Implementation of cervical screening in The Netherlands

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Conflicts of interest

- Speakers bureau Qiagen GSK, Roche, Merck, Gen-Probe
- Stock in Self-Screen, a small spin-off company of the VU University medical center
• Present nation wide screening program
• Arguments for HPV testing
• Which HPV test
• Triage of HPV pos. women
• HPV self-sampling
• Costs new HPV based screening program
Current Cervical cancer screening in The Netherlands: program characteristics

- Inhabitants: 16 M; 4 M women in screening age
- Incidence 7.0/100.000 (~650 cases/Year)
- Mortality 2.0/100.000 (~220 cases/Year)
- Target population: women 30-60 year,
- Screening system: call and recall
- Screening interval: 5 years, 7 rounds
Cervical cancer screening in The Netherlands: program characteristics

• Screening method: cervical cytology

• Cytological classification: CISOE-A

• Attendancy: 67%, funded by Min. Health, 5 scr. Org. nr smears/year in national screening program: ~550.000-600.000

• Total nr of smears made/year: ~650.000-700.000

• Costs: ~30 M €/year
Advantages of present cytology based screening programme

- Decrease in CxCa incidence from 1989-2004 by EAPC 1.1% per year

- Good classification system released in 1996 (CISOE-A=KOPAC-B)
  
  C: composition; I: Inflammation, S: squamous cells
  O: other, E: endocervical cells

- has decreased the number of slides with minor abnormalities (BMD or ASC-US/LSIL) from
  ~11.5% in 1990-1996 to ~2.1% in 2000-2009

Why considering a change in the present screening programme?

• Since 2004 the incidence of CxCa is not decreasing anymore

• Attendancy to Screening programme (67%) is not good enough

• Too much time (at least 6 months often longer ) to select women with HSIL out of the women with equivocal smears (BMD or ASC-US/LSIL)

• Incidence of AdenoCa has not decreased: adenocarcinoma and ACIS are missed

De Kok et al Int.J.Cancer 2011
What should be improved in present cervical screening programme

- No show: Netherlands: 67 % attendancy, 72% coverage
- Sensitivity Pap Smear: 62%, subjective
  ~10% false pos and false neg smears
- Lack of control F-up women with abnormal smears
How to improve cervical screening?

- **Attendence:**
  - Introduction HPV-Self-sampling,
  - Better involvement GP, fixed date and time

- **Test sensitivity:** Introduction HPV test

- **Improve f-up women with abnormal smears:** Screening organisation have control via Palga (nation-wide registry of pathology specimens) whether the women has had f-up visits by gynaecologists
• Introduction
• Present nationwide screening program
• Arguments for HPV testing
• Which HPV test
• Triage of HPV positive women
• HPV self-sampling
• Costs new HPV-based screening program
Arguments HPV testing

- **Objective**

- HPV testing (~95%) is more sensitive than cytology (at best ~62%) but less specific (2.5% - 4%) (cross-sectional studies)

- HPV testing protects better against CIN3+ and Cervical Cancer than cytology (longitudinal studies): 50% less CIN3+ and 70% less cancer after a neg HPV test

*Cuzick 2006 IJC; Bulkmans 2007 Lancet; Rijkaart 2012 Lancet oncology; Ronco 2013 Lancet, Arbyn 2012 Vaccine, Cage 2014 JNCI*
Meta-analysis of outcome of RCT: relative Detection rate of CIN3+ or CxCa in second round in women who were HPV neg or cytology neg at enrolment

50% less CIN3+ and significantly less cancer in second round in HPV screen neg women compared to cytology screen negative women at enrolment

➢ HPV protects better against CIN3+ and Cancer than cytology

* restricted to women of 35 years or older.
† continuity correction (+.5 in each cell because of zero cancer cases among HPV-negative women).
Cumulative detection of invasive carcinoma
Pooled data from POBASCAM, NTCC, ARTISTIC and SWEDESCREEN (>160,000 women)

Figure 2: Cumulative detection of invasive cervical carcinoma
*Observations are censored 2-5 years after CIN2 or CIN3 detection, if any.

