HPV vaccine and cervical cancer prevention

A. Meheus & C. Dochez

SAVIC-Gauteng 2009 EPI symposium - Introduction of new vaccines into national immunisation programmes.
Johannesburg, South Africa, 2-3 February 2009
Outline of presentation

- Cervical cancer
- Human papillomavirus (HPV)
- HPV vaccines
- Public health considerations
Cervical cancer worldwide

- 493,000 women affected each year
- 274,000 deaths annually
- Cervical cancer is the second largest cause of cancer deaths in women worldwide
- 80% are in developing countries (>90% by 2020)
- Cervical cancer is a global public health problem that disproportionately affects poor women in developing countries
- Cervical cancer is the first cause of cancer in African women
- 6742 new cases annually in South Africa
- 3681 deaths annually in South Africa
Cervical cancer screening

- Incidence and mortality of cervical cancer much reduced in industrialised countries by screening based on cervical cytology (Pap smears) - less impact on adenocarcinoma
- Screening programmes difficult to implement in low-resource settings
- “Opportunistic” screening is not very effective; should be well organised programmes with high coverage (call/recall system)
Improvements in Screening Coverage Can Reduce the Incidence of Cervical Cancer


Cervical cancer and Human Papillomavirus

- 1980s → discovery of link between cervical cancer and HPV - Prof. Harald Zur Hausen (Heidelberg, Germany) got the Nobel Prize for this last year
- Chronic infection with high-risk or oncogenic HPV types are essential for the development of cervical cancer
- Oncogenic HPV detected in more than 99% of cervical cancers
Cervical cancer is caused by a virus called the Human Papillomavirus

- Small, double-stranded DNA viruses that infect the epithelium.
- Icosohedral viral capsid is composed of two proteins, L1 and L2.
- More than 100 HPV types identified based on the genetic sequence of the outer capsid protein L1.
- Most HPV types infect cutaneous epithelium.
- 40 types infect the mucosal epithelium.

The rosette-like surface structures (arrowed) are pentamers each consisting of five molecules of L1; one molecule of L2 fits into the centre of each pentamer.

High risk or oncogenic HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82
→ 16 and 18 cause 70% of cervical cancer

3 HPV types classified as probable high-risk types: 26, 53, 66

Low risk or non-oncogenic types: 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108
→ 6 and 11 cause genital warts
Estimates of global burden of HPV associated cancer

- 100% cervical cancers
- 90% anal cancers
- 40% of cancers of the vulva, vagina and penis
- 12% of cancers of the oropharynx
- 3% of cancers of the mouth

Cutts et al., 2007, Bulletin of WHO
HPV genotype distribution in cervical cancer: worldwide estimates (N=469,723)

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Percentage</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>53.5%</td>
<td>251,199</td>
</tr>
<tr>
<td>18</td>
<td>70.7%</td>
<td>80,859</td>
</tr>
<tr>
<td>45</td>
<td>77.4%</td>
<td>31,549</td>
</tr>
<tr>
<td>31</td>
<td>80.3%</td>
<td>13,678</td>
</tr>
<tr>
<td>33</td>
<td>82.9%</td>
<td>12,134</td>
</tr>
<tr>
<td>52</td>
<td>85.2%</td>
<td>10,929</td>
</tr>
<tr>
<td>58</td>
<td>87.4%</td>
<td>10,242</td>
</tr>
<tr>
<td>35</td>
<td>88.8%</td>
<td>6,570</td>
</tr>
<tr>
<td>59</td>
<td>6.137</td>
<td>5,769</td>
</tr>
<tr>
<td>56</td>
<td>1.22</td>
<td>4,641</td>
</tr>
<tr>
<td>51</td>
<td>1.00</td>
<td>3,211</td>
</tr>
<tr>
<td>39</td>
<td>3.21</td>
<td>2,714</td>
</tr>
<tr>
<td>68</td>
<td>6.07</td>
<td>2,339</td>
</tr>
<tr>
<td>73</td>
<td>6.07</td>
<td>1,350</td>
</tr>
<tr>
<td>82</td>
<td>6.07</td>
<td>5,632</td>
</tr>
<tr>
<td>Other</td>
<td>0.13</td>
<td>20,769</td>
</tr>
</tbody>
</table>

