Elimination of Cervix Cancer

Novel Options combining Vaccination and HPV Screening

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Wolfson Institute of Preventive Medicine
St Bartholomew’s Medical School
London, UK
Disclosure of interests

• Jack Cuzick has received honoraria from Qiagen, Roche, Abbott, Becton Dickinson, Gen-Probe, GSK and Merck as a consultant, speaker or advisory board member
The Nobel Prize in Physiology or Medicine 2008 was divided, one half awarded to Harald zur Hausen "for his discovery of human papilloma viruses causing cervical cancer", the other half jointly to Françoise Barré-Sinoussi and Luc Montagnier "for their discovery of human immunodeficiency virus"
PERCENTAGES OF CERVICAL CANCER CASES ATTRIBUTED TO THE MOST FREQUENT HPV TYPES IN ALL WORLD REGIONS COMBINED

(A) IARC ANALYSIS OF 3,085 CASES

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Cumulative</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-16</td>
<td>53.5</td>
<td>53.5</td>
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<tr>
<td>HPV-18</td>
<td>17.2</td>
<td>70.7</td>
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<td>HPV-45</td>
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<td>HPV-52</td>
<td>2.3</td>
<td>85.2</td>
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<td>HPV-58</td>
<td>2.2</td>
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<tr>
<td>HPV-35</td>
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<tr>
<td>HPV-59</td>
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<td>HPV-39</td>
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<td>HPV-68</td>
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<td>93.7</td>
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<td>HPV-73</td>
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<td>94.2</td>
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<td>HPV-82</td>
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<td>HPV X</td>
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(B) META-ANALYSIS OF 14,500 CASES

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<td>Other</td>
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<td>HPV X</td>
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</tbody>
</table>
Screening

Mortality rate per 100,000 women

Age (yr)

20-24
30-34
40-44
50-54
60-64
70-74

Mortality rate per 100,000 women

0
5
10
15
20

1910-14
1920-24
1930-34
1940-44
1950-54
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
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
<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>HPV</td>
<td>96%</td>
<td>92%</td>
</tr>
<tr>
<td>CYTOLOGY</td>
<td>53%</td>
<td>97%</td>
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</tbody>
</table>
Double-testing studies after overview

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Sensitivity (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Kotaniemi, 2005</td>
<td>1.46 (0.68, 3.14)</td>
</tr>
<tr>
<td>Sankaranarayan, 2005</td>
<td>0.91 (0.80, 1.03)</td>
</tr>
<tr>
<td>Ronco, 2006</td>
<td>1.60 (1.22, 2.11)</td>
</tr>
<tr>
<td>Bulk, 2007</td>
<td>1.64 (1.17, 2.31)</td>
</tr>
<tr>
<td>Mayrand, 2007</td>
<td>1.74 (0.85, 3.56)</td>
</tr>
<tr>
<td>Naucler, 2007</td>
<td>1.50 (1.13, 2.01)</td>
</tr>
</tbody>
</table>

Overall (95% CI): 1.40 (1.03, 1.90)
Cumulative incidence rate for CIN3+ according to baseline test results excluding Denmark and Tubingen

### NTCC - INVASIVE CERVICAL CANCER

<table>
<thead>
<tr>
<th></th>
<th>HPV group</th>
<th>Cytology group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening round one</td>
<td>7</td>
<td>9</td>
<td>0.62</td>
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<tr>
<td>Screening round two</td>
<td>0</td>
<td>9</td>
<td>0.004</td>
</tr>
<tr>
<td>Total over first two</td>
<td>7</td>
<td>18</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Source: Ronco et al. Lancet Oncol 2009
Proposed New Screening Algorithm

Women aged 25-64 y
HPV Test

Negative
Normal 5 Year Recall

Positive
Cytology

Cyto Neg
HPV Neg
Normal 5 Year Recall

HPV Pos & Cyto < Mild
HPV Neg & Cyto Borderline

HPV & Cytology
at 6-12 months

≥ Mild
Colposcopy

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 p16
        - Negative
          - 3-5 Year Recall
        - Any positive
          - Colposcopy
      - ≥ Moderate
        - Colposcopy
Vaccination
## Merck Vaccine trials

