HPV Vaccines Up-to-Date

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Liv Hospital Ulus
Cervical Cancer Risk Factors

- Human Papilloma Virus (HPV) infection
- Smoking
- Multi partner
- Multiparity
- Early sexual intercourse
- Immun deficiency by drugs
- Nutritional factors
- Genetical factors
HPV Types and Potential Risks

HPV in Cervix Cancer (n=1918)

% 96.6

16, 18 6, 11

<table>
<thead>
<tr>
<th>High risk</th>
<th>16, 18, 45, 31, 33, 52, 58, 35, 59, 56, 51, 39, 68, 73, 82</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate risk</td>
<td>26, 53, 66</td>
</tr>
<tr>
<td>Low risk</td>
<td>6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108</td>
</tr>
</tbody>
</table>

HPV Serotypes in Cervical Cancer

Modified from Munoz N, Int J Cancer, 2004
Basırdan

• **Son söz Prof. Dr. …’ da (2012):**

• Türkiye’deki HPV tipleri bilinmiyor. Ülkemizde de aynı oranda etkili olacağını şüpheli...
HPV Serotype Distribution in Cx Ca

- HPV 16/18: 76%
- HPV 16: 64.7%
- HPV 45: 9.9%
- HPV 18: 9.9%
- HPV 31: 3.0%
- HPV X: 2.6%
- HPV 33: 2.2%
- HPV 39: 1.7%
- HPV 68 or 73: 0.9%
- HPV 35: 0.9%
- HPV 51: 0.9%
- HPV 52: 0.9%
- HPV 59: 0.4%

Usubutun A, Int J Gynecol Pathol, 2009
This is the one of two published studies on genital wart epidemiology in Turkey.

Annual Prevalence in this study is 154/100,000 women (30-65 Y)

Recurrence rate is 15-37%

Ozgul N, Asian Pacific Journal of Cancer Prevention 2011
# Projection of Weighted Data to General Population

<table>
<thead>
<tr>
<th>Genital Wart</th>
<th>Public</th>
<th>University</th>
<th>Private</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Not weighted in study group</td>
<td>13</td>
<td>3.4</td>
<td>60</td>
<td>3.8</td>
</tr>
<tr>
<td>Calculated according to general population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Based on all study facts</td>
<td>3.4</td>
<td>(3.4-4)</td>
<td>3.8</td>
<td>(2.2-6.5)</td>
</tr>
<tr>
<td>Based on pregnant women in study</td>
<td>3.3</td>
<td>(3.3-3.3)</td>
<td>1.8</td>
<td>(0.3-11.5)</td>
</tr>
</tbody>
</table>

*Point prevalence adjusted to age

Basıncandan

- **Prof. Dr. ... (Kadın Hastalıkları ve Doğum Uzmanı) [2012]**
- “Yılda iki kez simir testi yaptırım kadınların bu virus nedeniyle kanser olma riski yoktur.”

<table>
<thead>
<tr>
<th>ACS/ACOG/USPSTF/CDC/NCCN Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>21-29 Y</strong></td>
</tr>
<tr>
<td><strong>30-65 Y</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Efficacy of Screening Programs

Factors negatively effecting the screening programs:

- Low coverage
- Detection problems of atypical glandular cells for in adenocarcinomas
- Persistent oncogenic HPV infections
- False negative Pap smear results
- Lack of monitorings after screenings

# Cancers Associated with Infections

<table>
<thead>
<tr>
<th>Infections</th>
<th>Effected Organs</th>
<th># Ca</th>
<th>%Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. Pylori</td>
<td>Stomach</td>
<td>592,000</td>
<td>%5.5</td>
</tr>
<tr>
<td>HPV</td>
<td>Cx and others</td>
<td>561,200</td>
<td>%5.2</td>
</tr>
<tr>
<td>HBV, HCV</td>
<td>Liver</td>
<td>535,000</td>
<td>%4.9</td>
</tr>
<tr>
<td>HHV-8</td>
<td>Kaposi Sarcoma</td>
<td>54,000</td>
<td>%0.9</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>Bladder</td>
<td>9,000</td>
<td>%0.1</td>
</tr>
<tr>
<td>HTLV-1</td>
<td>Leukemia</td>
<td>2,700</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1,900,000</td>
<td>%18</td>
</tr>
</tbody>
</table>

Parkin DM, Int J Cancer, 2006
Epidemiology

- Sexual intercourse is low for girls but frequent for boys before marriage.
- Generally women are infected after marriage.
- Adolescent brides are more common in Turkey.
- Many men have more than one wife or relationships.
- It shows varieties in terms of sexual behaviours for young generation in Turkey.

