How to combine screening and vaccination

How to promote women’s health and prevent cancer with good screening strategies

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Declaration of Good Standing and Conflict of Interest Disclosure

My presentation complies with FIGO’s policy for declaration of good standing and conflict of interest disclosure;

I do not have a financial interest in any product or service related to my presentation;

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Learning objectives

How to decrease the HPV disease burden
How to find the best means to prevent cervical cancer incidence and mortality
How to use primary and secondary prevention together
Screening = secondary prevention

- Screening has been available for over 50 years
- It has been successful in many countries, BUT not everywhere
- Requires
  - a good infrastructure
  - resources
  - positive attitude of the target population
  - education & training
  - quality assurance
Screening

• Can be very effective, if implemented in an organized manner
• Spontaneous screening has also effect, but not as much
• EU guidelines recommend organized screening
  • Starting from age 25-30 years to 60-65 years, with 3-5 year interval
• Organized screening is the most cost-effective model
Cervical cancer incidence in Nordic countries

80% reduction
Finland as an example of the evolution of cervical cancer prevention

• Finland used to be a model country for screening almost 50 years
  • Smallest cervical cancer incidence and mortality figures in the world
• Now perhaps left behind compared to some other countries?

• Background
• New screening plans including screening test and vaccinated women
Organised cervical cancer screening programme in Finland

• Target population 1.3 million women (total population 5.5 milj)
• ~ 260,000 women invited (98%), >180,000 screened (72%)
• Follow-up cytology (intensive screening) recommended: 5.4%
• Referral to colposcopy: 1.1%
• CIN2+ cases treated: 0.4% of screened women

• Overall ~3000 CIN treatments per year
Screening in Finland

Screening by-law (screening programme):
• 30-60 year of age women, 5y interval
• Some municipalities: 25y- / -65y

Also a vast opportunistic screening activity!
5 year coverage of all screening tests

a) Tests / person / 5y

b) Organized ja opportunistic tests osuus

KUVA: Salo et al. Divergent coverage, frequency and costs of organised and opportunistic Pap testing in Finland, 2014 IJC. (PKS-aineisto 2004-08)
Cervical cancer incidence trends by age in Finland

Pap-screening has reached its performance limits in Finland

Is not very effective among younger women

Ca incidence increasing among younger women, <45 years of age

NORDCAN © Association of the Nordic Cancer Registries (6.3.2018)
New cancers 1961-65 and 2011-15

Ca of younger women!
The ”secret” behind good results in Finland

• Obviously the extremely good coverage (>90%) achieved with both organised and opportunistic screening + the good quality of the colposcopy activities, F-U and quality assurance..
• Stopping either screening mode would result in increased number of Ca
• However, opportunistic screening is more expensive and thus less cost effective
• Also...
Screening is not without problems!

Fig 2: Odds ratio for developing invasive cervical cancer stage IA or worse (in the next five year interval) in those screened in a given (three year) age band compared with those not screened in that age band (or in two previous years). Odds ratio and 95% confidence interval.
HPV-infection in age cohorts

Cervical HPV-infection:

• Extremely common: 30%+ prevalence soon after coitarche
• Major part transient infections
• Some persistent, relative proportion increases

DATA: Joukkotarkastusrekisteri, Patricia/Suomi
HPV-test based screening
Relative detection rates, observed in the second screening round

Less cancer with HPV screening!

BUT what to do with the younger women, < 30-35 years of age?

Marc Arbyn, Guglielmo Ronco, Ahti Anttila, Chris J.L.M. Meijer, Mario Poljak, Gina Ogilvie, George Koliopou...
HPV vaccines!

Are very effective

They can protect from cervical cancer and precancer

Total protection?