Ronco et al., Lancet 2013

A negative HPV test provides better protection against cancer than cytology
• Introduction
• Present nation wide screening program
• Arguments for HPV testing
• Which HPV test (discussed in next presentation)
• Triage of HPV pos. women
• HPV self-sampling
• Costs new HPV based screening program
HPV test in cervical screening

- HPV test should fulfill specific requirements: international guidelines for HPV tests
- Suitable for High Throughput
- Lower specificity of HPV test should be compensated for by triage testing
  - Presently: Cytology, HPV 16/18 genotyping or Combo

Why triage of HPV pos women?

HPV test detects women at risk for cervical (pre)cancer (CIN2+/3+).
  - many women with transient infections

Triage test detects women with disease = Cervical (pre)cancer (CIN2+/3+)
  - low number of women with transient infections
Evaluation of triage tests in VUSA-Screen and POBASCAM studies

- Cytology
- HPV 16/18 genotyping
- Combinations of these tests

Rijkaart et al Int. J Cancer 2011; Dijkstra et al CEBP 2013
Strategies should have a high NPV for CIN3+ of ≥98% (safety)

If the 3 year CIN3+ risk is:

- >10%: immediate referral for colposcopy
- 3-10%: short-term follow-up testing after 6-12 months
- ≤2%: referral to next screening round (3 or 5 years)

Castle et al 2008; Dutch screening council 2010; Rijkaart et al Int J Cancer 2011
Dijkstra et al CEPB 2013
### Three strategies with triage at baseline, without a repeat test

<table>
<thead>
<tr>
<th>Baseline triage strategy</th>
<th>Endpoint CIN2+</th>
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<th>Endpoint CIN3+</th>
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<th>Colpo referral rate</th>
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<th>Total screening population</th>
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<tbody>
<tr>
<td></td>
<td>Sens (95% CI)</td>
<td>Spec (95% CI)</td>
<td>NPV (95% CI)</td>
<td>PPV (95% CI)</td>
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<td>PPV (95% CI)</td>
<td>Sens (95% CI)</td>
<td>Spec (95% CI)</td>
<td>NPV (95% CI)</td>
<td>PPV (95% CI)</td>
<td>Colpo referral rate (95% CI)</td>
<td>Colpo referral rate (95% CI)</td>
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<td>I. Cytology</td>
<td>66.0% (59.6-71.9)</td>
<td>81.4% (78.0-84.4)</td>
<td>87.6% (84.5-90.2)</td>
<td>54.5% (48.5-60.4)</td>
<td>75.4% (67.9-81.7)</td>
<td>78.0% (74.6-81.1)</td>
<td>94.3% (92.0-96.0)</td>
<td>39.7% (34.0-45.6)</td>
<td>30.5% (27.5-33.7)</td>
<td>1.53% (1.38-1.69)</td>
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<tr>
<td>II. Cytology / HPV16+</td>
<td>86.1% (80.9-90.0)</td>
<td>62.6% (58.5-66.5)</td>
<td>93.0% (90.0-95.2)</td>
<td>43.8% (39.0-48.6)</td>
<td>94.1% (89.1-98.9)</td>
<td>58.8% (54.9-62.6)</td>
<td>98.1% (96.2-99.1)</td>
<td>30.5% (26.2-35.1)</td>
<td>49.7% (46.5-53.0)</td>
<td>2.49% (2.33-2.65)</td>
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<tr>
<td>III. Cytology / HPV16/18+</td>
<td>90.3% (85.7-93.5)</td>
<td>57.6% (53.3-61.7)</td>
<td>94.6% (91.7-96.6)</td>
<td>41.8% (37.3-46.6)</td>
<td><strong>96.6% (92.3-98.5)</strong></td>
<td><strong>53.6% (49.7-57.5)</strong></td>
<td><strong>98.8% (97.0-99.5)</strong></td>
<td><strong>28.5% (24.4-32.8)</strong></td>
<td><strong>54.5% (51.2-57.6)</strong></td>
<td><strong>2.73% (2.56-2.88)</strong></td>
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### Table 2. Seven strategies with baseline triage followed by one round of repeat testing

