Cervical Screening in Vaccinated and Unvaccinated Women

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UK audit - cases

• 62% of women with fully invasive cancer (age <70) had been screened within 5 years of diagnosis: 60% of squamous, 70% of adenocarcinoma.

• 10% of cases under age 65 were diagnosed >6 months after positive cytology.

• 52% had only negative smears
HPV
<table>
<thead>
<tr>
<th>HPV type</th>
<th>Number Positive (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 16 and related</td>
<td>HPV16</td>
<td>482 (53.0)</td>
</tr>
<tr>
<td></td>
<td>HPV 31</td>
<td>54 (5.9)</td>
</tr>
<tr>
<td></td>
<td>HPV 33</td>
<td>28 (3.1)</td>
</tr>
<tr>
<td></td>
<td>HPV 35</td>
<td>16 (1.8)</td>
</tr>
<tr>
<td></td>
<td>HPV 52</td>
<td>26 (2.9)</td>
</tr>
<tr>
<td></td>
<td>HPV 58</td>
<td>20 (2.2)</td>
</tr>
<tr>
<td>HPV 18 and related</td>
<td>HPV 18</td>
<td>140 (15.4)</td>
</tr>
<tr>
<td></td>
<td>HPV 39</td>
<td>15 (1.6)</td>
</tr>
<tr>
<td></td>
<td>HPV 45</td>
<td>81 (8.9)</td>
</tr>
<tr>
<td></td>
<td>HPV 59</td>
<td>15 (1.7)</td>
</tr>
<tr>
<td></td>
<td>HPV 68</td>
<td>11 (1.2)</td>
</tr>
<tr>
<td>Other</td>
<td>HPV 6/11</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td></td>
<td>HPV 56</td>
<td>16 (1.8)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td>26 (2.9)</td>
</tr>
<tr>
<td>Undetermined</td>
<td></td>
<td>14 (1.5)</td>
</tr>
<tr>
<td>Positive</td>
<td></td>
<td>907 (99.8)</td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Total Adequate</td>
<td></td>
<td>909 (100)</td>
</tr>
</tbody>
</table>

Impact of Vaccination

Invasive Cancer

- Estimated at 73% due to HPV 16/18 (all ages) by Clifford, 2005
- Potential for Cross-protection against 45/31 -- another 14% = 87%

CIN 3

- Moderate or worse cytology (Sergeant et al) - 53% in women of all ages
- In FUTURE I & II - 63.5% of women aged 15-26

Abnormal Smears

- 53% of high and 28% of low grade due to HPV 16/18
- Weighted average - 30% can be prevented by vaccination
## The English HPV vaccination programme

<table>
<thead>
<tr>
<th>Academic year HPV vaccine given</th>
<th>School Year 7</th>
<th>School Year 8</th>
<th>School Year 9</th>
<th>School Year 10</th>
<th>School Year 11</th>
<th>School Year 12</th>
<th>School Year 13</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Age 12-13</td>
<td></td>
<td></td>
<td>Age 15-16</td>
<td>Age 16-17</td>
<td>Age 17-18</td>
</tr>
<tr>
<td>2011/12</td>
<td></td>
<td>1/9/1998 to 31/8/1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Uptake of HPV vaccines

- HPV vaccine uptake rate varies by country
- School-based HPV vaccination programmes have the highest uptake rates

<table>
<thead>
<tr>
<th>Country</th>
<th>3rd dose vaccine uptake %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia(^1)</td>
<td>70.0(^*)</td>
</tr>
<tr>
<td>Canada(^2)</td>
<td>80(^†)</td>
</tr>
<tr>
<td>England (UK)(^3)</td>
<td>80.1</td>
</tr>
<tr>
<td>USA(^4)</td>
<td>17.9(^‡)</td>
</tr>
</tbody>
</table>

* All school cohorts vaccinated in New South Wales and Victoria
† Atlantic provinces
‡ General practice vaccination of 13–17-year-olds

Predicted impact of UK vaccination programme: cytological abnormalities

Predicted reduction in cytological abnormalities (with 80% vaccination coverage)

In population screened from age 20

Predicted impact of UK vaccination programme: CIN3

Predicted reduction in CIN3 (with 80% vaccination coverage)

<table>
<thead>
<tr>
<th>Year of diagnosis</th>
<th>Annual CIN3 rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>350</td>
</tr>
<tr>
<td>2012</td>
<td>300</td>
</tr>
<tr>
<td>2014</td>
<td>250</td>
</tr>
<tr>
<td>2016</td>
<td>200</td>
</tr>
<tr>
<td>2018</td>
<td>150</td>
</tr>
<tr>
<td>2020</td>
<td>100</td>
</tr>
<tr>
<td>2022</td>
<td>50</td>
</tr>
<tr>
<td>2024</td>
<td>0</td>
</tr>
</tbody>
</table>

Age 20–24

In population screened from age 20

Age 25–29

Effect of vaccine over time – invasive cancer

Invasive cancer in women aged 20-29 years

Cervical cancer rate per 100,000

Year of diagnosis

Coverage 100% —— 80% —— 70%

Cuzick et al, Br J Cancer 2010
Potential Role of HPV Testing in Cervical Screening