Significant decrease of HPV disease burden
Impact of vaccination on CIN 2/3

(88% reduction)

(94% reduction)
The effect of vaccination on screening
Routine Scottish data: performance of cytology in detecting CIN2+ and CIN3+ (from Professor ME Cruickshank):

<table>
<thead>
<tr>
<th></th>
<th>CIN2+ All women</th>
<th>CIN2+ Unvaccinated</th>
<th>CIN2+ 3 doses</th>
<th>CIN3+ All women</th>
<th>CIN3+ Unvaccinated</th>
<th>CIN3+ 3 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity of HSIL cytology</td>
<td>70.37&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>69.12&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>71.67&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>79.76&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>76.71&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>83.87&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>Specificity of LSIL cytology</td>
<td>79.49&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>77.76&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>81.10&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>65.52&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>62.6&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>69.89&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>PPV of HSIL+</td>
<td>74.69&lt;sup&gt;*&lt;/sup&gt;</td>
<td>76.73&lt;sup&gt;*&lt;/sup&gt;</td>
<td>69.30&lt;sup&gt;*&lt;/sup&gt;</td>
<td>37.06&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>37.97&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>34.32&lt;sup&gt;NS&lt;/sup&gt;</td>
</tr>
<tr>
<td>APV of LSIL and borderline changes</td>
<td>23.62&lt;sup&gt;†&lt;/sup&gt;</td>
<td>29.58&lt;sup&gt;†&lt;/sup&gt;</td>
<td>16.44&lt;sup&gt;†&lt;/sup&gt;</td>
<td>6.77&lt;sup&gt;†&lt;/sup&gt;</td>
<td>9.43&lt;sup&gt;†&lt;/sup&gt;</td>
<td>3.72&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Referral value</td>
<td>2.168&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1.942&lt;sup&gt;†&lt;/sup&gt;</td>
<td>2.679&lt;sup&gt;†&lt;/sup&gt;</td>
<td>4.950&lt;sup&gt;†&lt;/sup&gt;</td>
<td>4.353&lt;sup&gt;†&lt;/sup&gt;</td>
<td>6.333&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>76.04&lt;sup&gt;†&lt;/sup&gt;</td>
<td>70.40&lt;sup&gt;†&lt;/sup&gt;</td>
<td>82.78&lt;sup&gt;†&lt;/sup&gt;</td>
<td>92.71&lt;sup&gt;†&lt;/sup&gt;</td>
<td>90.04&lt;sup&gt;†&lt;/sup&gt;</td>
<td>95.85&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

NS not significant; * p = 0.199; † p < 0.0005
Conclusions

• Reduction in cytological abnormalities in vaccinated women

• Decline of PPV and Abnormal PV of cervical cytology

• The referral criteria for persistent low grade disease in immunised women may need to be reviewed.
  • Less than 4% with persistent LG cytology referred to colposcopy will have CIN3+
  • 45% more vaccinated women have to be seen at colposcopy to find one case of CIN3+

• The different results for PPV for CIN2+ and CIN3+ suggest that CIN2 in immunised women may be different from that in unimmunised women, and the diagnostic criteria for CIN2 should perhaps be revisited.
## Impact of vaccination on the performance of colposcopy

<table>
<thead>
<tr>
<th></th>
<th>High grade disease</th>
<th>Any grade disease</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Unvaccinated</td>
<td>Vaccinated</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>70.2</td>
<td>62.5</td>
</tr>
<tr>
<td></td>
<td>(60.3-78.6)</td>
<td>(25.9-89.8)</td>
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<tr>
<td><strong>Specificity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>85.9</td>
<td>93.4</td>
</tr>
<tr>
<td></td>
<td>(79.9-90.3)</td>
<td>(81.1-98.3)</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>73.0</td>
<td>63.0</td>
</tr>
<tr>
<td></td>
<td>(63.0-81.1)</td>
<td>(57.1-68.6)</td>
</tr>
<tr>
<td><strong>NPV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>84.1</td>
<td>93.5</td>
</tr>
<tr>
<td></td>
<td>(78.0-88.8)</td>
<td>(81.1-98.3)</td>
</tr>
</tbody>
</table>
Conclusions

• Vaccinated women referred to colposcopy have lower rate of high grade cytology and CIN2+ disease detected

• No differences seen in detecting colposcopic features of CIN

• Small numbers/under powered to detect difference in PPV of colposcopy

• But if PPV of colposcopy to detect CIN 2+ is 63%, this falls below QA standard for colposcopy
Vaccinated cohort 25 years old, HPV primary screening

Even good colposcopists show 60-80% sensitivity to identify CIN2+

Especially problem with TZ 3
Vaccination, do we need screening?