Human Papilloma Virus (HPV) infection is sexually transmitted!
Opinion Survey in Boys Whether They Need Sexual Experience Before Marriage

<table>
<thead>
<tr>
<th>Evlilik Öncesi Cinsel Deneyim Onayı</th>
<th>Kadın N</th>
<th>Kadın %</th>
<th>Erkek N</th>
<th>Erkek %</th>
<th>Toplam N</th>
<th>Toplam %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olumlu Bakıyorum</td>
<td>40</td>
<td>70,2</td>
<td>63</td>
<td>79,7</td>
<td>103</td>
<td>75,7</td>
</tr>
<tr>
<td>Olumsuz Bakıyorum</td>
<td>10</td>
<td>17,5</td>
<td>10</td>
<td>12,7</td>
<td>20</td>
<td>14,7</td>
</tr>
<tr>
<td>Kararsızım</td>
<td>7</td>
<td>12,3</td>
<td>6</td>
<td>7,6</td>
<td>13</td>
<td>9,6</td>
</tr>
<tr>
<td>Toplam</td>
<td>57</td>
<td>100</td>
<td>79</td>
<td>100</td>
<td>136</td>
<td>100</td>
</tr>
</tbody>
</table>

Ceyhan MŞ, Üniversite Gençliğinin Cinselliğe Bakış Açısı (Doktora Tezi) 2005
Opinion Survey in **Girls** Whether They Need Sexual Experience Before Marriage

<table>
<thead>
<tr>
<th>Evlilik Öncesi Cinsel Deneyim Olup-Onaylı</th>
<th>Kadın</th>
<th>Erkek</th>
<th>Toplam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td><strong>Olumlu Bakıyorum</strong></td>
<td>12</td>
<td>21,1</td>
<td>13</td>
</tr>
<tr>
<td><strong>Olumsuz Bakıyorum</strong></td>
<td>36</td>
<td>63,2</td>
<td>61</td>
</tr>
<tr>
<td><strong>Kararsızım</strong></td>
<td>9</td>
<td>15,8</td>
<td>5</td>
</tr>
<tr>
<td><strong>Toplam</strong></td>
<td>57</td>
<td>100</td>
<td>79</td>
</tr>
</tbody>
</table>

Ceyhan MŞ, Üniversite Gençliğinin Cinselliğe Bakış Açısı (Doktora Tezi) 2005
Mortality for Vaccine Preventable Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polio</td>
<td>1,000</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>4,000</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>15,000</td>
</tr>
<tr>
<td>Tetanus</td>
<td>198,000</td>
</tr>
<tr>
<td>Pertussis</td>
<td>294,000</td>
</tr>
<tr>
<td>Hib</td>
<td>386,000</td>
</tr>
<tr>
<td>Measles</td>
<td>540,000</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>600,000</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>716,000</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>402,000</td>
</tr>
<tr>
<td>HPV</td>
<td>240,000</td>
</tr>
</tbody>
</table>

Totally 3,396,000 deaths (2002)

WHO 2006
Country Implementations for HPV Vaccine Introductions

<table>
<thead>
<tr>
<th>Age</th>
<th>Target age</th>
<th>Catch up</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Australia</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Austria</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Belgium</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Canada</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Denmark</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>France</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Germany</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Greece</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Italy</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Luxembourg</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Norway</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Spain</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Sweden</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Switzerland</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>UK</td>
<td></td>
</tr>
</tbody>
</table>

Wright TC Jr, Gynecol Oncol, 2008
HPV Vaccines
Çocuk felci aşısının bulunuşu büyük bir memnuniyet yarattı

Dünyada heyecan uyandıran haber şehrimizde de alaka ile karşılandı. Türk doktorları katı ve ilmi malumat almadan fazla bir şey söylemek istemiyorlar

Amerika aşısı kullanmaya başlıyor

Savaş kazandı
Cervarix® and Gardasil® Vaccine Contents

**Cervarix®**

- **Antigens**
  - HPV 16 VLPs: 40 µg
  - HPV 18 VLPs: 20 µg
  - HPV 6 VLPs: 20 µg
  - HPV 11 VLPs: 40 µg