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<tr>
<th>Baseline triage test</th>
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<th>Endpoint CIN2+</th>
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<td>Sens (95% CI)</td>
<td>Spec (95% CI)</td>
<td>NPV (95% CI)</td>
<td>PPV (95% CI)</td>
<td>Repeat tests (95% CI)</td>
<td>Colpo referral rate (95% CI)</td>
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<td>IV. Cytology</td>
<td>98.9% (96.5-99.7)</td>
<td>36.1% (34.1-42.2)</td>
<td>99.1% (96.6-99.7)</td>
<td>35.0% (31.2-39.0)</td>
<td>100.0% (97.5-100)</td>
<td>34.1% (30.6-38.0)</td>
<td>100.0% (93.2-100)</td>
<td>22.5% (19.3-26.2)</td>
<td>69.5% (66.7-72.1)</td>
<td>71.3% (68.1-74.2)</td>
<td>3.57% (3.44-3.71)</td>
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<tr>
<td>V. Cytology / Cytology</td>
<td>89.2% (84.5-92.6)</td>
<td>70.1% (66.2-73.0)</td>
<td>95.1% (92.5-96.9)</td>
<td>50.2% (45.1-55.2)</td>
<td><strong>94.9% (90.1-97.5)</strong></td>
<td><strong>64.7% (60.9-68.4)</strong></td>
<td><strong>98.5% (96.8-99.3)</strong></td>
<td><strong>34.0% (29.4-39.0)</strong></td>
<td><strong>69.5% (66.7-72.1)</strong></td>
<td><strong>44.8% (41.5-48.2)</strong></td>
<td><strong>2.24% (2.09-2.41)</strong></td>
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<tr>
<td>VI. Cytology / HPV+</td>
<td>99.5% (97.4-99.9)</td>
<td>35.7% (31.8-38.9)</td>
<td>99.5% (97.2-99.9)</td>
<td>34.3% (30.6-38.3)</td>
<td>100.0% (97.5-100)</td>
<td>32.0% (28.4-35.7)</td>
<td>100.0% (98.1-100)</td>
<td>22.0% (18.8-25.9)</td>
<td>69.5% (66.7-72.1)</td>
<td>73.2% (70.1-76.0)</td>
<td>3.66% (3.51-3.80)</td>
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<tr>
<td>VII. Cytology / HPV16+</td>
<td>95.2% (91.5-97.3)</td>
<td>54.3% (50.1-58.4)</td>
<td>97.1% (94.6-98.5)</td>
<td>41.3% (37.0-45.8)</td>
<td>99.3% (94.7-99.5)</td>
<td>49.5% (45.6-53.3)</td>
<td>99.4% (97.8-99.8)</td>
<td>27.2% (23.4-31.4)</td>
<td>50.3% (47.3-53.2)</td>
<td>59.2% (55.0-61.4)</td>
<td>2.91% (2.75-3.07)</td>
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<tr>
<td>VIII. Cytology / HPV16+</td>
<td>99.5% (97.4-99.9)</td>
<td>27.9% (24.3-31.7)</td>
<td>99.4% (97.2-99.9)</td>
<td>31.8% (28.3-35.6)</td>
<td>100.0% (97.5-100)</td>
<td>25.0% (21.7-28.5)</td>
<td>100.0% (96.7-100)</td>
<td>20.4% (17.4-23.7)</td>
<td>50.3% (47.3-53.2)</td>
<td>79.1% (76.3-81.6)</td>
<td>3.96% (3.82-4.09)</td>
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<tr>
<td>IX. Cytology / HPV16/18+</td>
<td>97.8% (95.0-99.1)</td>
<td>50.0% (45.8-54.1)</td>
<td>98.6% (96.4-99.4)</td>
<td>39.7% (35.5-44.1)</td>
<td><strong>99.2% (96.0-99.8)</strong></td>
<td><strong>45.0% (41.2-48.9)</strong></td>
<td><strong>99.5% (98.0-99.9)</strong></td>
<td><strong>25.5% (22.0-29.6)</strong></td>
<td><strong>45.5% (42.6-48.5)</strong></td>
<td><strong>62.1% (58.9-65.1)</strong></td>
<td><strong>3.11% (2.95-3.26)</strong></td>
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</tr>
<tr>
<td>X. Cytology / HPV16/18+</td>
<td>100.0% (98.3-100)</td>
<td>26.4% (22.9-30.2)</td>
<td>100.0% (97.5-100)</td>
<td>31.4% (27.9-35.1)</td>
<td>100.0% (97.5-100)</td>
<td>23.5% (20.3-26.9)</td>
<td>100.0% (97.4-100)</td>
<td>20.0% (17.0-23.3)</td>
<td>45.5% (42.6-48.5)</td>
<td>80.3% (77.8-82.7)</td>
<td>4.02% (3.88-4.14)</td>
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</table>
Best triage strategies