G. Clifford et al. / Vaccine 24S3 (2006) S3/26–S3/34
HPV infection and cervical cancer

- Almost all Cervical Cancer is due to high-risk HPV
- Up to 80% of women will acquire an HPV infection in their lifetime\(^1,2\) and 50% of these infections will be with a high-risk HPV type\(^3\)
- HPV infection often acquired within 2-5 years after sexual debut
- Most infections are asymptomatic and are cleared within 2 years
- Only a fraction of women (chronically) infected with high-risk HPV will develop cervical cancer, most infections resolve spontaneously

1. Bosch FX, de Sanjose S. *J Natl Cancer Inst Monogr* 2003; 3-13
Natural history of HPV infection

Infection of the cervix with HR-HPV

Temporary HPV-infection

Persistent HPV-infection

CIN* 1

CIN 2/3

Clearance of HPV

Cervical cancer

*CIN: cervical intraepithelial neoplasia

Adopted from Burgmeijer et al. 2007
Progression to Cervical Cancer

Within months after sexual debut

Years

Normal epithelium

HPV infection; koilocytosis

CIN I

CIN II

CIN III

Carcinoma

Low-grade squamous intraepithelial lesions (LSILs)

High-grade squamous intraepithelial lesions (HSILs)

80%

20%

1%
Antibody responses are relatively poor after natural HPV infection

- Only 50-60% of women develop serum antibodies to HPV after natural infection
- No viraemia
- HPV does not induce cell death
  - no inflammation
  - no pro-inflammatory cytokines
  - downregulation of antiviral pathways in the cell
  - poor activation of epithelial antigen presenting cells (APC)
  - free virus particles are shed from mucosal surfaces with poor exposure to APCs

Risk factors

- Persistent infection with high risk (oncogenic) HPV is the necessary cause of cervical cancer

- Factors that could be adding to the risk of persistent HPV infection and cervical cancer:
  - Smoking
  - High parity
  - Long-term use of oral contraceptives
  - Immuno-suppression

HPV and HIV

- Prevalence of HPV infection much higher in HIV infected women
- Higher HPV viral load in HIV infected women
- Infection with multiple HPV genotypes is more common in HIV positive women
- HIV positive women at greater risk of lower genital tract cytological/histological abnormalities and (pre) cancers including vulvar and anal cancers.
- HIV positive women with invasive cervical cancer almost 5-10 years younger than HIV sero-negative women.
Role of vaccination

STOP INFECTION BEFORE IT STARTS – PREVENT WITH VACCINATION

Normal epithelium

HPV infection; koilocytosis

CIN I

CIN II

CIN III

Carcinoma

Low-grade squamous intraepithelial lesions (LSILs)

High-grade squamous intraepithelial lesions (HSILs)
Human Papillomavirus-Like Particles as HPV Vaccines