- **AS04 adjuvant**
  - Aluminium salt (Al(OH)_3): 500 µg
  - Immun stimulator MPL: 50 µg

**Gardasil®**

- **Antigens**
  - HPV 16 VLPs: 20 µg
  - HPV 18 VLPs: 20 µg
  - HPV 6 VLPs: 20 µg
  - HPV 11 VLPs: 40 µg

- **Adjuvant 225 µg**
  - Aluminium tuzu (amorphous aluminium hydroxyphosphate sulphate [AAHS])

**MPL** = monophosphoryl lipid A.
Cervarix®  FDA Approvals

• Cervical Cancer
• CIN 2+
• Cervical AIS
• CIN 1

FDA BL 125259/0, 16.10.2009
Cervarix® EMA* Approvals

- Cervikal cancer
- CIN
- VIN
- VaIN

*EMA: European Medicines Agency, 06/02/014
## Initial Assessment (FUTURE III)

<table>
<thead>
<tr>
<th>Initial assessment</th>
<th>GARDASIL #1911 (%)</th>
<th>Placebo #1908 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 HPV Types [Serologic/PCR (-)]</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>Pozitive ≥1 HPV (Serologic/PCR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 HPV Type</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>2 HPV Type</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>3 HPV Type</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>4 HPV Type</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>16 and 18 pozitive</td>
<td>1.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.3</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Before Vaccination

Cervical smear

HPV testing or serotyping

Not necessary
Gardasil® FDA Approvals

Girls and Women
- Cervical, vaginal, vulvar ca
- Genital warts
- CIN 1, 2, 3
- Cervikal AIS
- VAIN 2, 3
- Undifferentiated VIN (VIN2,3)
- AIN and Anal cancer

Boys and Men
- Anal warts
- AIN and Anal cancer
**HPV Virus-like Particles (VLPs)**

- **Noninfectious HPV VLP**
  - Capsid proteins: L1
  - Lacks viral DNA
  - Lacks L2 protein
  - High efficacy
  - No viral DNA
    - No HPV infections
    - No cancer formation

- **Infectious HPV**

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Proportion of Australian-Born Women Under 21 Years With Genital Warts

Donovan B, Lancet Infect Dis 2011
HGAs in Women Aged <18 Years, Before and After Introduction of qHPV Vaccine

HGA: High Grade Cervical Abnormalities

Brotherton JM, Lancet 2011
In 2010, data were collected only in the first 6 months: 40,793 new clients seen between 2007 and 2010; school-based program for 11–12-year-old girls, with catch-up for adolescents up to 20 years; vaccine coverage rate for Auckland DHB by end of 2009 school year = 51.7%.

Incidence of Genital Warts in California Following Introduction of qHPV Vaccine

Results

- Average annual number of clients served:
  - >1,754,000 females
  - > 258,000 males
- Overall diagnoses of genital warts:
  - 0.7% of females
  - 3.3% of males
- In males and females, highest rates of genital warts were observed in young adults aged 21 to 25 years
  - Lowest rates among those aged >30 years
- Among females aged <21 years, diagnoses of genital warts decreased from 0.94% to 0.61% ($P_{trend} < 0.001$)
- Decreases also observed among females aged 21 to 25 years, males <21 years, and males aged 21 to 25 years

Early Results of HPV Vaccination (NHANES Survey)

HPV types prevalence in 14-19 years girls (United States)

Cl=confidence interval; NHANES=National Health and Nutrition Examination Survey.
Incidence of Genital Warts in Belgium Following Introduction of qHPV Vaccine

Results

• Population analyzed:
  • 55,193 females aged 16 to 20 years, of whom 13,117 were vaccinated with qHPV vaccine
  • 435 cases of genital warts observed
    • 423 in nonvaccinated females
    • 12 in vaccinated females

<table>
<thead>
<tr>
<th></th>
<th>Vaccinated</th>
<th>Nonvaccinated</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative incidence estimates for genital warts</td>
<td>0.12%</td>
<td>0.93%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Nonvaccinated females aged 16 to 20 years were estimated to have 8 times greater risk of getting genital warts than vaccinated females.

