Cervical Cancer, HPV, and the Vaccine
Dr. Tito Lopes, Royal Cornwall Hospitals Trust
A Webber Training Teleclass

Overview
- Cervical cancer
- Screening
- HPV
- The vaccine

Cervical cancer
- Cervical Cancer in the UK
  - 13th most common cancer in women in 2005
  - 2,863 women developed invasive cervical cancer in 2005
  - 950 deaths from the disease in 2006
- Cervical Cancer Worldwide
  - Second most common cancer in women after breast cancer
  - 500,000 new cases a year
  - 270,000 deaths

The Nobel Prize in Physiology or Medicine 2008
Herald zur Hausen
- For his discovery of human papilloma viruses causing cervical cancer

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Cervical screening - the ‘Pap’ smear

Natural history of cervical cancer

Deaths from cervical cancer in England in relation to screening coverage

The NHS Cervical Screening Programme in England 2004 - 05

Limitations of cervical cytology screening

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Cervical cancer and the Human papilloma virus (HPV)

- Press Release WHO/47 3 July 1996
- CERVICAL CANCER:
  - Experts confirmed virus a major cause, new detection technologies available
  - Experts have formally labelled the human papilloma virus (HPV) types 16 and 18 as "carcinogenic to humans", HPV types 31 and 33 as "probably carcinogenic", and suggested that some other HPV types were "possibly carcinogenic".

- 99.7% of cervical cancers contain HPV DNA

Human Papilloma Virus

- Member of the Papovaviridea family – two strands of DNA with a spherical protein shell, the capsid
- There are more than 100 types of HPV – approximately 40 can infect the genital tract and of these about 10 are carcinogenic
- Two genes in the circular genome of papillomaviruses, E6 and E7 are well established oncogenes that are the causative factors in cervical cancer.

Genital ‘high risk’ HPV infection – natural history

- Infection is caused by skin to skin contact
- 75% lifetime risk of infection
- Prevalence greatest (approx 50%) in women under 25 years
- Infections usually transient (80%)
  - asymptomatic & resolve spontaneously
- Some become persistent – ↑ risk of cancer

HPV types in cervical cancer – all world regions

HPV types in cervical cancer – by regions

The role of HPV and cancer

Assembly of papillomavirus virus-like particles (VLPs)

Prophylactic HPV vaccines: Virus Like Particles (VLPs)

Prophylactic HPV vaccines: Virus Like Particles (VLPs)

Development of HPV vaccines

- Discovery of self assembly of L1 coat protein into virus-like proteins (VLP)
- Animal studies - cottontail rabbit papillomavirus (CRPV) - canine oral papillomavirus (COPV)
- Vaccine manufacture - vaccine components - expression systems - adjuvants
- Clinical trials - proof of principle - safety - immunogenicity - effectiveness

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HPV-11 neutralising response to HPV-11 VLPs

Immunization with HPV VLPs elicits a vigorous serum immune response in a high percentage of women.

Current HPV vaccines
Sanofi Pasteur MSD quadrivalent vaccine HPV 16/18/6/11 + Alum
- Gardasil® (FDA approval June 2006)
- GSK bivalent vaccine HPV 16/18 + novel adjuvant (AS04)
- Cervarix® (EU approval Sept 2007)
- Both involve 3 dose regimen

Trials - End points
- Immunogenicity
- Efficacy
  - Incident type specific infections (6, 12 months)
  - Persistent type specific infections (6, 12 months)
  - Cytological abnormality
  - CIN (CIN2/3 = WHO and FDA endpoints for trials)
- Safety

Immunogenicity - Gardasil
HPV 16 L1 VLP vaccine component of GARDASIL.


Immunogenicity - Cervarix
Harper – Lancet 2008, Sustained efficacy

Vaccine efficacy - Cervarix
HPV 16/18 related events
Histology

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine</th>
<th>Total</th>
<th>Event</th>
<th>Vaccine efficacy, % (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ASCUS</td>
<td>505</td>
<td>2</td>
<td>497</td>
<td>95.7 (83.5 to 99.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥LSIL</td>
<td>505</td>
<td>2</td>
<td>497</td>
<td>92.6 (70.5 to 99.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CIN1+</td>
<td>481</td>
<td>0</td>
<td>470</td>
<td>100.0 (42.4 to 100.0)</td>
<td>0.0035</td>
</tr>
<tr>
<td>CIN2+</td>
<td>481</td>
<td>0</td>
<td>470</td>
<td>100.0 (-7.7 to 100.0)</td>
<td>0.0292</td>
</tr>
</tbody>
</table>

