Human Papillomavirus Vaccines as a Potential Novel Tool for Global Prevention of Cervical Cancer in Women

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World Health Organization
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1. Disease burden
2. Prevention strategies
3. Vaccine development and introduction
The role of WHO in HPV vaccine development and introduction

**Mission**

A world in which all people at risk are protected against vaccine-preventable diseases

Cervical cancer to become a vaccine preventable disease
Dealing with the spectrum of a vaccine continuum

- Accelerating Innovation and Introduction of Novel Vaccines
- Quality and Safety of Vaccines and Biologicals
- Maximizing Access to Effective Immunization
### Papillomaviruses and Human Diseases

<table>
<thead>
<tr>
<th>SITES</th>
<th>DISEASES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anogenital tract</strong></td>
<td>Cervical neoplasias and carcinoma</td>
</tr>
<tr>
<td></td>
<td>Anal carcinoma, Penile carcinoma, Vulvar carcinoma</td>
</tr>
<tr>
<td></td>
<td>Anogenital warts</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>Common warts, deep plantar warts</td>
</tr>
<tr>
<td></td>
<td>Mosaic warts, flat warts, etc</td>
</tr>
<tr>
<td></td>
<td>Melanomas</td>
</tr>
<tr>
<td><strong>Respiratory tract</strong></td>
<td>Juvenile laryngeal papillomatosis, recurrent respiratory papillomatosis,</td>
</tr>
<tr>
<td></td>
<td>non-small cell lung cancer, Laryngeal, sinusial, tonsillar and oro-pharyngeal squamous cell carcinomas (HNSCC)</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>Conjunctival papillomatosis, carcinoma and keratosis in epidermodysplasia verruciformis, Carcinomas associated with immune deficiency</td>
</tr>
</tbody>
</table>
Estimated world prevalence of subclinical and clinical HPV infections

- HPV infections: 2 billion
  - Other HPV infections
    - Low grade lesions: 80 million
    - High grade lesions: 35 million
    - Invasive Cervical Cancer: 1.5 million
  - Genital HPV Infections: 440 million
    - Skin warts: 900 million
    - Anogenital warts: 40 million

Based on world population of 6.271.698.000 (World Bank) and surveys among subjects at reproductive age (15-50 years old)

* Koutsky 1997, § seroprevalence or *DNA prevalence ** Herrero et al. 2000, 1997; ** Sankaranarayanan et al. 2004; *** Parkin et al. 2001
Cancer prevention and control are among the most important scientific and public health challenges of this era.

(Adapted from World Health Report, 2004)
Cervical cancer is the foremost cause of cancer mortality among women in developing countries.

(Adapted from Globocan, 2002)
Distribution of adult female population
and deaths due to cervical cancer in %

Adult female population

Cervical cancer deaths

least developed countries

India

China

medium developed countries w/o India-China

most developed countries

UNDP 2000 (adapted from Drain, 2002)
Global distribution of total number of new cervical cancer cases per year

Asia accounts for about half of all cases

(adapted from Globocan 2002,)
Regional distribution of incidence rates* of new cervical cancer cases per year worldwide

Incidence of Cervix uteri cancer: ASR (World) (All ages)

* Per 100,000 women
Age distribution of new cervical cancer cases

<table>
<thead>
<tr>
<th>Age group</th>
<th>0-14</th>
<th>15-44</th>
<th>45-54</th>
<th>55-64</th>
<th>65+</th>
</tr>
</thead>
<tbody>
<tr>
<td>developing</td>
<td>146</td>
<td>102673</td>
<td>114522</td>
<td>89338</td>
<td>72474</td>
</tr>
<tr>
<td>developed</td>
<td>1</td>
<td>30320</td>
<td>18568</td>
<td>15399</td>
<td>27163</td>
</tr>
</tbody>
</table>

(adapted from Globocan, 2000)
Changes that impact upon disease burden

Environmental:
Hygiene, smoking, dietary, condom use

Behavioural:
Age at sexual debut, age at first delivery, number of sexual partners

Technology:
Screening, tests, diagnostics

Biological:
Vaccination, genetics, medicinal drugs

Target disease: Invasive cervical cancer
The etiology of cervical cancer and opportunities for prevention

Co-factors for cancer development:
- HPV type
- Age at infection
- High parity
- Immune deficiency
- Chronic Chlamydia infection
- Hormonal, genetic, and environmental factors...
## Natural History of CIN

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Regress</th>
<th>Persist</th>
<th>Progression to CIN 3</th>
<th>Invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 1</td>
<td>57%</td>
<td>32%</td>
<td>11%</td>
<td>1%</td>
</tr>
<tr>
<td>CIN 2</td>
<td>43%</td>
<td>35%</td>
<td>22%</td>
<td>5%</td>
</tr>
<tr>
<td>CIN 3</td>
<td>32%</td>
<td>&lt;56%</td>
<td>-</td>
<td>&gt;12%</td>
</tr>
</tbody>
</table>

Molecular basis for HPV vaccines

- HPV is a small circular dsDNA non-enveloped epitheliotropic virus
- Family includes more than 120 types, ~30 cause genital infections*
- Four types that cause the greatest burden of cervical cancer*
- Sexually transmitted HPV virus DNA are associated with over 99% of cervical cancer cases*

*(zur Hausen; Bosch et al., 1995; Walboomers et al. 1999)
Regional distribution of HPV type prevalence in cervical cancer (% of all cases analysed)