Van Tielen R, EUROGIN 2012
Early Indicators of the Real World Effectiveness of qHPV Vaccine: Summary

- Significant population level declines in genital warts have been observed since the qHPV vaccine was introduced.
- Significant declines in the incidence of high-grade cervical abnormalities among young females in Australia.
- Apparent decrease in HPV 16/18 infection among young females in Belgium.
- The most significant decreases in disease or HPV infection seen in young females who were vaccinated (or who were likely vaccinated) with qHPV vaccine.
- No evidence of disease reductions in older women or in men who have sex with men.
- Data strongly suggest population-level impact of qHPV vaccination programs.
Efficacy of Prophylactic Vaccines: A Systemetic Review & Meta-Analysis

B. CIN2+ associated with HPV 18

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccine Events</th>
<th>Vaccine Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Risk Ratio IV, Fixed, 95% CI</th>
<th>Risk Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat populations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FUTURE II</td>
<td>6</td>
<td>6087</td>
<td>29</td>
<td>6080</td>
<td>0.21 [0.09, 0.50]</td>
<td></td>
</tr>
<tr>
<td>Harper et al</td>
<td>0</td>
<td>481</td>
<td>0</td>
<td>470</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>PATRICIA</td>
<td>2</td>
<td>7455</td>
<td>24</td>
<td>7480</td>
<td>0.08 [0.02, 0.35]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>8</td>
<td>14023</td>
<td>53</td>
<td>14030</td>
<td>0.16 [0.08, 0.34]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi^2 = 1.10, df = 1 (P = 0.29); I^2 = 9%
Test for overall effect: Z = 4.76 (P < 0.00001)

Per-protocol populations

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccine Events</th>
<th>Vaccine Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Risk Ratio IV, Fixed, 95% CI</th>
<th>Risk Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUTURE II</td>
<td>0</td>
<td>5055</td>
<td>11</td>
<td>4970</td>
<td>0.04 [0.00, 0.73]</td>
<td></td>
</tr>
<tr>
<td>PATRICIA</td>
<td>2</td>
<td>6794</td>
<td>15</td>
<td>6746</td>
<td>0.13 [0.03, 0.58]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2</td>
<td>11849</td>
<td>26</td>
<td>11716</td>
<td>0.10 [0.03, 0.38]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi^2 = 0.48, df = 1 (P = 0.49); I^2 = 0%
Test for overall effect: Z = 3.39 (P = 0.0007)

Beibei Lu, BMC Infect Dis 2011
HPV Vaccination after HGSIL Treatment

- 2007-2010 cases: 737
- Monitored CIN2-3 after LEEP
  - 360 cases vaccinated
  - 377 cases w/o vaccination
- Recurrent disease with related HPV serotypes
  - Vaccinated group: %2.5
  - Non-vaccinated group: %8.5 (HR=2.840; CI: 1.335-6.042; p<0.01)

Kang WD, Gynecol Oncol, 2013
Change in Sexual Behaviour after Vaccination

- Cases# 339 (13-21 Y girls)
- In period for STI, %42.5 cases had no sexual intercourse, % 57.5 cases had sexual experience before (OR 0.13, 95% CI 0.03–0.69)
- No change in sexual behaviour after HPV vaccination has shown

<table>
<thead>
<tr>
<th>Risk perceptions (5-item subscales)</th>
<th>All (n = 339)</th>
<th>Sexually Experienced at Baseline (n = 195)</th>
<th>Sexually Inexperienced at Baseline (n = 144)</th>
<th>P value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for safer sexual behaviors(^b)</td>
<td>1.6 (1.6)</td>
<td>1.6 (1.7)</td>
<td>1.5 (1.4)</td>
<td>0.59</td>
</tr>
<tr>
<td>STI risk perceptions(^c)</td>
<td>3.9 (2.0)</td>
<td>3.7 (2.1)</td>
<td>4.0 (2.0)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Mayhew A, Pediatrics 2014
Targeted Group for HPV Vaccination

Vaccine introduction to 11-12 years of girls and boys

Preferred timing is before sexual intercourse

Catch-up vaccination for 13-26 years girls and women, 13-21 years boys and men (except special groups)

Have indication for 45 years women, no age limit for bivalent vaccine
HPV Vaccination to Whom and How (EMA)