• Two triage strategies for HPV+ women showed the best balances for negative risk stratification, colposcopy referral rates and ease of implementation:

   A) Baseline cytology and cytology in follow-up (6 or 12 months), lowest referral rate (33%-44%), good safety

   B) Baseline cytology & HPV16/18 genotyping and cytology in follow-up (6 or 12 months), higher referral rate (50%-62%), good safety

• One strategy (HPV 16/18 genotyping & cytology) was less save in VUSA-Screen study but has advantage of no follow-up step: no loss of women in follow-up, referral rate 43%-54%, safety ~97-98%

• The exact algorithm to be used for triage depends on the quality of cytology and the minimum positive predictive value for CIN3+ referral acceptable by local health decision makers (resources available)

Rijkaart et al Int.J Cancer 2011; Dijkstra CEPB 2013
What are the characteristics of the new HPV based cervical screening program implemented in 2016?
New HPV based cervical screening program implemented in 2016

- HPV test as primary screening tool will be implemented in the population-based cervical screening program.

- Invitation for screening at 30-35-40-50-60 years, two rounds less compared to old program.

- Triage by twice cytology (baseline and 6 months).

- Women at 40, 50 and 60 years who are HPV positive and 2x cytology triage negative (at baseline and 6 months) are rescreened after 5 years (at 45, 55, or 65 years).
For determining the length of the screening interval the long term CIN3+ risk of HPV + women with a negative triage test is important.
Long term observations in HPV pos women

- Only for HPV screen neg women the screening interval can be extended to 10 y

- For HPV + women with negative triage test results (2x Cyto, Cyto/HPV16/18-cyto 6mo) the screening interval can not be extended above 5y because their CIN3+ risk exceeds > 2%
New triage tests which are now available (not implemented yet)

- $p16^{INK4A}/Ki67$ dual staining

✓ Objectivates triage by cytology

- Methylation analysis host cell genes
  - Verhoef et al CEPB 2014

✓ High Reassurance against CxCa and advanced CIN 2/3 with a high short term risk on CxCA
• Introduction
• Present nation wide screening program
• Arguments for HPV testing
• Which HPV test
• HPV triage
• HPV self-sampling
• Efficiency and costs new HPV based screening program
New HPV based cervical screening program implemented in 2016

- Vaginal Self sampling for HPV testing for non-responders in screening program
Offering Self-Sampling of cervico/vaginal material for HPV testing (HPV self-sampling)

- Women obtain by mail package with device
- Women takes C/V sample by device
- Device: Swabs, Brush, lavage, tampon
- Material is returned to lab for HPV testing
- HPV test result is sent to women/physician and SO
- Triage of HPV pos women by cytology on extra smear taken by physician
Arguments for introduction HPV-Self-sampling derived from PROHTECT Studies

- 50% of cervical carcinomas is found in non-attendees of screening programme (30% of screening invitees)

- In the Netherlands 1/3 of non-attendees respond to HPV-self-sampling

Delphi Screener and Viba brush both from Rovers medical devices, Oss, Netherlands

Arguments for introduction HPV-Self-sampling derived from PROHTECT Studies

(PR)tection by (O)ffering (HPV t)e(sting on) Cervicovaginal specimens T

- Never screened women respond better than underscreened women

- Yield of CIN2/3+ is higher in non-attendees than in responders of screening program. (CIN2+: 1.4% vs 0.8%; CIN3+: 1.0% vs 0.53%; CxCa 0.09%vs 0.03%).

