Human Papillomavirus (HPV) Vaccination and Implications for Cervical Cancer Screening

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Geneva University Hospital

"I'd have been here sooner if it hadn't been for early detection."
HPV, DNA virus

- More than 120 different type
- High-risk: 16-18-31-34
  - 16: 68% SCC
  - 18: 71% AdenoCx
+ 70% of sexually active people face the Papillomavirus during their lifetime

Incidence estimated to be 6.2 million/year for genital HPV infection in U.S.
HPV and related diseases
5.2% of all cancers worldwide attributable to HPV infection  
(Parkin et al. Vaccine 2006)

<table>
<thead>
<tr>
<th>Organ Site for women</th>
<th>% HPV Related CANCER</th>
<th>Estimated number/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>95-98</td>
<td>500,000</td>
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<tr>
<td>Vulva</td>
<td>30-35</td>
<td>16,000</td>
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<tr>
<td>Vagina</td>
<td>65-90</td>
<td>Total with vulva</td>
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<tr>
<td>Anal</td>
<td>90-93</td>
<td>14,000</td>
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<tr>
<td>Oral/larynx</td>
<td>25</td>
<td>3,000</td>
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<tr>
<td>Oro-pharynx</td>
<td>30-75</td>
<td>1,000</td>
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<tr>
<td>TOTAL</td>
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<td>534,000</td>
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WHO Information Center
HPV Burden

- These worldwide and U.S. estimates show:
  - the burden of noncervical HPV-related cancers is substantial, approximately equal among men and women
  - oropharyngeal cancers constitute a high proportion of noncervical HPV-related cancers, particularly among men

- Additionally, the burden of noncervical cancers approximates that of cervical cancers in the United States
  - such an equilibrium may be true only for developed nations with established Pap smear screening programs

- In developing countries without organized Pap smear screening programs, the burden of cervical cancers far exceeds that of noncervical cancers.
Estimated HPV burden in women in Europe: Nearly 1.4 million events/year

<table>
<thead>
<tr>
<th>Oncogenic types</th>
<th>Pre-cancerous Cervical Lesions</th>
<th>Cervical Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non Oncogenic types</td>
<td>Low Grade Cervical Lesions</td>
<td>Genital warts</td>
</tr>
<tr>
<td>Calculations</td>
<td>817,000 cases/yr</td>
<td>250,000 cases/yr</td>
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</tbody>
</table>


Europe 25 member states plus Iceland, Norway and Switzerland.
## Estimated HPV burden in women in Switzerland

<table>
<thead>
<tr>
<th>Oncogenic types</th>
<th>Pre-cancerous Cervical Lesions</th>
<th>Cervical Cancer</th>
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<td>Low Grade Cervical Lesions</td>
<td>Genital Warts</td>
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<td>Calculations</td>
<td>?</td>
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</table>

Commission fédérale pour la vaccination, 2007
Cervical cancer and HPV

Secondary prevention:
Pap smear
Screening with the Conventional Pap Smear

- Widely available
- Inexpensive
- But not perfect
  - Screening test – not diagnostic
  - 7-10% of women need further evaluation
  - Low sensitivity – need regular repeats

Incidence of cervical cancer in the Nordic countries

From Hakama, 1992
Cervical cancer and HPV

Secondary prevention:
HPV testing
HPV Testing: Pcr test

- HPV testing is approved for use in two contexts:
  1. As a triage test following an equivocal cytology result of ASCUS
  2. Primary screening in conjunction with cervical cytology for women aged 30 years and older.

Interpretation HPV-based screening is more effective than cytology in preventing invasive cervical cancer, by detecting persistent high-grade lesions earlier and providing a longer low-risk period. However, in younger women, HPV screening leads to over-diagnosis of regressive CIN2.

