HPV entry point

### 2. A study by Frisch et al examined histological specimens from 386 patients with anal cancer:<sup>21</sup>

- a. 58% of anal cancers in heterosexual men were positive for high-risk HPV DNA
- b. 90% of anal cancers in women were positive for high risk HPV DNA

- c. Predominant HPV types:
    - i. HPV 16: 87%
    - ii. HPV 18: 7%
    - iii. HPV 33: 6%
    - iv. HPV 31: 1%
    - v. Other HPV types: 3%
  - d. Presence of HPV DNA strongly correlated with several distinguishing characteristics: basaloid features, poor or absent keratinization and adjacent anal intraepithelial neoplasia
  - e. Tumors in only 4% of women and 6% of men contained low-risk HPV
3. Epidemiology (based on 1998 to 2003 NCP/SEER data)<sup>17</sup>
- a. 4,660 cases of anal cancer per year
  - b. 93% of cases associated with HPV infection (95% CI, 86 to 97)
  - c. 2,211 HPV 16/18 associate cancers per year (95% CI, 2,078 to 2,318)
  - d. The number of anal cancers in the U.S. has increased significantly since the 1970s

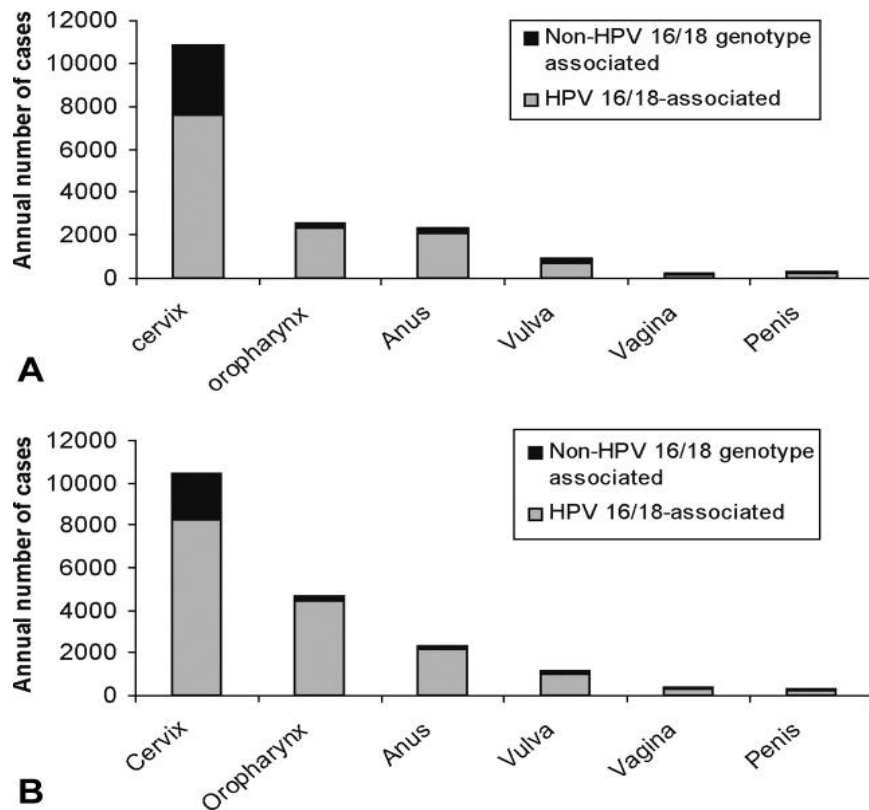


Figure 6: Estimated annual number of HPV-associated cancers in the US, 1998-2003 based on (A) worldwide estimates and (B) NCP/SEER data<sup>15</sup>