  Highest yield of CIN2/3+ in never screened women
  

- When a standardised SS-device in combination with a clinically validated HPV test is used, the sensitivity for CIN3+ is non-inferior to sensitivity of an HPV test on a physician taken smear

PROHTECT studies

PRotection by Offering HPV Testing on Cervico-vaginal specimens Trial

Women invited to pap smear screening in 2005-2006
(n = 230 509)

Non-attendees
(n = 54 482)

Self-sampling
(n = 52 447)

Re-call
n=538
12%

Non-eligible
(n = 1 497)

Screening participants
(n = 176 027)

HPV-testing on self-samples
(n = 15 274) (29%)

29%

CIN2 n = 61 (0,4%)
CIN3 n = 144 (0,9%)
Cancer n = 13 (0,09%)

Histology after 18 months

Yield of (pre-)cancer in regular (pap-smear) and under-screened women (self-sampling): pooled PROHTTECT studies: higher risk for non-attendees

Women invited to pap smear screening in 2005-2006
(n = 230 509)

Non-attendees
(n = 54 482)
Re-call
(n=538)
Self-sampling
(n = 52 447)
Non-eligible
(n = 1 497)

Screening participants
(n = 176 027)

HPV-testing on self-samples
(n = 15 274) (29%)

Histology after 18 months

≥CIN2+ 1.4%
CIN2 n = 61 (0,4%)
CIN3 n = 144 (0,9%)
Cancer n = 13 (0,09%)

Histology after 18 months

≥CIN2+ 0.8%
CIN2 n = 540 (0,3%)
CIN3 n = 941 (0,5%)
Cancer n = 59 (0,03%)
RCT: Difference in participation rate (PP) 

\[ P_{self} - P_{control} \]

<table>
<thead>
<tr>
<th>Study</th>
<th>Proportion (95% CI)</th>
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<td>Mail to all</td>
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<tr>
<td>Bais, 2007</td>
<td>0.14 (0.09, 0.19)</td>
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<td>Gok, 2010</td>
<td>0.11 (0.07, 0.15)</td>
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<tr>
<td>Giorgi-Rossi, 2011</td>
<td>0.09 (0.06, 0.13)</td>
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<tr>
<td>Piana, 2011</td>
<td>0.19 (0.18, 0.21)</td>
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<tr>
<td>Szarewski, 2011</td>
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<td>Virtanen, 2011</td>
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<td>Wikström, 2011</td>
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<td>Gok, 2012</td>
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<td>Darlin, 2013</td>
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<td>Sancho-Garnier, 2013</td>
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<td>Haguenoer, 2014</td>
<td>0.02 (0.00, 0.04)</td>
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<tr>
<td><strong>Total (I²=98.5%, p=0.000)</strong></td>
<td><strong>0.12 (0.07, 0.17)</strong></td>
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</tbody>
</table>

| Mail if request     |                     |
| Giorgi-Rossi, 2011  | -0.02 (-0.05, 0.01) |
| Broberg, 2014       | 0.01 (-0.01, 0.04)  |
| **Total (I²=64.9%, p=0.091)** | **-0.00 (-0.03, 0.03)** |
Relative sensitivity and specificity for CIN2+
hrHPV DNA testing of self- vs clinician-collected