Essential Traits Of HPV Screening as Compared With Standard Cytology

- GAIN IN SENSITIVITY 30% to 40%
- LOSS IN SPECIFICITY 5% to 8%
- HIGH REPRODUCIBILITY and AUTOMATIZATION

- Not beneficial in young women
  - (transient HPV infection)
Cervical cancer and HPV

Primary prevention: vaccine
## Current HPV Vaccines: VLP Vaccines

<table>
<thead>
<tr>
<th>Vaccine/Manufacturer</th>
<th>HPV Types</th>
<th>Schedule</th>
<th>Adjuvant</th>
<th>Target Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadrivalent</td>
<td>6/11/16/18</td>
<td>0,1,6 mos</td>
<td>Alum</td>
<td>females &amp; males</td>
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<tr>
<td><em>Merck</em></td>
<td></td>
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<tr>
<td>Bivalent</td>
<td>16/18</td>
<td>0,1,6 mos</td>
<td>Alum and MPL (ASO4)</td>
<td>females</td>
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<tr>
<td><em>GSK</em></td>
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<tr>
<td>HPV type</td>
<td>Pre-cancerous Cervical Lesions</td>
<td>Cervical Cancer</td>
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<tr>
<td>Types 16, 18</td>
<td>50–70% 4–7</td>
<td>70% 8</td>
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<tr>
<td>Types 6, 11</td>
<td>90% 2, 3</td>
<td>34% 1</td>
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</tr>
</tbody>
</table>

Delivering promised benefits
The Australian Experience

- 48% Reduction of Genital Warts in all women <28 years old
  Maximum risk reduction for women <28 years

- 32% Reduction of Genital Warts in all women
  Vaccinating the recommended cohorts show an impact on all consulting women

- 18% Reduction of Genital Warts in all men
  Some risk reduction for men (Heterosexual Men) but not for Homosexual Men « Herd Immunity »

The high vaccination coverage is the major factor of a successful implementation of vaccination program

Fairley C K et al – Melbourne, Australia
The Australian Experience: Study Results

Vaccination program started July 2007

Proportion of new cases with Warts per quarter

-1.8%, P=0.03
+1.0%, P=0.43
-25.1, P=<0.001
P for change<0.001

-4.7%, P=0.34

Fairley C K et al – Melbourne, Australia 2009
## Efficacy Against HPV 6/11/16/18-related External Genital Lesions in MALES

<table>
<thead>
<tr>
<th>HPV 6/11/16/18-related</th>
<th>Efficacy, %</th>
<th>95% CI, %</th>
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</thead>
<tbody>
<tr>
<td>All EGL</td>
<td>90.4</td>
<td>69.2-98.1</td>
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<tr>
<td>Condylomas</td>
<td>89.4</td>
<td>65.5-97.7</td>
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<tr>
<td>PIN</td>
<td>100</td>
<td>0-100</td>
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</tbody>
</table>

Implications of HPV Vaccines

- Females are not protected if they have been infected with HPV prior to vaccination
- HPV vaccine does not protect against less common HPV types, not included in the vaccine
- Duration of protection, need for booster doses, not certain
- Routine vaccination of 11-12 year old girls will take decades to show a discernable effect on the incidence of cervical cancer; screening needs to continue for other women
Preliminary Evaluation of the Geneva Vaccination Program
# Estimated HPV burden in women in Geneva

<table>
<thead>
<tr>
<th>Oncogenic types</th>
<th>CIN 3/in situ</th>
<th>Cervical Cancer</th>
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</thead>
<tbody>
<tr>
<td>Non Oncogenic types&lt;br&gt;Genital Warts</td>
<td>Lower than CIN3</td>
<td>400 cases/yr</td>
</tr>
<tr>
<td>Calculations</td>
<td>?</td>
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</table>

Registre Genevois des Tumeurs, 2009
Earlier age of sexual debut in Europe

15–40% of 15 years old girls are sexually active

Vaccination Campaign

Aims & Population

- Resident of the Geneva canton
- Free vaccine if distributed in the organized programme « programme cantonal de vaccination » as defined in http://www.admin.ch/ch/f/as/2007/6839.pdt
- Best coverage for the best price ... and best expected decrease in HPV related disease in the cervix
Vaccination Campaign
Where... to be vaccinated

