Monitoring impact of HPV vaccination

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Human Papillomavirus (HPV)

- Condylomas: HPV 6 (80-90%)
- Laryngeal papillomatosis: Mainly HPV11.
- Cervical cancer; Cervical intraepithelial neoplasia (CIN): HPV16 (50-60%), 18 (15%), 31, 33, 45, 52, 58
- Cervical adenocarcinoma: Mainly HPV18, 16
- Cancer of vagina, vulva, penis, anus and tonsils: Mainly HPV16.
- Effective vaccines licenced against HPV6/11/16/18 and against HPV16/18
Global incidence of cervical cancer

Incident cases in 2002

<table>
<thead>
<tr>
<th>Region</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>33,386</td>
</tr>
<tr>
<td>Worldwide</td>
<td>493,243</td>
</tr>
</tbody>
</table>

Deaths in 2002

<table>
<thead>
<tr>
<th>Region</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>14,638</td>
</tr>
<tr>
<td>Worldwide</td>
<td>273,505</td>
</tr>
</tbody>
</table>

Incidence differences attributable to:
- Sexual behaviour
- Organised Pap smear screening programs

Age standardised incidence rate (world) per 100,000 population


www-depdb.iarc.fr/globocan/GLOBOframe.htm (accessed on May 27, 2005)
WHO/IARC, Global estimates 2002: 17.9% of all cancer (1.600.000 cases/year) avoidable if established cancer-causing infections are eradicated. Human Papillomavirus (HPV) = 5.2% of all cancers
From Papillomavirus infection to cancer

Papilloma Virus Infection → Persistent infection → CIN 1 ASCUS → CIN 2/3 → Cervical cancer

1 year  Up to 5 years  >10 years later

CIN = cervical intraepithelial neoplasia; HPV = human PapillomaVirus; HSIL = high grade squamous intraepithelial neoplasia; LSIL = low-grade squamous intraepithelial neoplasia.

Cleared Papillomavirus Infection
Estimated contribution of HPV6/11/16/18 to health care costs in Sweden: Disease in males 31.5%

(Swedish National Board of Health and Welfare, 2008)

- **Cervical cancer**: 94 MSEK
- **Other HPV-associated cancers (vulva, vagina, anus, tonsil)**: 36 MSEK
- **Condyloma Acuminata, women**: 27 MSEK
- **Condyloma Acuminata, men**: 24 MSEK
- **Other HPV-associated cancers (penis, anus, tonsil)**: 29 MSEK
- **LSIL**: 5 MSEK
- **HSIL**: 13 MSEK

Based on nationwide registry data, 9 MSEK = 1 MEuro.
Modelled demands on HPV eradication:
High Coverage, Catch-up and Both sex vaccination (Swedish Natl Board of Health & Welfare 2007; Vaccine 2008)
Why HPV surveillance and why is HPV special?

Incubation time from infection to cancer is decades.

- Evaluation of whether the program works or should be improved cannot wait for cancer endpoints.

Infection is asymptomatic.
- Standard clinical case reporting systems not possible for oncogenic HPV. Surveillance based on laboratory testing required.

Many HPV types.
- Requests for monitoring against type replacement
Prime lesson from the cervical screening experience

• Programs must be organised and target the entire population in order to be effective.
• Disorganised testing primarily reaches low risk women – low effectiveness.

• Disorganised vaccination program likely to have similarly low effectiveness.
• Inadequate organisation and evaluation - more imminent threat than type replacement.
Strategy evaluation

Different countries that use different vaccination strategies should have comparable evaluation systems- rapid accumulation of data on which strategy works best.

Exact strategy choice probably less important than using comparable evaluation systems!

Early evaluation components:
1. An HPV Vaccination Registry (determines coverage; enables registry linkages)
2. Condyloma Surveillance with HPV typing
3. Quality-assured HPV testing and typing in the target age groups (e.g. anonymised Chlamydia screening samples or cervical screening samples)
The Swedish HPV vaccination registry

- Based on Ethical Permission/Informed Consent.
- Patient information+ Registration form enclosed in syringe package
- 2009-08-31: 178234 registered vaccinations (74667 unique subjects). 169049 consents to registry & biobank-based follow-up
Condyloma

- The most common clinical manifestation of a viral STI
- About 80-90% of condyloma are caused by HPV6/11
- Short incubation time (1-6 months)
- Non-eradication/ re-emergence of condylomas will rapidly detect if vaccination-induced population level immunity is insufficient.
  - Early, clinical marker of efficacy of vaccination program.
- Can be monitored, e.g. with
  - Reporting systems
  - Patient visit registries
  - Prescription registries (podophyllotoxin and imiquimod prescriptions)
  - HPV typing of condylomas seen at sentinel STD clinics
First effectiveness report: 25th IPV, May 14th 2009

RAPID DECLINE IN WARTS AFTER NATIONAL QUADRIVALENT HPV VACCINE PROGRAM

C Fairley, University of Melbourne, Melbourne, Australia
J Hocking, University of Melbourne, Melbourne, Australia
M Chen, University of Melbourne, Melbourne, Australia
B Donovan, University of New South Wales, Sydney, Australia
C Bradshaw, Monash University, Melbourne, Australia

HPV-vaccine free for women 12-26 years of age. Organised vaccination in schools for women 12-18 years of age since april 2007. Sentinel STD clinics with condyloma reporting.