<table>
<thead>
<tr>
<th>Protocol</th>
<th>005 Proof of Principle</th>
<th>007 FUTURE I</th>
<th>013 FUTURE I</th>
<th>015 FUTURE II</th>
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</thead>
<tbody>
<tr>
<td>Phase</td>
<td>IIa</td>
<td>IIb</td>
<td>III</td>
<td>III</td>
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<tr>
<td>No entered</td>
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<td>552</td>
<td>5455</td>
<td>12167</td>
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<td>Sites</td>
<td>USA</td>
<td>International</td>
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<td>International</td>
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<tr>
<td>HPV types</td>
<td>16</td>
<td>6,11,16,18</td>
<td>6,11,16,18</td>
<td>6,11,16,18</td>
</tr>
<tr>
<td>Age</td>
<td>16-23</td>
<td>16-23</td>
<td>16-23</td>
<td>16-26</td>
</tr>
<tr>
<td>No Sex partners</td>
<td>0-5</td>
<td>0-4</td>
<td>0-4</td>
<td>0-4</td>
</tr>
<tr>
<td>Average FU</td>
<td>3.5y</td>
<td>2.5y</td>
<td>2.5y</td>
<td>2.5y</td>
</tr>
</tbody>
</table>
Merck- Quadrivalent HPV Vaccination Trial  
FUTURE II

12,167 women aged 15-26

HPV 6,11,16,18, VLP @ 0, 2, 6 mo

Any CIN2+ 219
HPV 16/18 CIN2+ 83

Completed Vaccine per protocol - 5305
HPV 16/18 CIN2+ 1

6087

36m Median FU
17% (1-31)
44% (26-58)

98% (86-100)

6080

Placebo Vaccine

Any CIN2+ 266
HPV 16/18 CIN2+ 148

Completed Vaccine per protocol - 5260
HPV 16/18 CIN2+ 42

(Koutsky, et al, NEJM, 2007)
• Nonavalent Vaccine in late development by Merck
  – HPV16,18
  – HPV 6,11 (genital warts)
  – 5 new oncogenic types – 31,33,45,52,58
GSK Phase 3 Study - PATRICIA

(PPapilloma TRIal against Ccancer In young Adults)

End of Study Analysis

- Phase III efficacy trial* conducted in 14 countries¹ from: Europe, Asia-Pacific, North America, Latin America

Randomization
Age 15–25 years
N=18,644

HPV-16/18 vaccine
Control (Hepatitis A vaccine)

Month 0 1 6 7 12 18 24 30 36 48
Visit 1 2 3 4 5 6 7 8 9 10

Interim Analysis²
Mean follow-up 14.8 months (TVC-E)

Final Analysis¹
Mean follow-up 39.5 months (TVC-naive)

End of study Analysis
Mean follow-up 44.2 months (TVC-naive)

² Paavonen J et al. Lancet 2007; 369: 2161–70

*Study HPV-008 -NCT00122681
Number of cases of CIN2+ and CIN3+ associated with vaccine and non-vaccine types in the TVC-naive

Lehtinen et al Lancet Oncol 2012 1:89-99
Vaccine - Issues

• Need for 3 doses
• Cross - protection
• Durability of protection
• Age groups – focus adolescent girls
• Vaccination of boys
• More rugged vaccines not needing careful cold chain storage
• Not effective after HPV infection
Potential future opportunities for HPV vaccination

- **Cervical cancer prevention: improved vaccination coverage**
  - Extending the age range for vaccination (paediatrics and adult women)
  - Alternative dose schedules, e.g. two doses\(^1\)

- **Vaccinate and screen algorithms for older women**
  - Screen to remove all current disease
  - Vaccine esp with polyvalent vaccines to prevent future disease

- **Next-generation HPV vaccines**
  - Polyvalent L1 virus-like particle (VLP) vaccines\(^2\)
  - L2 peptide vaccines\(^2\)
  - Chimeric L1/L2 VLP HPV vaccines\(^3\)
  - Combined prophylactic and therapeutic HPV vaccination\(^2\)

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Screen and Vaccinate Trial Schema

Women aged 25-50 y Attending screening

HPV based screening + HPV Vaccine (first dose)

1 mo - treat HPV+ and 2nd dose
5 yr repeat HPV test

HPV based screening

1 mo - treat cyto/HPV+
5 yr repeat HPV test
Cervical cancer is preventable!

- Cervical cancer is the only cancer with a single, known cause: the human papillomavirus (HPV)
- Vaccination can prevent infection, but not eliminate it or subsequent cancer once it occurs
- Screening can identify precursor lesions which are treatable and HPV testing has a sensitivity approaching 100%
- Combined screening and vaccination in women aged 25-50 offers the best chance of rapid elimination of cervix cancer