Preventive Vaccines against HPV

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Content

1. HPV associated diseases
2. Preventive vaccines
   • Efficacy
   • Safety
   • Duration of protection
3. Vaccination policy
   • Strategy (target group/delivery)
   • Herd immunity
   • Coverage
   • Cost-effectiveness
4. Conclusion
1) HPV-associated diseases

1. Cervical cancer and precancer
   • Prerequisite: persistent infection high-risk type

2. Genital warts

3. Squamous cell cancers
   • Vulvar/Vaginal cancer
   • Anal cancer
   • Penile cancer
   • Head and neck cancer
Natural history of HPV infection

Figure 1. Natural history of HPV infection. CIN3: Cervical intraepithelial neoplasia grade 3. Adapted from reference [2].

Moscicki, Vaccine 2012
List of cancer sites with sufficient or limited evidence of an HPV association*

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Topography</th>
<th>Subsite potentially HPV related</th>
<th>HPV Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oropharynx incl. base of tongue,</td>
<td>09.0-9, 10.0-9</td>
<td></td>
<td>HPV16</td>
</tr>
<tr>
<td>tonsil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>C01.9, 02.4, 14.2</td>
<td></td>
<td>HPV16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HPV18</td>
</tr>
<tr>
<td>Anus</td>
<td>C21</td>
<td></td>
<td>HPV16</td>
</tr>
<tr>
<td>Larynx</td>
<td>C32</td>
<td></td>
<td>HPV16</td>
</tr>
<tr>
<td>Skin (nonmelanoma cancer)</td>
<td>C44</td>
<td></td>
<td>HPV5, 8 (in patients with epidermodysplasia verruciformis)</td>
</tr>
<tr>
<td>Vulva</td>
<td>C51</td>
<td></td>
<td>HPV16</td>
</tr>
<tr>
<td>Vagina</td>
<td>C52</td>
<td></td>
<td>HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 73, 82</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>C53</td>
<td></td>
<td>HPV26, 53, 66, 67, 68, 70, 73, 82</td>
</tr>
<tr>
<td>Penis</td>
<td>C60</td>
<td></td>
<td>HPV16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HPV18</td>
</tr>
</tbody>
</table>

## Burden of disease

<table>
<thead>
<tr>
<th></th>
<th>female</th>
<th>Incidence /100,000 male</th>
<th>MSM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer</td>
<td>7.3(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital warts (GW)</td>
<td>190(^2)</td>
<td>150(^2)</td>
<td></td>
</tr>
<tr>
<td>Anal cancer</td>
<td>~2(^1)</td>
<td>~1(^1)</td>
<td>~37</td>
</tr>
<tr>
<td>Penile cancer</td>
<td>&lt;1(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV-associated oropharyngeal cancers</td>
<td>US: 1.8(^3)</td>
<td>US: 8.2(^3)</td>
<td></td>
</tr>
</tbody>
</table>

MSM: men who have sex with men

\(^1\) www.hpvcentre.net; \(^2\) Kraut, BMC Inf Dis 2010; \(^3\) Jemal, JNCI 2013
Number of new HPV-ass. cancer cases US, 2009

Jemal, JNCI 2013
2) Preventive vaccines
Vaccines: Virus-like particles (VLPs)

HPV major capsid protein, L1, can spontaneously self-assemble into VLPs

<table>
<thead>
<tr>
<th>Gardasil® (qHPV)</th>
<th>Cervarix® (bHPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>„Baker’s yeast“</td>
<td>Insect cells</td>
</tr>
<tr>
<td>6,11,16,18</td>
<td>16,18</td>
</tr>
<tr>
<td>225 µg amorphous aluminum hydroxyphosphate sulfate</td>
<td>AS04: 500 µg aluminum hydroxide 50 µg 3-O-desacyl-4' monophosphoryl lipid A</td>
</tr>
<tr>
<td>0, (2), 6</td>
<td>0, (1), 6</td>
</tr>
<tr>
<td>2006</td>
<td>2007</td>
</tr>
</tbody>
</table>
Vaccine trials

1. Clinical trials designed for
   a) Immunogenicity
   b) Efficacy
      i. against HPV vaccine type related infections
      ii. and clinical outcomes (CIN 2-3, CiS) -> any type (!)
   c) Safety

2. All trials of different designs
   a) Definition of populations (per protocol, ITT, etc)
   b) Inclusion/exclusion criteria
   c) Outcomes/outcome definition
   d) Methods
      i. Recruiting
      ii. Laboratory
### Vaccine efficacy