- Prophylactic vaccines are based on recombinant L1 proteins self-assembled into VLPs.
- L1 is expressed in yeast or baculovirus expression systems, and the protein self-assembles into virus-like-particles (VLP).
- VLPs are non-infectious (contain no DNA) and non-oncogenic.
- Safe, immunogenic and well tolerated
<table>
<thead>
<tr>
<th>Quadrivalent vaccine</th>
<th>Bivalent vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Produced in Yeast</td>
<td>Baculovirus expression system</td>
</tr>
<tr>
<td>HPV types 6, 11, 16, 18,</td>
<td>HPV types 16,18</td>
</tr>
<tr>
<td>Protects against cervical Neoplasia caused by HPV 16 and 18 - some cross protection against other HPV types</td>
<td>Protects against cervical Neoplasia caused by HPV 16 and 18 - some cross protection against other HPV types</td>
</tr>
<tr>
<td>Protects against genital warts caused by HPV 6 and 11</td>
<td>Does not prevent genital warts</td>
</tr>
<tr>
<td>Adjuvant: aluminium hydroxyphosphate sulphate</td>
<td>Adjuvant: ASO4 (aluminium hydroxide and 3-deacylated monophosphoryl lipid A)</td>
</tr>
<tr>
<td>Schedule 0, 2, 6 months</td>
<td>Schedule: 0, 1, 6 months</td>
</tr>
<tr>
<td>Intramuscular injection</td>
<td>Intramuscular injection</td>
</tr>
<tr>
<td>Liquid, storage 2°C - 8°C; must not be frozen</td>
<td>Liquid, storage 2°C - 8°C; must not be frozen</td>
</tr>
</tbody>
</table>
Both vaccines are highly immunogenic and produce high levels of antibodies that are substantially greater than those produced during natural infections.

- Antibody levels after vaccination inversely related to age.
- Antibody levels in young adolescents in bridging studies (9-14 years old) higher than in adolescents/young adults (15-25 years old).
HPV vaccines: Immunogenicity/safety

- Duration of protection up till 6.4 years
- Experimental booster after 5 years showed immunologic memory
- Safety profile (adverse events):
  - Mild local reactions: pain, swelling
  - Fever, nausea
  - No differences in the proportion of women developing a serious adverse event in the vaccine or placebo group
# Bivalent HPV vaccine
Protection against HPV 16/18 CIN 2/3+

776 women, 15-25 years of age at time of vaccination

<table>
<thead>
<tr>
<th>HPV 16/18 related CIN2+</th>
<th>Bivalent vaccine</th>
<th>Control</th>
<th>Vaccine efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>27 months(^1)</td>
<td>0</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>4.5 years(^2)</td>
<td>0</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>5.5 years(^3)</td>
<td>0</td>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td>6.4 years(^4)</td>
<td>0</td>
<td>9</td>
<td>100</td>
</tr>
</tbody>
</table>

3. Presentation Gall 2007, AACR, abstract 4900
4. Presentation Harper 2008, SGO.
ELISA titers through 6.4 years after bivalent HPV vaccination

More than 98% of women remain seropositive for both HPV-16 and 18 up to 6.4 years

Bivalent vaccine

Cross protection against 6 months persistent infection - phase III study

<table>
<thead>
<tr>
<th>Causal HPV type</th>
<th>Vaccine N</th>
<th>Vaccine Cases</th>
<th>Placebo N</th>
<th>Placebo Cases</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 45</td>
<td>6734</td>
<td>10</td>
<td>6747</td>
<td>25</td>
<td>59.9</td>
</tr>
<tr>
<td>Type 31</td>
<td>6615</td>
<td>47</td>
<td>6667</td>
<td>74</td>
<td>36.1</td>
</tr>
<tr>
<td>Type 33</td>
<td>6702</td>
<td>31</td>
<td>6736</td>
<td>49</td>
<td>36.5</td>
</tr>
<tr>
<td>Type 52</td>
<td>6532</td>
<td>79</td>
<td>6573</td>
<td>116</td>
<td>31.6</td>
</tr>
<tr>
<td>Type 58</td>
<td>6688</td>
<td>43</td>
<td>6734</td>
<td>33</td>
<td>-31.4</td>
</tr>
</tbody>
</table>

Quadrivalent HPV vaccine efficacy
CIN & AIS
Per-protocol population (protocols 007, 013, 015)
End-of-study data, mean follow-up 44 months