- **bHPV**
  - 9-14 years girls (0.-6.)
  - >15 years girls and women 3 doses

- **qHPV**
  - 9-13 years boys and girls 2 doses (0.-6.)
## Gardasil® in Pregnancy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Quadrivalent HPV vaccine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>(%)</td>
</tr>
<tr>
<td>Women with pregnancies</td>
<td>1,115</td>
<td>(10.7)</td>
</tr>
<tr>
<td>No. of pregnancies</td>
<td>1,244</td>
<td></td>
</tr>
<tr>
<td>Infants/fetuses with known outcomes</td>
<td>996</td>
<td></td>
</tr>
<tr>
<td>Live births*</td>
<td>621</td>
<td>(62.3)</td>
</tr>
<tr>
<td>Spontaneous miscarriage*</td>
<td>249</td>
<td>(25.0)</td>
</tr>
<tr>
<td>Late fetal deaths*</td>
<td>11</td>
<td>(1.1)</td>
</tr>
<tr>
<td>Congenital anomalies*</td>
<td>15</td>
<td>(1.5)</td>
</tr>
</tbody>
</table>

**Source:** Food and Drug Administration.

Goss MA, Obstet Gynecol 2014
## Cervarix® in Pregnancy

<table>
<thead>
<tr>
<th>Confidance results (TVC)</th>
<th>&gt; 25 Y women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cervarix®</td>
</tr>
<tr>
<td>Pregnancy#</td>
<td>28</td>
</tr>
<tr>
<td>Pregnancy Results, %</td>
<td></td>
</tr>
<tr>
<td>Normal infant/continuing pregnancy</td>
<td>82.1</td>
</tr>
<tr>
<td>Premature infant</td>
<td>-</td>
</tr>
<tr>
<td>Elective termination</td>
<td>10.7</td>
</tr>
<tr>
<td>Spontanious abortus</td>
<td>7.1</td>
</tr>
</tbody>
</table>

| Pregnancy in Vaccinated cohort#* | 9 | 2 | 17 |

## Pregnancy Results, %

<table>
<thead>
<tr>
<th></th>
<th>&gt; 25 Y women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cervarix®</td>
</tr>
<tr>
<td>Normal infant/continuing pregnancy</td>
<td>77.8</td>
</tr>
<tr>
<td>Premature infant</td>
<td>-</td>
</tr>
<tr>
<td>Elective termination</td>
<td>11.1</td>
</tr>
<tr>
<td>Spontanious abortus</td>
<td>11.1</td>
</tr>
</tbody>
</table>

---

Descamps D, Hum Vaccine 2009
Vaccination in Pregnancy

- Don’t start vaccination in pregnancy
- If pregnancy noticed after first vaccination, 3 doses after birth beginning from the start
- If pregnancy noticed after 2 doses the last dose has to be administered after birth within 1 year
- Safe in breast feeding period
Immunogenicity and Safety of qHPV Vaccine in HIV-1-Infected Women

- Multicenter, prospective trial among HIV-infected women aged 13-45 years
- Found that the qHPV vaccine was highly immunogenic
- But women with CD4 cell counts under <200 cells/mm³ had lower seroconversion rates compared with women higher CD4 cell counts

Kojic EM, Clin Infect Dis 2014
Immune Memory

GMT 95% CI 
[log₁₀ scale]

0 2 3 6 7 12 18 24 30 36 54

Vaccine in 0., 2. and 6. months
Immune challenge 60. month

Gardasil
n = 78

Placebo (Sero (-) ve PCR (-))
n = 70

Immune memory continues

Olsson SE, Vaccine, 2007
Booster Dose

Positive immune memory after 5th year

No need for booster dose
Advers Events
Basıändan

• HPV aşısıyla ilgili yeni araştırma, ...
• “... Kanada’da bulunan İngiliz Kolombiya Üniversitesi’nden iki araştırmacı, humiliyetlerin rahim ağzı kanseri aşısının zararsız olduğunu yönelik tavsiyelerini eleştirdiler.”
Human papillomavirus (HPV) vaccine policy and evidence-based medicine: Are they compatible?

Lucija Tomljenovic1, and Carol A. Shaw1,2

1Neural Pathway Group, Department of Ophthalmology and Visual Sciences, University of British Columbia, 828 W. 10th Ave, Vancouver, Canada and 2Program in Experimental Medicine and the Graduate Program in Neuroscience, University of British Columbia, BC, Canada

Tomljenovic L ve Shaw CA are not medical doctors!
Adverse Events

No relationship with vaccine virus related infection or cancer due to having no live or inactivated virus in vaccine composition

Local reactions;