<table>
<thead>
<tr>
<th></th>
<th>female</th>
<th>Vaccine efficacy VE (95% CI)</th>
<th>male</th>
<th>MSM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cervical cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥CIN 2 (any type)</td>
<td></td>
<td></td>
<td>41-70%(^1)</td>
<td></td>
</tr>
<tr>
<td><strong>Genital warts</strong></td>
<td></td>
<td></td>
<td>89.4% (65.5-97.7)(^2)</td>
<td>100% (8.2-100)(^3)</td>
</tr>
<tr>
<td>Any type: 51% (32-65)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AIN</strong></td>
<td></td>
<td></td>
<td>Any type: 54.9% (8.4-79.1)(^3)</td>
<td></td>
</tr>
<tr>
<td><strong>PIN</strong></td>
<td></td>
<td></td>
<td>100% (-141-100)(^2)</td>
<td></td>
</tr>
<tr>
<td>HPV 16/18 oral infection</td>
<td>93.3% (62.5-99.7)(^4)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AIN: anal intraepithelial neoplasia, PIN: penile intraepithelial neoplasia, MSM: men who have sex with men

\(^1\): Deleré, Dt Ärzteblatt int 2013; \(^2\): Giuliano, NEJM 2011; \(^3\): Palefsky, NEJM 2011; \(^4\): Herrero, PLOS one 2012
Safety data, register based

1. Cohort study
2. Denmark/Sweden
3. 2006-2010
4. Follow-up: 180 days after each dose
5. 997,585 girls aged 10-17 years
   a) Vaccinated: 296,826
   b) Given doses qHPV: 696,420
6. 53 outcomes:
   a) Autoimmune diseases
   b) Neurological disorders
   c) Venous thromboembolic events
Safety

Association between exposure to qHPV and adverse events in adolescent girls in Denmark and Sweden, October 2006-December 2010.

Lisen Arnheim-Dahlström et al. BMJ 2013;347:bmj.f5906

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Duration of protection

Systematic review (STIKO/RKI 2014):

- **Two follow-up periods**
  - <5 year (short term)
  - ≥5 years (long term)
Duration of protection <5 years
Duration of protection ≥ 5 years

Deleré, Dt. Ärzteblatt international, 2014
3) Vaccination policy

Translation of evidence into a recommendation:

- Burden of disease in target groups
- Evidence of protection: efficacy/safety
- Herd immunity
- Cost-effectiveness
- Coverage/Acceptability
- Message for public communication
Vaccination strategies

- Main target group: Girls
- Age of vaccination: Before starting sexual activities (before first sex) -> 9-12 years (maybe 13/14)
- Delivery: Organised programmes (e.g. school based), invitation/reminder, “offer“ (funded) via Ped./GPs/Gyn.
- Catch-up: Girls and young women
- Extension: In some countries boys are included

2012: 21 of 29 EU states with HPV recommendation
Coverage

- **England**: ~76% of 12-13-year-old girls 2009/10
  - School-based programme

- **Denmark**: ~83% of 13-15-year-old girls 2010
  - Vaccination by GP, invitation, reminder

- **Germany**: ~40% of 16-17-year-old girls
  - Vaccination by Gyn./Ped./GPs, if opportunity
Mutual effects: Herd immunity (Australia)

Figure 1  Proportion of Australian-born women, heterosexual men, and men who have sex with men (MSM) diagnosed as having genital warts at Melbourne Sexual Health Centre, from July 2004 to June 2014: stratified by (A) all age group, (B) <21 years, (C) 21–32 years and (D) >32 years. The vertical line represents the implementation of the national HPV vaccination programme.

Donovan, Lancet Inf Dis 2011
Cost-effectiveness (girls)

• Mathematical models for UK suggests, that vaccination of girls (11-12 years, coverage 80%, lifelong protection) is cost effective

• Mathematical models for Germany suggests, that vaccination of girls (12 years, coverage 50%, protection 10 years with waning 10% every year starting year 11) is cost effective
Cost-effectiveness (both sexes)

• Mathematical models for UK suggest that vaccination of boys is unlikely to be cost effective, even if vaccination results in lifelong protection (Jit, BMJ 2008).

• In a model for Germany, additional vaccination of 12-year-old boys (coverage 50% in both sexes) would increase incremental cost-effectiveness ratio (ICER) 8-fold per quality-adjusted life year (QALY) from about 15,000 to nearly 120,000 EUR per gained QALY (www.rki.de/infektionsschutz/impfen).
4) Conclusion

- Burden of HPV associated diseases is high, cervical cancer remains a cause of premature death worldwide.
- Prophylactic HPV vaccines are remarkable both for their efficacy against HPV infections and related diseases.
- Strong evidence that autoimmune, neurological and thromboembolic diseases are not triggered by qHPV.
- In settings with high vaccination coverage in girls, additional HPV vaccination for boys will not be cost-effective.
- Efforts to raise the coverage among girls seems to be more efficient.
Take home message

Do not miss any opportunity to get girls vaccinated!
Thank you for your attention!