4. Screening programs for HPV-induced anal intraepithelial neoplasia (AIN)<sup>15</sup>
    - a. Anal Pap test is commercially available
    - b. Same procedure as cervical Pap test
    - c. CDC currently does not recommend anal Pap tests as there is not enough evidence to indicate that removing abnormal anal cells prevents anal cancer from developing in the future
- C. Certain high risk populations have increased susceptibility to HPV 16/18 infection and disease
1. Immunosuppressed individuals
    - a. Chronic immunosuppression, regardless of etiology, results in increased risk of squamous cell carcinomas from many anatomical sites<sup>22</sup>
    - b. Most likely due to persistent HPV infection
    - c. Daling et al: chronic corticosteroid use associated with higher risk for anal cancer (OR 3.2; 95% CI, 1.4 to 7.2)<sup>22</sup>
    - d. Renal transplant patients: 100 fold higher risk for anal cancer<sup>22</sup>
    - e. Frisch et al: higher risk for anal cancer in individuals with Human Immunodeficiency Virus (HIV)<sup>21</sup>
      - i. men RR 6.8 (95% CI, 2.7 to 14.0)
      - ii. women RR 37.9 (95% CI, 33.0 to 43.4)
    - f. Development of precancerous lesions has been shown to be inversely related to CD4 count<sup>22</sup>
  2. Men who have sex with men (MSM)
    - a. 58% of anal tumors in heterosexual men are associated with high risk HPV vs. 100% in homosexual men<sup>21</sup>
    - b. The risk for anal cancer is significantly higher in men who are not exclusively heterosexual (OR, 17.3; 95% CI, 8.2 to 36.1)<sup>22</sup>
    - c. Unlike in immunocompetent patients, immunity to specific HPV types does not persist in HIV patients, thus individuals are susceptible to persistent reinfection<sup>21</sup>
    - d. When anal HPV lesions were removed in HIV positive patients, the recurrence rate was 79% at 12 months and almost 100% at 50 months<sup>23</sup>
- D. Decreased incidence of cervical cancer in females through herd immunity<sup>24-27</sup>
1. Male HPV infection contributes significantly to infection and subsequent cervical disease in women
  2. All projection models indicate that including males in a national HPV vaccination program would result in a greater decrease in cervical cancer than vaccinating females alone
  3. Vaccinating males against HPV-associated non-cervical cancers would provide the added benefit of indirectly decreasing cervical cancer rates

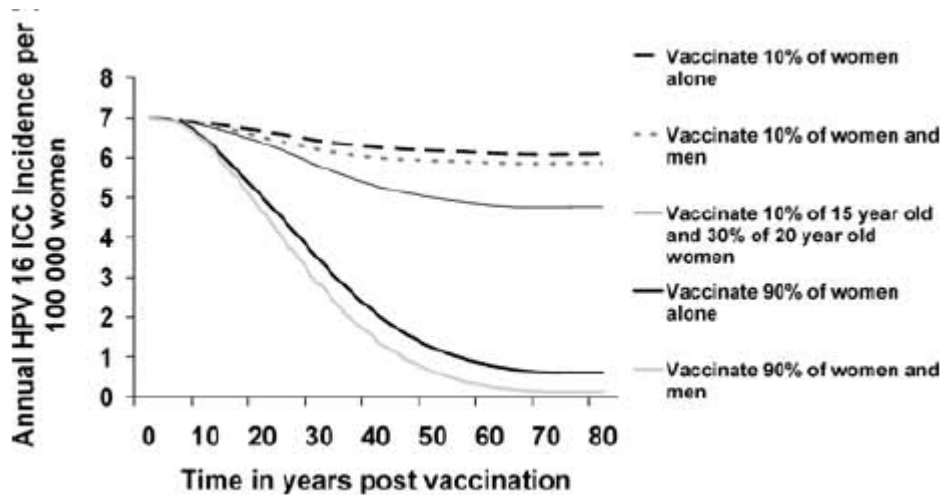


Figure 7: Effect of routinely vaccinating men and women compared to vaccinating women alone at low (10%) and high (90%) coverage<sup>25</sup>