- Erithem
- Little pain
- Swelling
- Fever

Nausea, dizziness, blackout
Total AE (severe and mild) = 21.194/ 56 million doese
The Vaccine Adverse Event Reporting System (VAERS) severe AE’s; hospitalization, prolonged hospitalization, constant disability, severe diseaseses for mortality
Deaths

• 32 deaths in clinical studies
• None of them are related to vaccines
• Cause of mortalities
  • Viral infections; akut myocarditis, meningoencefalitis, influenza B viral sepsis
  • Cardiac aritmia due to cardiomyopathy
  • Diabetic ketoasidosis
  • Ephileptic attack in ephileptic patients
  • Pulmoner emboli, DVT
  • Over limit uptake in drug abusers
  • Traffic accident
  • Other drugs
  • Murdery

The Vaccine Adverse Event Reporting System (VAERS), The Vaccine Safety Datalink (VSD), The Clinical Immunization Safety Assessment (CISA) Network
http://www.cdc.gov/vaccinesafety/Vaccines/HPV/jama.html
Autoimmune Diseases

<table>
<thead>
<tr>
<th>Conditions</th>
<th>GARDASIL (N = 10,706)</th>
<th>AAHS Control* or Saline Placebo (N = 9412)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Arthralgia/Arthritis/Arthopathy**</td>
<td>120 (1.1)</td>
<td>98 (1.0)</td>
</tr>
<tr>
<td>Autoimmune Thyroiditis</td>
<td>4 (0.0)</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>Celiac Disease</td>
<td>10 (0.1)</td>
<td>6 (0.1)</td>
</tr>
<tr>
<td>Diabetes Mellitus Insulin-dependent</td>
<td>2 (0.0)</td>
<td>2 (0.0)</td>
</tr>
<tr>
<td>Erythema Nodosum</td>
<td>2 (0.0)</td>
<td>4 (0.0)</td>
</tr>
<tr>
<td>Hyperthyroidism***</td>
<td>27 (0.3)</td>
<td>21 (0.2)</td>
</tr>
<tr>
<td>Hypothyroidism†</td>
<td>35 (0.3)</td>
<td>38 (0.4)</td>
</tr>
<tr>
<td>Inflammatory Bowel Disease‡</td>
<td>7 (0.1)</td>
<td>10 (0.1)</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>2 (0.0)</td>
<td>4 (0.0)</td>
</tr>
<tr>
<td>Nephritis§</td>
<td>2 (0.0)</td>
<td>5 (0.1)</td>
</tr>
<tr>
<td>Optic Neuritis</td>
<td>2 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Pigmentation Disorder§</td>
<td>4 (0.0)</td>
<td>3 (0.0)</td>
</tr>
<tr>
<td>Psoriasis§</td>
<td>13 (0.1)</td>
<td>15 (0.2)</td>
</tr>
<tr>
<td>Raynaud's Phenomenon</td>
<td>3 (0.0)</td>
<td>4 (0.0)</td>
</tr>
<tr>
<td>Rheumatoid Arthritis††</td>
<td>6 (0.1)</td>
<td>2 (0.0)</td>
</tr>
<tr>
<td>Scleroderma/Morphea</td>
<td>2 (0.0)</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>Stevens-Johnson Syndrome</td>
<td>1 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td>1 (0.0)</td>
<td>3 (0.0)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>3 (0.0)</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td><strong>All Conditions</strong></td>
<td>245 (2.3)</td>
<td>218 (2.3)</td>
</tr>
</tbody>
</table>
Safety of Prophylactic Vaccines: A Systematic Review & Meta-Analysis

### B. Injection-related serious adverse events

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccine Subjects</th>
<th>Vaccine Total</th>
<th>Control Subjects</th>
<th>Control Total</th>
<th>Risk Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUTURE I</td>
<td>1</td>
<td>2673</td>
<td>0</td>
<td>2672</td>
<td>3.00 [0.12, 73.58]</td>
</tr>
<tr>
<td>FUTURE II</td>
<td>3</td>
<td>6019</td>
<td>2</td>
<td>6031</td>
<td>1.50 [0.25, 8.99]</td>
</tr>
<tr>
<td>Harper et al</td>
<td>0</td>
<td>531</td>
<td>0</td>
<td>538</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Koutsky &amp; Mao et al</td>
<td>0</td>
<td>1194</td>
<td>0</td>
<td>1198</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Munoz et al</td>
<td>0</td>
<td>1908</td>
<td>0</td>
<td>1902</td>
<td>Not estimable</td>
</tr>
<tr>
<td>PATRICIA</td>
<td>11</td>
<td>9319</td>
<td>6</td>
<td>9325</td>
<td>1.83 [0.68, 4.96]</td>
</tr>
<tr>
<td>Villa et al</td>
<td>0</td>
<td>272</td>
<td>0</td>
<td>274</td>
<td>Not estimable</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>15</td>
<td>21916</td>
<td>8</td>
<td>21940</td>
<td>1.82 [0.79, 4.20]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.14, \text{df} = 2 (P = 0.93); I^2 = 0\%$

