HPV vaccines and the future of cervical cancer prevention in Europe

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Potential conflict of interest

• Research and educational institutional grants:
  GSK, SPMSD, Merck, Qiagen
• Personal / speaking / travel grants:
  GSK, SPMSD, Merck, Qiagen, RMS

This presentation is the sole responsibility of the author
Agenda

• Burden of HPV infections and disease in Europe
• Current strategies for prevention
European Union (30 countries) HPV-Related Disease Burden:
Annual estimations of 52,000 Cancers and close to 6M precancerous lesions

- Penile cancer: 2,390 males, 3,386 females
- Vulva & Vagina Cancer: 2,390 males, 3,386 females
- Anal Cancer: 1,042 males, 2,390 females
- Oropharyngeal Cancer: 4,505 males, 1,166 females
- AIN2/3 + ValN2/3 + VIN2/3: 2,390 males, 3,386 females
- Cervical Cancer: 2,390 males, 3,386 females
- Genital Warts: 34,708 males, 5,570,988 females
- ASCUS+: 399,165 females
- CIN2+: 388,980 females
- Pop ≥ 20y: 198,714,613 males, 213,332,641 females

(Reference: Hartwig et al. submitted; Forman et al. 2012 Vaccine; World Population Prospects 2012 Revision)
## Options to control cervical cancer

<table>
<thead>
<tr>
<th></th>
<th>SCREENING (PAP)(^1-3)</th>
<th>SCREENING (HPV)</th>
<th>HPV 16/18 VACCINATION(^3-6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Cervical cancer / pre-cancer</td>
<td></td>
<td>Cervical cancer / pre-cancer &amp; Interrupt Transmission</td>
</tr>
<tr>
<td><strong>Impact</strong></td>
<td>Participant</td>
<td></td>
<td>Participant + Herd effect</td>
</tr>
<tr>
<td><strong>Number of interventions</strong></td>
<td>10...50+ tests lifetime</td>
<td>5+ tests lifetime</td>
<td>3 / 2 doses no booster dose to date</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>Local diagnostic &amp; treatments network</td>
<td></td>
<td>Phase IV studies in selected countries</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Mild / Obstetrics /over-diagnostics</td>
<td></td>
<td>Local/short-lived</td>
</tr>
<tr>
<td><strong>Impact on other cancers</strong></td>
<td>Limited / none</td>
<td></td>
<td>Significant in all HPV-related cancers</td>
</tr>
</tbody>
</table>

## The arrival of HPV screening

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cytology</th>
<th>HPV tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>50 - 70%</td>
<td>90-95%</td>
</tr>
<tr>
<td>Specificity</td>
<td>70 - 95%</td>
<td>90-92%</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>Low</td>
<td>Very high</td>
</tr>
<tr>
<td>High throughput &amp; Automation</td>
<td>Requires human resources Limited</td>
<td>High to very high Point of care technology</td>
</tr>
<tr>
<td>Coverage / Follow up / diagnostics / treatment</td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td>Logistics and cost</td>
<td>Difficult to comply</td>
<td>Technology calibrated to work in remote areas. Allows self-sampling</td>
</tr>
</tbody>
</table>
State of the opinion

• In spite of screening proposals the burden of HPV infections and disease in Europe remains important notably in Eastern countries
• HPV screening is the technology of choice for secondary prevention
• *Achievements of 10 years of HPV vaccination*
  – Efficacy in Phase III
  – Worldwide Coverage
  – Predicted impact
HPV vaccines in 2017

bi-valent HPV vaccine (Cervarix)

- 16
  - 20µg
- 18
  - 20µg

quadri-valent HPV vaccine (Gardasil)

- 6
  - 20µg
- 11
  - 40µg
- 16
  - 40µg
- 18
  - 20µg

nine-valent HPV vaccine (Gardasil 9)

- 6
  - 30µg
- 11
  - 40µg
- 16
  - 60µg
- 18
  - 40µg
- 31
  - 20µg
- 33
  - 20µg
- 45
  - 20µg
- 52
  - 20µg
- 58
  - 20µg

ASO4-AL

AAHS 250

AAHS 500
HPV type-specific contribution to cervical cancer and potential for prevention of existing vaccines