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine</th>
<th>Placebo</th>
<th>% Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=9075</td>
<td>N=9075</td>
<td></td>
</tr>
<tr>
<td>HPV 6/11/16/18 related CIN or AIS</td>
<td>9</td>
<td>225</td>
<td>96</td>
</tr>
<tr>
<td>By Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 6-related</td>
<td>0</td>
<td>47</td>
<td>100</td>
</tr>
<tr>
<td>HPV 11-related</td>
<td>0</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>HPV 16-related</td>
<td>8</td>
<td>137</td>
<td>94</td>
</tr>
<tr>
<td>HPV 18-related</td>
<td>1</td>
<td>61</td>
<td>98</td>
</tr>
<tr>
<td>By Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN 1</td>
<td>7</td>
<td>170</td>
<td>96</td>
</tr>
<tr>
<td>CIN 2/3</td>
<td>2</td>
<td>110</td>
<td>98</td>
</tr>
<tr>
<td>AIS</td>
<td>0</td>
<td>7</td>
<td>100</td>
</tr>
</tbody>
</table>

Haupt, presented at Feb 2008 ACIP meeting, Atlanta, GA
Quadrivalent vaccine: Five-year duration of antibody titers against HPV type 16

ACIP meeting, June 2006
## Quadrivalent vaccine

### Cross protection against CIN 2/3 and AIS

<table>
<thead>
<tr>
<th>Causal HPV types</th>
<th>Vaccine</th>
<th>Placebo</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>31, 45</td>
<td>N=4616</td>
<td>N=4680</td>
<td>59%</td>
</tr>
<tr>
<td>31,33,45,52,58</td>
<td>11</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>31,33,35,39,45,51,52,56,58,59</td>
<td>44</td>
<td>66</td>
<td>33%</td>
</tr>
<tr>
<td>31,33,35,39,45,51,52,56,58,59</td>
<td>62</td>
<td>93</td>
<td>33%</td>
</tr>
</tbody>
</table>

Adjuvants

HPV vaccine candidate formulated with AS04 induces higher frequency of memory B cells as compared to the same vaccine formulated with $\text{Al(OH)}_3$.

Giannini et al., Vaccine 2006; 24: 5937
Slide from Dr. Benninghoff
The risk for HPV infection starts from the first sexual encounter and lasts throughout a woman’s life\(^1,2\)

- Prophylactic vaccine, not therapeutic → optimal if used before sexual debut

1. Bosch FX, de Sanjose S. *J Natl Cancer Inst Monogr* 2003; 3-13
Ideal age group to vaccinate: 10-13 year old girls - not a standard target population (=adolescent vaccination).

Implement vaccination in a one year cohort every year, e.g. 10, 11 or 12 years old; can be implemented for girls in last year of primary school/first year of secondary school.

Catch-up vaccination in older adolescents and adult women?
  - Not recommended in a public health programme
  - Could be considered through private sector
Will targeting young adolescent girls for a vaccine to protect from a STI be a problem; communicate on HPV vaccine as a cancer prevention vaccine.

- Vaccinate both sexes?
  - Only modest benefit of male vaccination on herd immunity if coverage of females is sufficiently high (also not cost-effective now)
  - Vaccinating males could provide benefits against HPV-related penile, anal, head and neck cancers in males
Public health considerations

- Vaccine will impact on cancers caused by HPV types in vaccine but there is still need for a cervical screening programme to deal with HPV types not in the vaccine (simplified screening programme to be developed).
South Africa

- Bivalent and quadrivalent vaccines licensed in South Africa since March 2008
- Support for HPV vaccine
- National screening policy since 2000 → but difficulties in implementing
- Optimal target population: 9-15 year old girls, with a preference towards 9 years
- 95.5% of school aged children are enrolled in primary schools in SA → possibility for school based vaccination
- Communication as vaccine for cervical cancer prevention as opposed to focusing on the fact that HPV is sexually transmitted

Source: Harries et al., Vaccine 27 (2009)
Study in Western Cape Province
Conclusions

- Cervical cancer is caused by a persistent oncogenic HPV infection.
- Immunogenic and safe prophylactic HPV vaccines are available.
- Prophylactic vaccine → optimal if used before sexual debut.
- Interaction between different disciplines: sexual and reproductive health, adolescent health, EPI and cancer control programmes.
Saving children’s life through immunisation