Test for overall effect: $Z = 1.39 (P = 0.16)$

Beibei Lu, BMC Infect Dis 2011
SGO is committed to partnering with organizations that share our vision to eradicate gynecologic cancers.

Join the HPV Vaccine Campaign

Working together to prevent cervical cancer, SGO and the Centers for Disease Control and Prevention (CDC) encourage SGO members to connect with pediatricians and others who are in a position to provide the vaccination against human papillomavirus (HPV) to boys and girls.
SGO Position Statement: HPV Vaccination of Girls and Boys

December 2013

As the health care providers for women who suffer from cervical and lower genital tract cancers, members of the Society of Gynecologic Oncology (SGO) have long been primary advocates for the prevention of cervical and other human papillomavirus (HPV)-related cancers. **SGO strongly supports vaccination of both girls and boys against HPV to prevent HPV-related cancers.** Use of these vaccines, coupled with recommended cervical cancer screening, would eliminate most cervical cancer. Other cancers associated with HPV including cancer of the vulva, vagina, anus, penis, and some head and neck cancers may also be prevented with use of the HPV vaccine.

The Centers for Disease Control and Prevention and the Food and Drug Administration has monitored the safety of the HPV vaccines since the FDA licensed them in 2006 and 2009. In the 57 million doses administered from June 2006 through March 2013, there were no new or unusual patterns of adverse events to suggest any safety concerns.
Committee on Adolescent Health Care

This Committee Opinion was developed with the assistance of the Immunization Expert Work Group. The document reflects emerging clinical and scientific advances as of the date issued and is subject to change. This information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Human Papillomavirus Vaccination

ACOG Recommendations
Human Papillomavirus Vaccination

**ABSTRACT:** The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention recommends that human papillomavirus (HPV) vaccination routinely be targeted to females and males aged 11 years or 12 years as part of the adolescent immunization platform to help reduce the incidence of anogenital cancers and genital warts associated with HPV infection. The quadrivalent HPV vaccine is approved for use in males and females, whereas the bivalent HPV vaccine is approved for use only in females. For those not vaccinated at the target age, catch-up vaccination is recommended up to age 26 years. The American College of Obstetricians and Gynecologists endorses these recommendations. Although obstetrician–gynecologists are not likely to care for many patients in the initial HPV vaccination target group, they have the opportunity to educate mothers about the importance of vaccinating their children at the recommended age and are critical to vaccinating adolescent girls and young women during the catch-up period. Obstetrician–gynecologists should advise patients and parents that HPV vaccines are most effective in preventing genital cancers when administered before the onset of sexual activity. However, sexually active individuals can receive some benefit from the vaccination because exposure to all HPV types prevented by the vaccines is unlikely in persons aged 13 years through 26 years. Although HPV vaccination in pregnancy is not recommended, neither is routine pregnancy testing before vaccination. Lactating women can receive either HPV vaccine. The need for ongoing cervical cytology screening should be emphasized in all women aged 21 years and older, even those who received HPV vaccination before the onset of sexual activity.
Need for screening?

Absolutely Yes

• Vaccine not effective to all serotypes
• Vaccine immunogenecity can be reduced due to improper compliance to vaccination schedules
• There can be infections due to non vaccine serotypes before vaccination started
Implemented and Future Strategies in Cx Ca Screening

Screening Program

- Pap smear
- HPV DNA Test 1
- HPV DNA Test 2

Future

- HPV Vaccination

HPV (+) continue screening!
Messages to Take Home

Important Problems

- Non evidence based messages in media
- Investment to screening and vaccination
- Prioritization for NIP inclusion
- Infrastructure for adolescent vaccination
Messages to Take Home

For any country; If HPV vaccines will be purchased with adequate prices, it's not acceptable with an ethical and political view to exclude HPV vaccination from NIP.
Thank You for Your Attention!