• It takes quite a long time to see a significant decrease of cervical cancer on population level after implementation of vaccine programmes
• Youngest age cohorts benefit sooner (where screening is not very effective)
• Older will never get the full benefits if any (herd effect)
• A part of the precancers and cancers are not prevented with the present vaccines
• The HPV disease burden will start to decrease sooner
  • Less the milder abnormalities
Optimizing the synergy of vaccination and screening

- Mathematical models to simulate different options of screening and vaccination to decrease the HPV disease burden
- Each country or region need their own HPV disease data (incidence, prevalence, type distribution, management, costs etc.) to set the correct parameters
- An example from Finland
Mathematical modelling of HPV disease burden in Finland

• Data collected from every registry available
  • Cancer registry
  • Screening registry
  • Diagnosis and procedures registry
  • Other registries in health care

• Modelling with dynamic methods (National Institute of Health and Welfare 2011):
  • screening
  • vaccination

• To find the most cost-effective methods for prevention

Model structure

- **INFECTION**
  - TRANSMISSION MODEL
  - NATURAL HISTORY MODEL

- **INTERVENTIONS**
  - VACCINATION
  - SCREENING TREATMENT
Scenario: Org. programme vs. present practice

<table>
<thead>
<tr>
<th>30:5:60</th>
<th>Present practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>C53 187</td>
<td>C53 135</td>
</tr>
<tr>
<td>CINt 1600</td>
<td>CINt 2300</td>
</tr>
<tr>
<td>1510 QALY</td>
<td>1380 QALY</td>
</tr>
<tr>
<td>14,4 MEUR</td>
<td>34,0 MEUR</td>
</tr>
</tbody>
</table>

ICER = \( \frac{150\,000\,\text{EUR}}{\text{QALY}} \)
NNT = \( \frac{14,1}{\text{Tx/prevented Ca}} \)

30:5:60 vs. no screening:
- NNT ~ 3 CINt/ prev. Ca
- ICER < 1000 EUR/QALY

- Cancer ~ 50 less
- CINt ~700 more
- QALY loss, no changes
- Incremental benefits expensive

NNT = *number needed to treat*, number of CIN treatments per prevented Ca
ICER = *(incremental cost-effectiveness ratio)*
Modelling better screening algorithms

**Present practice**
- C53: 135, 1380 QALY
- CINt: 2300, 34,0 MEUR

**25:5:60**
- C53: 157, 1370 QALY
- EH: 1900, 15,8 MEUR

**30:5:65E**
- C53: 143, 1250 QALY
- EH: 1700, 16,1 MEUR

**Organized scr 30:5:60**
- C53: 187, 1510 QALY
- EH: 1600, 14,4 MEUR

**25:5:65E**
- C53: 112, 1110 QALY
- EH: 2000, 17,2 MEUR

**25:5:35 HPV: 5:65E**
- C53: 98, 990 QALY
- CINt: 2200, 17,9 MEUR

- Even less Cancer and QALY-loss
- Cost effective, 16 MEUR savings compared to present

- 150 000 EUR/QALY NNT 14,1
- 7 000 EUR/QALY NNT 6,4
- 10 000 EUR/QALY NNT 10,5
- 6 600 EUR/QALY NNT 3,7
- 5 700 EUR/QALY NNT 9,1
Cancer incidence with scenario 25:5:35HPV:5:65E

- The peak among younger remains
- Insidence decrease among 35+ faster (HPV-test)
- The other peak vanishes
- The first peak taken care with vaccines!? 
Screening and vaccination together

*Figure 4. Cost-effectiveness analysis of different HPV vaccination/screening combination by quality adjusted life years (QALY) lost.*
Conclusions

• Vaccination and screening are completing each other

• To decrease efficiently the HPV disease burden:
  The most important factor in vaccination programmes and screening programmes is

• High coverage and attendance rates to both programmes

• Mathematical models using the best possible “local” data produce the most cost-effective ways to decrease HPV disease burden

• In the future few life-time hrHPV-tests with molecular marker triage in vaccinated populations?
Key Messages

1. Screening and vaccination are synergistic
2. Mathematical modelling and simulation are of great help when designing the best prevention strategies
3. High coverage is the most important factor for good results both in vaccination and screening programmes