One year after program start, incidence of condyloma among women <28 yrs lowered by 48%, among heterosexual men <28 yrs by 17%. No change among older subjects or among homosexual men.
HPV DNA-based surveillance systems

Early evaluation:

1. HPV typing in teenage cohorts, e.g. in the Chlamydia trachomatis screening program.
   - Optimal targeting of age groups most active in spreading HPV. Most rapid evaluation of HPV vaccination program efficacy.
2. Typing/reporting system for condyloma acuminata
3. HPV typing in the cervical screening program (population-based, organised sampling) – surveillance is yet another good reason for HPV screening.

Medium/long-term evaluation + Disease burden:

Typing of all HPV-associated cancers and at least some of the CIN2/3 lesions.
Registry-Based Follow-Up

Vaccination Program with Catch-Up to 18 years of age

Early and late evaluation possibilities: When can we start to see effects?

- HPV DNA testing surveys in teenagers
- Condyloma incidence
- CIN incidence & HPV DNA testing surveys in screening population
- Cancer incidence


Vaccination Program with Catch-Up to 18 years of age
Laboratory testing will have a key role in monitoring/evaluation.

The 2006 launch of the **WHO Global HPV LabNet** is significant news for HPV vaccination monitoring/evaluation.

Mission: To contribute to improving quality of laboratory services for effective surveillance and monitoring of HPV vaccination impact, through enhancing, state-of-the-art and internationally comparable laboratory analyses.

Support 1) the introduction of HPV vaccines and 2) surveillance of disease and infection.

Works e.g. by establishing quality criteria, international standards & proficiency panels & piloting surveillance systems.
Assigned tasks for WHO global reference lab

*Proficiency Testing
  - HPV DNA proficiency panel. HPV serology proficiency panel.

*International Standards
  - HPV DNA: Large plasmid prep defining amount of HPV DNA (copy number traceable to biological standard)
  - HPV antibodies: Large serum bleed defining an international unit of antibodies
Assigned tasks for WHO global reference lab

*Design pilot projects to gain practical experience of how to follow-up the effects of HPV vaccination programs in a practical and (cost-)efficient manner.
- Condyloma reporting and typing in sentinel clinics
- Monitoring of sexually active youth groups by anonymised testing of Chlamydia screening samples
- Typing of all HPV-associated cancer in the country
High Throughput HPV DNA typing
(Söderlund et al, Clin. Chem. 2008)

- Based on robotic PCR on a microscale followed by typing with Mass Spectrometry. Same technology as is used for throughput genetic epidemiology (SNP-testing; Sequenom).
- About 14 SEK/sample.
- Tested in batches of 2000 samples at a time. Typing of 16 HPV types (HPV6,11 and the 14 most common HPV types).
- Anonymised HPV-testing of all Chlamydia-screening samples in Southern Sweden (about 80,000 samples/year) started in January 2009.
Post vaccination surveillance: Three ambition levels

- Low: Coverage and safety.
- Medium: Effectiveness surveillance systems.
  - HPV DNA testing (in teenager surveys or in cervical screening program);
  - Immunogenicity;
  - Monitoring of HPV-associated diseases.
- High: Registry-based follow-up systems

Registry-based long-term follow-up

What is it?

- Denotes an extended follow-up over several decades of all subjects who have received the vaccine.

- Data on disease endpoints, health care resource utilization and any possible side effects are accrued using registry linkages with population-based health data registries.

- Cases of disease (e.g. CINII+) are retrieved from smear and tissue biobanks for HPV typing.

- Linkage with population-based serum biobanking system to determine antibody levels
Registry-based follow-up: Why do it?

- Long term effects and duration of protection
- Real life documentation of the health care cost benefits, for example, reductions in the use of Smears/Biopsies/Colposcopies/Cancer treatments
- Reliable evaluation of any possible late side effects.
- Long term data on persistence over time of the level and functional activity of the vaccine-induced HPV antibodies (search for correlates of immunity).

- Will booster vaccination be required?
- Is there really a protection against HPV types not included in the vaccine and for how long does it last?
- Will there be type replacement or escape mutants?
Including randomised vaccination trials in the long-term follow-up

Vaccination

Phase III Study  Registry-Based Follow-Up

Efficacy Report  Vaccine available

3.5 yr  6 yr  8 yr  10 yr

2 yr  4 yr  6 yr


A sentinel cohort with a 4 year head start
Summary

**Internationally standardised** laboratory testing and global reporting systems will be important for HPV surveillance

- Early evaluation of effectiveness (HPV testing surveys; condyloma surveillance).
- Medium term evaluation (HPV typing of cases of HPV-associated diseases)
- **Advanced evaluation programs** with registry-based follow-up etc in some countries