- Service de Sante Jeunesse/ Département de l’Instruction Publique
- Pediatrician/ Primary health care practitioner/ gynecologist
- Vaccination centers inside the Geneva University Hospital (HUG)
Vaccination Campaign
Cohorte

- September 2007:
  - potentially 22,693 candidates
  - Plus about 2,400 candidates of 11y.o. to add each year
  - Total for 2007-2009: 25,062 candidates
  - Mailed invitation to every eligible candidate
Vaccination Campaign
Preliminary Analysis: 33,460 doses


- 1 dose: 12,000 doses (90%)
- 2 doses: 11,500 doses (86%)
- 3 doses: 12,000 doses
Vaccination Campaign
Preliminary Analysis: 33,460 doses

% of vaccinated candidate according to age

- 1 dose
- 2 doses
- 3 doses

Age groups: 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11
Vaccination Campaign

who actually did the vaccination?

**Vaccination sites**

- **HUG**
- **Doctors**
- **SSJ**

Legend:
- 1 dose %
- 2 doses %
- 3 doses %
HPV Penetration Rate YTD June 2010: Comparison

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>F-CH</td>
<td>59.1</td>
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<tr>
<td>D-CH</td>
<td>30.6</td>
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<tr>
<td>I-CH</td>
<td>30.7</td>
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<tr>
<td>CH</td>
<td>37.7</td>
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</table>
Guideline Conclusions

Fitting vaccination with existing screening strategies
Adherence to cervical screening in the era of human papillomavirus vaccination

- Mathematical model of vaccination, screening, and disease incidence

- For a population with opportunistic screening and 30% vaccine coverage:
  - Screening rates in vaccinated women would have to decline by at least 80% before the incidence of cervical cancer would increase in the era since the introduction of the vaccine.

- In populations that have highly effective cervical screening programmes, incidence of cervical cancer starts to increase after smaller, but still substantial, decreases in screening.

- Introduction of vaccine is unlikely to lead to an increased incidence of cervical cancer as a result of diminished screening.

Cervical Cancer Screening at the vaccine age

- Cervical cancer screening – no change

- 30% of cervical cancers caused by HPV types not prevented by the quadrivalent HPV vaccine
- Vaccinated females could subsequently be infected with non-vaccine HPV types
- Coverage of the population never = 100%
- Sexually active females could have been infected prior to vaccination
Conclusions: Screening for Cervical Cancer Prevention

- Non vaccinated women:
  - Continue program / change to HPV screening

- Vaccinated women while sexually active:
  - HPV screening/continue program

- Vaccinated women while presexually active:
  - HPV screening
Where ...
Thank you!

Helmut Newton
Cervical Cancer Screening Guidelines

- First screen 3 years after first intercourse or by age 21
- Screen annually with regular Paps or every 2 years with liquid-based tests
- After three normal tests, can go to every three years
- Stop at 65-70 years with history of negative tests
- Still need annual check-ups

### Recommendations for HPV Vaccination October 2007

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</tbody>
</table>

**Main age**

**Catch up**

*HPV Today Issue No 14 2008*
Suggested Cost-Effectiveness Strategies
### Suggested Cost-Effectiveness Strategies

<table>
<thead>
<tr>
<th>Unvaccinated women</th>
<th>Screening</th>
<th>Triage</th>
<th>Cost x Qualy</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 21</td>
<td>Cytology x 3 y</td>
<td>HPV Test</td>
<td>78,000</td>
</tr>
<tr>
<td>At 30</td>
<td>HPV Test</td>
<td>Cytology</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Girls vaccinated at 12</th>
<th>Screening</th>
<th>Triage</th>
<th>Cost x Qualy</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 25</td>
<td>Cytology</td>
<td>HPV Test</td>
<td>41,000</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>If x 5 years</td>
</tr>
<tr>
<td>At 35</td>
<td>HPV Test</td>
<td>Cytology</td>
<td>188,000</td>
</tr>
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<td>If x 3 years</td>
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</tbody>
</table>