V. Trials of Efficacy in Males  
 A. Palefsky et al

|   |   |
|---|---|
| <p>AR Giuliano and J Palefsky (for the Male Quadrivalent HPV Vaccine Efficacy Trial Study Group). The efficacy of quadrivalent HPV (Types 6/11/16/18) vaccine against HPV-related genital disease and infection in young men. 25th International Papillomavirus Congress. Malmo, Sweden. May 8<sup>th</sup> to 14<sup>th</sup>, 2009. Abstract O-01.07.</p> |   |
| <p><b>Study Methods</b></p>   | <ul style="list-style-type: none"> <li>• Multi-center, randomized, double-blind, placebo-controlled trial</li> <li>• 4,065 young men aged 16 to 26 years           <ul style="list-style-type: none"> <li>◦ Heterosexual men (HM) aged 16 to 23 years (n=3,463)</li> <li>◦ Men having sex with men (MSM) aged 16 to 26 years (n=602)</li> </ul> </li> <li>• Inclusion criteria: no evidence of genital warts or lesions, &lt; 5 lifetime sexual partners, HIV negative</li> <li>• Subjects received three doses of vaccine or placebo at day 1, months 2 and 6</li> <li>• Genital exams and swabs at day 1, months 7, 12 and every 6 months thereafter. All new lesions were biopsied for pathological diagnosis and PCR testing</li> <li>• Blood samples gathered at day 1, months 7, 24 and 36 for HPV 16/18 antibodies</li> </ul> <p>Two study cohorts:</p> <ul style="list-style-type: none"> <li>• Per protocol population: men receiving all doses of vaccine who had no virologic evidence of infection with HPV 16/18 through 1 month after third dose of vaccine</li> <li>• Intention to treat population: all men who received at least one dose of vaccine and returned for follow up</li> </ul> |

|  |   |
|--|---|
| <p><b>Outcomes:</b><br/><b>Primary</b></p> | <ul style="list-style-type: none"> <li>• Immunogenicity, seroconversion</li> <li>• HPV 6/11/16/18 related lesions: genital warts, penile/anal intraepithelial neoplasia (PIN/AIN), penile/anal cancer</li> </ul>  |
| <p><b>Secondary</b></p>                    | <ul style="list-style-type: none"> <li>• Incidence of HPV 6/11/16/18 DNA detection</li> <li>• Incidence of persistent HPV 6/11/16/18 infection</li> </ul>   |
| <p><b>Results</b></p>                      | <ul style="list-style-type: none"> <li>• Planned follow up: 36 months after last dose of vaccine; mean 24 months in current follow up</li> <li>• Rate of seroconversion: HPV-6 98%, HPV-11 99%, HPV-16 98%, HPV-18 97%</li> <li>• Efficacy against any HPV 6/11/16/18 related external genital lesions was 90.4% (CI, 69.2 to 98.1).</li> <li>• Vaccine efficacy against HPV 6/11/16/18 persistent infection was 85.6% (CI, 73.4 to 92.9)</li> <li>• Vaccine efficacy against penile intraepithelial neoplasia was 100%</li> </ul> <p><u>MSM Cohort:</u></p> <ul style="list-style-type: none"> <li>• Efficacy against any HPV 6/11/16/18 related external genital lesions was 79.0% (CI, &lt;0 to 99.6).</li> <li>• Vaccine efficacy against HPV 6/11/16/18 persistent infection was 94.4% (CI, 64.4 to 99.9)</li> </ul> |
| <p><b>Conclusions</b></p>                  | <ul style="list-style-type: none"> <li>• The quadrivalent HPV vaccine is efficacious in reducing HPV 6/11/16/18-related external genital lesions and infection in men aged 16 to 26 years naïve to the relevant HPV type at baseline</li> </ul>   |

- VI. Reasons for caution: Unanswered questions about the HPV vaccine
- A. How long does immunity conferred by the HPV vaccine last?
1. Follow up studies of efficacy currently extend to 5 years (Gardasil) and 6.4 years (Cervarix)<sup>30,31</sup>
  2. Gardasil extended follow up study<sup>30</sup>
    - a. 241 subjects
    - b. Average follow up time 5.06 years
    - c. Persistent immune response (as measured by geometric mean titers) equal to or greater than that observed during natural infection was maintained through 5 years
    - d. Vaccine provided 96% (CI, 12 to 100%) efficacy against combined incidence of HPV 6/11/16/18-related persistent infection or disease
  3. Cervarix extended follow up study<sup>31</sup>
    - a. 776 subjects
    - b. Average follow up time 6.4 years
    - c. Vaccine provided efficacy of 100% (CI, 51 to 100%) against HPV-related CIN 2+ lesions