• Primary Screening
  – Adjunct to Cytology
    ▪ Higher Sensitivity
    ▪ Longer Screening Interval
    ▪ Reduced Inadequate Rate
  – Sole Primary Test
    ▪ Use of Cytology for Triage
  – Self Sampling
    ▪ Improved Coverage
Baseline Results of HPV Testing in European & North American Screening Studies

Jack Cuzick
Christine Clavel, Ulli Petry, Peter Sasieni
Chris Meijer, Sam Ratnam
Philippe Birembaut, Anne Szarewski
Shalini Kulasingam, Heike Hoyer
Thomas Iftner

Int J Cancer 119:1095-1101, 2006
Cytology Sensitivity - CIN2+ (all ages)

Cytology Positivity

HART
Tuebingen
Hannover
Jena
French Public
French Private
Seattle
Canada
Combined
## Summary

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV</td>
<td>96%</td>
<td>92%</td>
</tr>
<tr>
<td>CYTOLOGY</td>
<td>53%</td>
<td>97%</td>
</tr>
</tbody>
</table>
## Double-testing studies after overview (CIN2+)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Italian Phase I</strong></td>
<td>HPV</td>
<td>97.3</td>
</tr>
<tr>
<td>(experimental arm)</td>
<td>Cytology</td>
<td>74.0</td>
</tr>
<tr>
<td><strong>Canadian</strong></td>
<td>HPV</td>
<td>94.6</td>
</tr>
<tr>
<td></td>
<td>Cytology</td>
<td>55.4</td>
</tr>
</tbody>
</table>
Relative Sensitivity of HPV vs cytology for CIN2+ in randomised trials

Arbyn et al Lancet Oncol 2009
Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: Joint European cohort study

Joakim Dillner, Matejka Rebolj, Philippe Birembaut, Karl-Ulrich Petry, Anne Szarewski, Christian Munk, Silvia de Sanjose, Pontus Naucler, Belen Lloveras, Susanne Kjaer, Jack Cuzick, Marjolein van Ballegooijen, Christine Clavel, Thomas Iftner,

Br Med J. 2008
Cumulative incidence rate for CIN3+ according to baseline test results excluding Denmark and Tubingen

CIN3+ rates after a negative screening test

- Cytology @ 3 yrs: 0.51% (0.23 – 0.77%)
- HPV @ 6 yrs: 0.27% (0.12 – 0.45%)
Proposed New Screening Algorithm

Women aged 25-64 y
HPV Test

Negative

Normal 5 Year Recall

Positive

Cytology

Normal or Borderline

≥ Mild

HPV & Cytology at 6-12 months

Colposcopy

Cyto Neg
HPV Neg
Normal 5 Year Recall

HPV Pos & Cyto < Mild
HPV Neg & Cyto Borderline

HPV & Cytology at 6-12 months

Cyto ≥ Mild

Colposcopy
Potential Future Screening Algorithm

Women aged 25-64 y
Sensitive HPV Test

Negative
- Normal 5 Year Recall

Positive
- Cytology
  - Normal, border or Mild
    - HPV 16 typing mRNA p16
      - Negative: 3-5 Year Recall
      - Any positive: Colposcopy
  - ≥ Moderate
    - Colposcopy
Screening – Post Vaccination

• Lower Prevalence of CIN2+ due to lack of HPV 16/18 induced lesions
  
  – Decreased PPV
    o True positives decreased – false positives unchanged
  
  – Decreased Sensitivity for cytology
    o Abnormalities rarer – loss of concentration
Screening – Post Vaccination

• Screening less cost effective

• Objective, automated methods of HPV testing will be even more important for low prevalence setting

• May be a role for computer assisted cytology based primary screening (with new IHC markers) – not yet proven
Screening – Post Vaccination

• Longer screening intervals
  – Requires knowledge of vaccination history
  – Older women beyond vaccination age still need screening for 40+ years

• Self – Sampling ??
  – Only sensitive with HPV testing
Screening – Post Vaccination

- Better (more specific, but highly sensitive) molecular markers for testing?
  - HPV typing
  - HPV mRNA testing
  - Proliferation markers (mcm)
  - Improved cytology
    - Computer assisted reading
    - p16
    - Proliferation markers
Cervical cancer is preventable!

- Cervical cancer is the only cancer with a single, known cause - the Human Papillomavirus
- Only when infection with high-risk types persists can cervical cancer develop
- Vaccination can prevent infection (currently against HPV 16/18), but not eliminate it once it occurs
- Screening can identify precursor lesions which are treatable
Overall Conclusions

• Vaccines are effective, but are mostly for the next generation of women
  – Current generation of women will need screening

• Screening will be more difficult and less cost effective in vaccinated women
  – Longer intervals and ? Self sampling?
  – Registries of vaccinated women needed to inform screening

• Screening will benefit from use of HPV testing as the primary screen
  – Newer more specific tests even more critical
  – HPV testing before vaccination in women aged 16+ ?

• Until truly multivalent vaccines become widely available, screening will remain an important part of cervix cancer prevention