Validated PCRs

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<td>Nobbenhuis, 2002</td>
<td>0.89 (0.72, 1.10)</td>
<td>Nobbenhuis, 2002</td>
<td>1.61 (1.03, 2.53)</td>
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<td>Brink, 2006</td>
<td>0.97 (0.86, 1.10)</td>
<td>Brink, 2006</td>
<td>0.96 (0.63, 1.45)</td>
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<td>Dijkstra, 2012</td>
<td>1.03 (0.90, 1.16)</td>
<td>Dijkstra, 2012</td>
<td>1.00 (0.75, 1.33)</td>
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<td>van Baars, 2012</td>
<td>0.91 (0.68, 1.21)</td>
<td>van Baars, 2012</td>
<td>1.00 (0.83, 1.21)</td>
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<td>Geraets, 2013</td>
<td>0.90 (0.80, 1.00)</td>
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<td>1.25 (1.00, 1.56)</td>
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<td>Subtotal (I^2 = 0.0%, p = 0.540)</td>
<td>0.95 (0.89, 1.01)</td>
<td>Subtotal (I^2 = 31.3%, p = 0.213)</td>
<td>1.11 (0.95, 1.29)</td>
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</table>

Abbott RT PCR
Jentschke, 2013b

HPV risk assay® Self-Screen
qPCR targeting E6-E7
Hesselink, 2014

<table>
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<th>RR (95% CI)</th>
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<tr>
<td>1.03 (0.88, 1.21)</td>
<td>0.93 (0.66, 1.30)</td>
</tr>
<tr>
<td>0.96 (0.75, 1.24)</td>
<td>0.94 (0.67, 1.33)</td>
</tr>
<tr>
<td>0.98 (0.95, 1.02)</td>
<td>1.02 (0.94, 1.09)</td>
</tr>
</tbody>
</table>

Overall (I^2 = 0.0%, p = 0.744) 0.98 (0.95, 1.02) Overall (I^2 = 18.2%, p = 0.281) 1.02 (0.94, 1.09)

Arbyn et al 2014 Lancet oncology
HPV self-sampling in new Dutch Cervical screening programme: only in non-attendees

- Women who do not attend the screening programme will get a reminder within 6 weeks and a letter that the woman has the possibility to receive an HPV-Self-sample set. If they agree they should send in the preprinted letter.

- The preprinted letter states that the women likes to receive the SS set and can be sent to the Screening organisation without costs. (opt-in)
• Introduction
• Present nation wide screening program
• Arguments for HPV testing
• Which HPV test
• Triage of HPV pos women
• HPV self-sampling
• Efficiency and costs new HPV based screening program
Characteristics of HPV based cervical screening program

• New HPV based cervical screening is based on risk assessment of test positive women

Not based on follow-up of women with HPV persistence

• It is a balance between efficiency of the programme (CIN2/3+ detection), the costs and the burden of the screened women without disease (investigations and f-up)
Simplified Organisation of Dutch screening programme

M. of Health:
ordering party provides budget

Centre for Population based screening (RIVM):
central control, management and implementation

Screening organisations and Professionals (GP and screeninglabs)

Advise: health Council
Advise: Program cie Consisting of representatives of Societies of professionals GP, PA, GY, Technicians etc
Expected results of new screening program
Cost estimation based on data 2011

- 94% HPV negative, 5% HPV+ in regular screening attendees,
- 91% HPV negative and 9% pos in initial non-responders
- ~30% of HPV screen positives Has abnormal cytology
- Increase referrals for colpoBx from 3900 to 5200/year
- Repeat investigations: Decrease from 14.600 to 12.200
- Extra 75 new CxCa/year detected and extra 20 death/year prevented

- Effect of introduction HPV- self-sampling: better coverage of non-responders: ~66 new CxCa and 24 death by CxCa
- Cheaper: extra costs (€ 4.7M/year) of HPV test and referrals for colpoBx are overcompensated by less screening rounds
Estimated costs new screening program

- Costs 13% less than in present screening program (~€ 27.5M vs € 31.6M)

- 140,000 women per year less invited

- Cost per screened women higher (estimated € 63.22 vs € 57.47)

- Implementation costs € 4.7 M /year over 5 years.