<table>
<thead>
<tr>
<th>VIRAL TYPES</th>
<th>Relative Contribution – RC (%)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>16+18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+33+45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+52+58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 + 11</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Type specific Vaccine efficacy</th>
<th>RC %</th>
<th>Gardasil</th>
<th>Cervarix</th>
<th>Gardasil9</th>
</tr>
</thead>
<tbody>
<tr>
<td>16+18</td>
<td>71</td>
<td>95+%</td>
<td>95+%</td>
<td>95+%</td>
</tr>
<tr>
<td>+31</td>
<td>75</td>
<td>Parcial</td>
<td>Parcial</td>
<td>95+%</td>
</tr>
<tr>
<td>+33+45</td>
<td>84</td>
<td>-</td>
<td>Parcial</td>
<td>95+%</td>
</tr>
<tr>
<td>+52+58</td>
<td>89</td>
<td>-</td>
<td>-</td>
<td>95+%</td>
</tr>
<tr>
<td>6 + 11</td>
<td>90</td>
<td>90 %</td>
<td>-</td>
<td>90 %</td>
</tr>
</tbody>
</table>

de Sanjósé S et al. Lancet Oncol, 2010
Serrano B et al. Infect Ag Cancer, 2012
Schiller J et al Vaccine 30 S 5 2012
Lehtinen M et al. Nat Rev Clin Oncol. 10 2013
Relative contribution of the 7 and 2 Hr HPV Types to HPV positive cancer by organ site

*HPV 6/11/16/18/31/33/45/52/58

Relative contribution of the 7 and 2 Hr HPV Types to HPV positive cancer by stage of cervical cancer

QUADRIVALENT HPV VACCINE EFFICACY STUDIES IN MEN

<table>
<thead>
<tr>
<th>Vaccine efficacy against EGL, (mostly GW) in men</th>
<th>Vaccine efficacy against anal intraepithelial lesions in MSM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>90.6% (70-98)</strong></td>
<td><strong>77.5% (40-93)</strong></td>
</tr>
</tbody>
</table>
| Giuliano *et al*., NEJM 2011  
Per protocol cohorts | Palefsky *et al*., NEJM 2011  
Per protocol cohorts |
HPV VACCINATION COVERAGE IN EUROPE (FULL COURSE MOSTLY IN GIRLS 12-14)

Coverage of the last reported vaccinated cohort

By 2015 23 countries from EU-28 have introduced HPV vaccines

Updated November 2015
ESTIMATED INCIDENT CERVICAL CANCER AVERTED BEFORE AGE 75 YEARS IN THE 36 MILLION WOMEN EVER TARGETED BY HPV VACCINATION PROGRAMMES in 2014

Based on Bruni 2016 Lancet Glob Health

67% preventable with G9
State of the opinion

- HPV vaccination is having a significant impact on infection and disease prevention
- Broad spectrum vaccines and gender neutral vaccination are the alternatives of choice in the most advanced countries
Women in middle age groups, found HPV negative and receiving a broad spectrum HPV vaccine (expected 90% protection against oncogenic HPV types) has a subsequent risk of cervical cancer extremely low.

Under these risk estimates, the requirements for further screening are likely to be minimal (one/two lifetime) and necessarily HPV based (sensitivity 90%+).
Proposed HPV FASTER initiative for countries in the planning phases (female program)

At least one HPV screen & triage & treatment

HPV screen x 1/3 lifetime

Exact age limits to be defined
HPV FASTER ISSUES: 1 DEVELOPED COUNTRIES

Women 25-65
ONE HPV SCREENING & TREATMENT

At each round < 2% follow up required

1 / 2 visits

Women will recognize the right to receive and the Health Services will have the obligation to provide unbiased information on the value of vaccination and its implications for future screening

At each round 5-10% follow up required

7 to 9 visits

Dose 1
Dose 2
Dose 3

X 5 / 7 / 10y

ICO Hospitalet.
Cancer Epidemiology Research Program (CERP)
Conclusion

• In Europe HPV cancer prevention will include intelligent *combinations* of HPV vaccination and HPV based screening

• New protocols are being conceived and tested as we learn more on the potential of these technologies
  – Extension of vaccination to *women in screening ages*
  – Systematic vaccination of *high risk groups*
  – Less frequent screening, diagnostics and treatment events using *HPV tests*
  – *Self sampling* in screening programs