4. Modeling of long-term antibody persistence based on the above data predicts that anti-HPV 16/18 antibodies will remain detectable for at least 20 years<sup>32</sup>
- B. Will protection against surrogate markers ultimately translate to decreased incidence of cancer?
1. Cervical and non-cervical cancers usually occur 20 years or more after HPV infection<sup>1,3,4</sup>
  2. Current follow up studies are too short to directly evaluate efficacy against cervical and non-cervical cancers
  3. CIN 2 and 3 have a high probability of progressing to cancer, but they are only precancerous lesions and therefore an indirect measure of vaccine efficacy
  4. Non-cervical cancer have even less specific surrogate markers to measure vaccine efficacy
- C. Will the HPV vaccine be effective at preventing HPV associated non-cervical cancers?
1. In clinical trials for cervical cancer vaccine efficacy has been 90 to 100%<sup>5-7</sup>
  2. Trials are ongoing for prevention of oropharyngeal and anogenital cancers
  3. It is unclear whether the HPV vaccine will be as effective at preventing other types of HPV associated cancer
  4. However, since a greater proportion of these cancers are associated with HPV 16/18, vaccine efficacy against these cancers may be even higher<sup>17</sup>
- D. Will there be selective pressure on other oncogenic HPV strains which will emerge as significant cause of disease?
1. Interim analysis of FUTURE II study showed an increase in the proportion of CIN 2 and 3 caused by HPV serotypes other than HPV 16/18<sup>33</sup>
  2. This has raised the question whether other HPV types may eventually fill the 'biologic niche' left behind by HPV 16/18<sup>28,33</sup>
  3. This increase was not statistically significant and has not been reproduced in subsequent phases of the FUTURE II study<sup>28</sup>
  4. Future generations of HPV vaccines may protect against additional oncogenic HPV strains
- E. Is widespread immunization of males cost-effective?
1. Economic models are used to predict cost-effectiveness of widespread HPV vaccination programs
  2. Economic modeling is based on many factors that are extremely difficult to predict:<sup>24</sup>
    - a. Length of vaccine-conferred immunity
    - b. Vaccine efficacy
    - c. Proportion of population receiving vaccine coverage
    - d. Rate of HPV transmission
    - e. Frequency of HPV screening programs

3. Most models have found that including boys in a national vaccination program is not as cost-effective as increasing vaccination coverage of girls<sup>24-27</sup>

Table 6: Cost-effectiveness of vaccinating pre-adolescent girls in the context of current screening guidelines<sup>24</sup>

| Author                      | Setting     | Cost per vaccinated per son | Duration of vaccine-induced protection (years) | ICER HPV-16,18 (\$ per QALY) | ICER HPV-6,11,16,18 | Currency (year)      |
|-----------------------------|-------------|-----------------------------|--|------------------------------|---------------------|----------------------|
| Sander GD and Taira AV 2003 | USA         | 300                         | Lifelong                                       | 12,700                       | -                   | US (2001)            |
|                             |             |                             | Wane (10 y), with booster                      | 22,800                       | -                   |                      |
| Taira AV et al, 2004        | USA         | 300                         | Wane (10 y), with booster                      | 14,600                       | -                   | US (2001)            |
| Goldie SJ et al, 2004       | USA         | 400                         | Lifelong                                       | 20,600                       | -                   | US (2002)            |
| Elbasha EH et al, 2007      | USA         | 360                         | Life long<br>Wane (10 y), no booster           | -                            | 3,000               | US (2005)            |
| Kim JJ et al, 2007          | USA         | 500                         | Lifelong                                       | <50,000                      | <50,000             | US (2006)            |
| Brisson M et al, 2007       | Canada      | 400<br>167 (booster)        | Lifelong                                       | 31,100                       | 21,500              | Euros (2005)         |
|                             |             |                             | Wane (30 y), no booster                        | 114,800                      | 64,600              |                      |
|                             |             |                             | Wane (30 y), with booster                      | 56,000                       | 37,000              |                      |
| Boot HJ et al, 2007         | Netherlands | 320                         | Lifelong                                       | 24,000 (YLS)                 | -                   | Euros                |
|                             |             |                             | Boosters (every 10 y to age 50)                | 39,500 (YLS)                 | -                   |                      |
| Kulasingam S et al, (2007)  | Australia   | 380<br>150 (booster)        | Lifelong                                       | 18,700                       | -                   | Australia (2005)     |
|                             |             |                             | Wane (10 y), no booster                        | 52,600                       | -                   |                      |
|                             |             |                             | Wane (10 y), with booster                      | 25,000                       | -                   |                      |
| Ginsberg GM et al, 2007     | Israel      | 430                         | Lifelong                                       | 81,400                       | -                   | International (2007) |
|                             |             |                             | Wane (every 10 y), no booster                  | 272,000                      | -                   |                      |