- Cytological investigations 17,400 vs 484,000

*Rivm rapport 225121002: uitvoeringstoets wijzigingen BVO Baarmoederhalskanker 2014*
Quality of new screening programme

- 5 screening regions and 5 screening labs

- Quality control for the whole chain of screening: from selection to treatment by gynaecologist. Monitoring and evaluation by RIVM via data warehouse (filled in by Dutch cancer registration, SO’s and Palga (nation wide pathology data base))

- In the future, coupling of registries of HPV vaccinated women with screening registries
Implementation

• Preparation Phase till 2016
  • a.o Tenders selecting which HPV test, which self-sampler and which screening lab
  • Optimizing logistics and monitoring etc

Implementation phase 2016-2021:

  From 2016: only HPV based screening per invitation round

• Definitive Phase 2021:
  – all women have received an HPV based screening test
Conclusions

- Efficient screening program targeting women 30-60 years
- Efficient in terms of invitation, yield of CIN2+ and costs
- Available for all women
- Directed to the future:
  - Coupling with vaccination registry
  - Possibility to go full molecular
Thank you for your interest.
Thanks to HPV Team VUmc 2004-2015

From L to R: Peter, Sigrid, Feja, Aletta, Folkert, Nicole, Chris, Antoinette, Bart, Saskia, Maaike

From L to R: Dorien, Daniëlle, Bart, Maaike, Renske, Chris, Mariëlle, Peter, Jacqueline, Murat

Coöperating Gynaecologists Rene Verheijen, Theo Helmerhorst, Gemma kenter

430 participating general Practitioners and more than 250.000 women
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Midden-West, Oost and zuid

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- Nynke van der Veen

DEPT OF PATHOLOGY ERASmus mc
- F. van Kemenade

EEC consortia
- PreHDICT
- CoHeaHr

ERC advanced Grant
- Mass-care

Dutch Cancer foundation
ZON-MW
Requirements for new population based cervical screening

- Population based screening (call and recall) should be efficient in terms of:
  - reaching target population,
  - applied technique,
  - health gain

- Programme should be:
  - safe, and country wide available
  - Cost-effective
  - part of the total health chain to guarantee good connection with diagnostic and treatment units so that programme is efficient and can be evaluated
Cytomorphological classification; the CISOE-A and Pap classification compared to Bethesda 2001 classification.

<table>
<thead>
<tr>
<th>CISOE-A</th>
<th>S0, O0, E0</th>
<th>S1, O1 E1-2</th>
<th>S1, O1 E1-2</th>
<th>S2-3, O3, E3</th>
<th>S4, O4, E4</th>
<th>S5, O5, E5</th>
<th>S6, O6, E6</th>
<th>S7, E7</th>
<th>S8-9, O7-8, E9</th>
</tr>
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<tbody>
<tr>
<td>CISOE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
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<td>Pap1</td>
<td>Pap1</td>
<td>Pap2</td>
<td>Pap3a1</td>
<td>Pap3a2</td>
<td>Pap3b</td>
<td>Pap4</td>
<td>Pap5</td>
</tr>
<tr>
<td>Descrip</td>
<td>Inadequate</td>
<td>Normal</td>
<td>Borderline</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Carcinoma</td>
<td>Carcinoma</td>
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</tr>
<tr>
<td>Bethesda 2001</td>
<td>Unsatisfactory for evaluation</td>
<td>NILM</td>
<td>Atrophy, NILM</td>
<td>ASC-US / ASC-H</td>
<td>ASC-H / LSIL</td>
<td>HSIL</td>
<td>AGC</td>
<td>AGC favor neoplastic</td>
<td>AIS</td>
</tr>
</tbody>
</table>

CISOE-A, C composition, I inflammation, S squamous epithelium, O Other abnormalities and endometrium, and E endo-cervical columnar epithelium; the acronym CISOE-A is KOPAC-B in Dutch. NHIL, negative for intra-epithelial lesions or malignancy; ASC-H, atypical squamous cells cannot exclude HSIL; ASC-US, atypical squamous cells of undetermined significance; AGC, atypical glandular cells; LSIL, low grade squamous intraepithelial lesion; HSIL, high grade squamous intraepithelial lesion; AIS, endocervical adenocarcinoma in situ; SCC, squamous cell carcinoma; AC, adenocarcinoma