➢ More effective and more cost-effective than screening women all ages with PAP or PAP + HPV TRIAGE annually or bi-annually

Proposed New Screening Algorithm

Use of HPV TESTING as the primary screening test and of CYTOLOGY to triage HPV-positive women

WOMEN AGED 25 - 64 YEARS
HPV TEST

Negative

NORMAL
5 YEAR RECALL

Positive

CYTOLOGY

Normal or Borderline

≥ Mild

HPV & CYTOLOGY at 6 – 12 months

COLPOSCOPY

Cytology Negative
HPV Negative

NORMAL
5 YEAR RECALL

HPV Positive & Cytology < Mild
HPV Negative & Cytology Borderline

HPV & CYTOLOGY at 6 – 12 months

COLPOSCOPY

Cytology ≥ Mild

Demonstration of Immune Memory with an Antigen Challenge at Month 60

HPV 18

- Long lived plasma cells for sustained antibody
- Memory B cells for recall response

Anamnestic Response
Antigen Challenge

Vaccination Period

## HPV test vs Cytology: summary

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity CIN2</th>
<th>Specificity CIN2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-DNA</td>
<td>96%</td>
<td>92%</td>
</tr>
<tr>
<td>Cytology</td>
<td>53%</td>
<td>97%</td>
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</table>
Impact of Human Papillomavirus (HPV)-6/11/16/18 Vaccine on All HPV-Associated Genital Diseases in Young Women


<table>
<thead>
<tr>
<th>Endpoint and population</th>
<th>Vaccine group</th>
<th>Placebo group</th>
<th>% Reduction [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of women</td>
<td>No. of women with a lesion</td>
<td>Rate†</td>
</tr>
<tr>
<td>Negative to 14 HPV types population‡</td>
<td>4616</td>
<td>272</td>
<td>1.7</td>
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<tr>
<td>Any CIN1 or worse irrespective of causal HPV type</td>
<td>4616</td>
<td>77</td>
<td>0.5</td>
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<tr>
<td>Any CIN2 or worse irrespective of causal HPV type</td>
<td>4616</td>
<td>241</td>
<td>1.5</td>
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<tr>
<td>By lesion severity</td>
<td>4616</td>
<td>57</td>
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<td>CIN1</td>
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<td>CIN2</td>
<td>4616</td>
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<tr>
<td>CIN3</td>
<td>4616</td>
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<td>AIS</td>
<td>4689</td>
<td>29</td>
<td>0.2</td>
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<td>Any genital wart irrespective of causal HPV type</td>
<td>4689</td>
<td>25</td>
<td>0.2</td>
</tr>
<tr>
<td>Any VIN1 or ValveN1 irrespective of causal HPV type</td>
<td>4689</td>
<td>7</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>
HPV infection is most prevalent in young women

![Chart showing prevalence rates of HPV infection across different age groups.]

Prevalence rates of HPV infection:
- Total mucosal PV
- Oncogenic PV
- Wart-causing PV


Cumulative Incidence of HPV Infection among Female College Students, by Time Since Sexual Debut

Winer et al. Am J Epidemiol 2003;157
38% the first 12 months!
Loss of screening performance due to vaccination

- As successive cohorts of women are vaccinated, we will achieve a significant (50% +) reduction in the prevalence of the most significant cytologic abnormalities resulting in:
  
  Decrease in positive predictive value of cytology
  Increase in false positive rates will lead to overdiagnosis and over-treatment
  
  Negative impact on technician training and quality assurance (largely avoided by HPV tests)
Vaccination Campaign
Preliminary Analysis: 33,460 doses