Adapted from Clifford et al. 2002
HPV 16/18 vaccine candidates are becoming available

- Prophylactic vaccine candidates are being developed: Recombinant L1 proteins self-assemble into VLPs
  
  - Safe, immunogenic and well tolerated
  
  - Complete protection against persistent HPV infections in vaccinated women has been demonstrated in two independent studies (Koutsky, 2002; EUROGIN 2003)

*adapted from Nieland*
Milestones for HPV vaccines

introduction

• Safety, immunogenicity,
• Efficacy
• Effectiveness
  – Epidemiology
  – Delivery-coverage
• Cost-effectiveness
• Impact on cervical cancer prevention
## Summary of two independent phase IIb studies

<table>
<thead>
<tr>
<th></th>
<th>Merck</th>
<th>GSK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Candidate</strong></td>
<td>HPV 16 VLPs</td>
<td>HPV 16/18 VLPs</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>2392 subjects</td>
<td>1113 subjects</td>
</tr>
<tr>
<td><strong>Study population</strong></td>
<td>16 to 25 year olds with &lt;6 lifetime sexual partners</td>
<td>15 to 25 year olds with ≤6 lifetime sexual partners</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>Includes baseline positives</td>
<td>Excluded baseline positives</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>Persistent HPV16 infection or HPV 16-related CIN</td>
<td>Transient or persistent HPV 16/18 infection</td>
</tr>
</tbody>
</table>
## Summary of two independent phase IIb studies

<table>
<thead>
<tr>
<th>ATT cohort analysis</th>
<th>Merck (16)</th>
<th>GSK (16+18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety Collection</td>
<td>1533 subjects</td>
<td>721 subjects</td>
</tr>
<tr>
<td>Safety Data</td>
<td>14 days post vax</td>
<td>7 days post vax</td>
</tr>
<tr>
<td>% w/any AE</td>
<td>93% (V) vs. 92% (P)</td>
<td>96% (V) vs. 93% (P)</td>
</tr>
<tr>
<td>% w/injection site AE</td>
<td>86% (V) vs. 82% (P)</td>
<td>95% (V) vs. 86% (P)</td>
</tr>
<tr>
<td>Seroconversion</td>
<td>99.7%</td>
<td>99.8%</td>
</tr>
<tr>
<td>Efficacy criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent Infection (Per-Protocol)</td>
<td>100% (HPV 16)</td>
<td>100% (HPV 16/18)</td>
</tr>
<tr>
<td>Persistent Infection (Intention-To-Treat)</td>
<td>93% (HPV 16)</td>
<td>84% (HPV 16/18)</td>
</tr>
<tr>
<td>Transient or Persistent Infection (Per-Protocol)</td>
<td>91% (HPV 16)</td>
<td>87% (HPV 16)</td>
</tr>
<tr>
<td>CIN</td>
<td>100% (9 women)</td>
<td>n.a.</td>
</tr>
</tbody>
</table>
Milestones for HPV vaccines

introduction

• Efficacy: Desirable to have a globally-agreed measurable endpoint
  • Ethical and time considerations make it necessary to use surrogate endpoints, rather than invasive cervical cancer
  • Recommend CIN of moderate or high grade as primary endpoint, and cancer as secondary endpoint
  • Once this surrogate endpoint is validated, virological or immunological correlates of protection may be considered for future evaluation and product development
  • Document breakthrough cases following long periods
  • 100% Efficacy against HPV 16 and 18 would prevent about 70% of cervical cancer cases
Milestones for HPV vaccines introduction

- Effectiveness: Malignancies develop slowly and are relatively infrequent in a given population and therefore cancer outcomes require very large and lengthy studies
  - Duration of protection
  - Demonstration project

- Modelling
  - A model calibrated to Indian specific data by Shalini Kulasingam and colleagues (Duke university), using parameters in an existing model
Two different models were developed using data from New Delhi and from Madras

With permission of Kulasingam et al.
Baseline assumptions Vaccine

- Age of Vaccination is 12
- Vaccine efficacy is 90% (8) (lower bound of 95%CI from Koutsky et al. NEJM, 2002)
- Vaccine duration is 30 years- assumed
- Proportion of HPV types covered is 70% (9,10)
- Vaccine coverage is 70%- assumed
Age-Specific Cancer Incidence
New Delhi Model

Age-Specific Cancer Incidence
Madras Model

With permission of Kulasingam et al.
Outstanding issues

- Effectiveness in field conditions, immunodefficiency
- Duration of protection:
  - Infections later in life
  - Latent infections
- HPV type replacement in disease
- Role of male vaccination in disease burden
- Impact of vaccination on invasive cancer
Additional research for HPV vaccine evaluation relevant for public health use

- Immunogenicity and safety in immunocompromised subjects
- Feasibility of vaccinating adolescents
- Monitor the prevalence of HPV types in vaccinated populations by periodic sampling surveys
- Monitor the occurrence of invasive cervical cancer in specific early age groups to accelerate evaluation of impact of vaccination on cancer
Conclusion

As impact of vaccines on cancer is not yet empirically demonstrated, and health professionals still need to prevent cancers not related to the vaccine types:

• For the next decades, combinations of primary and secondary prevention strategies will be needed, and the modalities of these combinations may change over time, depending on many factors that are likely to be country specific.