ICER: Incremental cost-effectiveness ratios; QALY: Quality-adjusted life years

4. Economic models to date have focused only on prevention of cervical cancer and have not examined the cost-effectiveness of preventing non-cervical HPV associated cancers in females and males (Table 6)
5. More robust economic models are needed which take into account:
  - a. Prevention of non-cervical cancers in males and females
  - b. Heterosexual as well as homosexual transmission models
  - c. Special populations
    - i. MSM
    - ii. HIV/AIDS

#### F. Other considerations

1. Religious issues
2. Social issues
3. Cultural issues
4. Legislative issues (Figure 8)

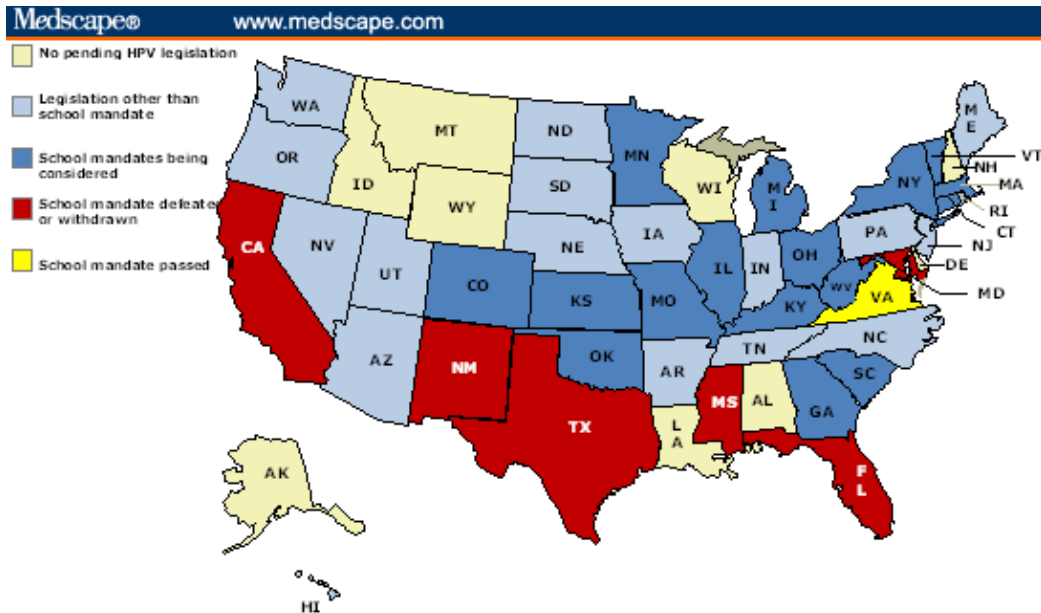


Figure 8: Pending legislation regarding mandatory HPV vaccination for females entering sixth grade (2008)

VII. Conclusion

- A. The annual number of non-cervical cancers caused by HPV 16/18 in the U.S. roughly approximates the number of cervical cancers
- B. HPV associated non-cervical cancers, regardless of anatomic site, have higher correlation (86 to 95%) with HPV types 16/18 than cervical cancer (70%)<sup>14</sup>
- C. A substantial proportion (~25%) of cancers caused by HPV infection arise in men<sup>14</sup>
- D. The overall long-term incidence of HPV associated non-cervical cancers in the U.S. is rising<sup>20</sup>
- E. There are currently no effective screening programs for HPV-associated non-cervical cancers
- F. Results are promising for use of the HPV vaccine in males, but more data are needed from:
  - 1. Efficacy trials in males and females
  - 2. More robust economic models

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