Sample endpoint for WHO & FDA

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Vaccine efficacy - Gardasil

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine cases</th>
<th>Placebo cases</th>
<th>Vaccine efficacy, % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN3</td>
<td>0</td>
<td>47</td>
<td>100 (92 to 100)</td>
</tr>
<tr>
<td>AIS</td>
<td>0</td>
<td>9</td>
<td>100 (49 to 100)</td>
</tr>
<tr>
<td>HPV 6/11/16/18 related external genital lesions (VIN, VaIN &amp; genital warts)</td>
<td>0</td>
<td>40</td>
<td>100 (88 to 100)</td>
</tr>
</tbody>
</table>

www.cdc.gov/nip/acip/slides/jun06/hpv-2-barr.pdf

Safety: Serious adverse events in phase 2 trials

GSK
2006 Harper – Sustained efficacy
Unrelated adverse event
number of women with at least 1 SAE
Vaccine (n=373) Placebo (n=371)
16 (4%) 19 (5%)

MSD
Adverse events reported
Vaccine (n=272) Placebo (n=274)
2 (1%) 2 (1%)

Prophylactic HPV L1 VLP vaccines

Efficacy
>90% for persistent infection
100% for disease (5 years post vaccination) in subjects naive for vaccine HPV types

Immunogenic
high antibody concentrations up to 1000x > than in natural HPV infection

Duration of protection
vaccine induced antibody levels maintained over 5 years

Safe
no vaccine related serious adverse events identified in the trials to date (70,000 women)

Safety: Serious adverse events - post licensure

- Thromboembolic
- Guillain-Barré syndrome
- Death

- MSD - 30 million doses distributed, at least 8 million in USA have received 1 dose

Outline of the HPV vaccination programme

- Girls aged 12-13 years (school year 8) will be immunised routinely, starting from September 2008.
- A catch-up programme, over two years, will start in autumn 2009:
  - girls aged 16 to 18 (years 12 and 13) will be offered immunisation in 2009/2010
  - girls aged 15 to 17 (years 11 and 12) will be offered immunisation in 2010/2011.
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Uptake of Cervarix in the UK

<table>
<thead>
<tr>
<th>Age</th>
<th>1st dose</th>
<th>2nd dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-13</td>
<td>84.3%</td>
<td>78.2%</td>
</tr>
<tr>
<td>17-18</td>
<td>78.2%</td>
<td>28%</td>
</tr>
</tbody>
</table>

Scotland

<table>
<thead>
<tr>
<th>Age</th>
<th>1st dose</th>
<th>2nd dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-13</td>
<td>93.3%</td>
<td>92.2%</td>
</tr>
<tr>
<td>17-18</td>
<td>89.5%</td>
<td>87.8%</td>
</tr>
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</table>

Monitoring - MHRA (May 09)

<table>
<thead>
<tr>
<th>SAE</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site (pain/swelling)</td>
<td>573</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>343</td>
</tr>
<tr>
<td>Psychogenic (syncope/dizzy)</td>
<td>988</td>
</tr>
<tr>
<td>Others (nausea/headache/dizzy)</td>
<td>1383</td>
</tr>
<tr>
<td>Not currently recognised (1GB)</td>
<td>394</td>
</tr>
</tbody>
</table>

At least 800,000 doses

Cross Protection

<table>
<thead>
<tr>
<th>Number of types</th>
<th>HPV type</th>
<th>Cumulative %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HPV 16</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>+ HPV 18</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>+ HPV 45</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>+ HPV 31</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>+ HPV 33</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>+ HPV 58</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>+ HPV 52</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>+ HPV 35</td>
<td>95</td>
</tr>
</tbody>
</table>

The Future?

- Developed countries
- Developing countries
- Increased HPV subtypes in the vaccine
- Different administration routes

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The Future?

• Developed countries
• Developing countries
• Increased HPV subtypes in the vaccine
• Different administration routes

The Future?

• Developed countries
• Developing countries
• Increased HPV subtypes in the vaccine
• Different administration routes
• Prevention of cervical cancer!

Impact on HPV 16/18-Related CERVICAL CANCER INCIDENCE with 16/18 Vaccine and Vaccine Lifetime Coverage Starting at Age 12 Years

Impact on HPV 16/18-Related CIN 2/3 INCIDENCE with 16/18 Vaccine and Vaccine Lifetime Coverage Starting at Age 12 Years

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