The HPV FASTER consortium: Searching for the best combinations of vaccination and screening

FX Bosch
Institut Catala d’Oncologia
Salzburg
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Potential conflict of interest

- Research and educational institutional grants:
  GSK, SPMSD, Merck, Qiagen
- Personal / speaking / travel grants:
  GSK, SPMSD, Merck, Qiagen, RMS

This presentation is the sole responsibility of the author
Two major stages in vaccine introduction

Licensing (Phase I-III)

- Safety
- Efficacy
- Product specific / trial restricted / regulators’ agreed
- Defined evaluation criteria & protocols
- **FDA / Advisors / EMA / MoH & National advisory boards…**

Recommendations

- Uses in a given population
  - Vaccination ages, dosing and schedule
- Adverse events incidence and evaluation
- Cost-effectiveness
- **ACIP / WHO GACVS / National expert bodies & societies**
Potential new indications for HPV vaccination / screening (before the absence of formal Phase III clinical trials)

**PROPHYLACTIC** (prevent new infections and transmission)
- Adult women
  - To 26, 30, 45+…
- Males
  - To 18, 50+…
- Infants (EPI)

**AS PART OF THERAPY** (interrupt reinfections and prevent transmission)
- HPV + women in screening
- Post treatments in CIN lesions
- RRP
- GW and survivors of HPV related cancers
- Therapeutic / mixed vaccines

**HIGH RISK GROUPS** (selective vaccination & new screening)
- HIV cohorts / MSM
- Transplants & immunosuppressed
- Autoimmune patients
- STI clinics
- Partners of HPV+
- Migrants / marginal
- Abused children
Cervical Cancer prevention: Social Partners

<table>
<thead>
<tr>
<th>Screenologists</th>
<th>Vaccinologists</th>
<th>Policy makers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gynecologists</td>
<td>Pediatricians</td>
<td>Centralized public health programs organizers</td>
</tr>
<tr>
<td>Pathologists</td>
<td>GP’s</td>
<td>Communication &amp; education</td>
</tr>
<tr>
<td>GP’s</td>
<td>Vaccine experts</td>
<td>International Phase IV follow up</td>
</tr>
<tr>
<td>Treatment</td>
<td>Infectious diseases</td>
<td>Financing &amp; equity</td>
</tr>
<tr>
<td>HPV screening technologies</td>
<td>Vaccine industry</td>
<td></td>
</tr>
</tbody>
</table>

ICO Hospitalet.  
Cancer Epidemiology Research Program (CERP)  
Institut Català d’Oncologia
# Options to control cervical cancer

<table>
<thead>
<tr>
<th></th>
<th>SCREENING (PAP)(^1\text{–}^3)</th>
<th>SCREENING (HPV)</th>
<th>HPV 16/18 VACCINATION(^3\text{–}^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Cervical cancer / pre-cancer</td>
<td></td>
<td>Cervical cancer / pre-cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>HPV infection &amp; Interrupt Transmission</em></td>
</tr>
<tr>
<td><strong>Impact</strong></td>
<td>Participant</td>
<td>Participant</td>
<td>Participant + <em>Herd effect</em></td>
</tr>
<tr>
<td><strong>Number of interventions</strong></td>
<td>(10\text{…}50+ \text{tests lifetime})</td>
<td>(5+ \text{tests lifetime})</td>
<td>3 / 2 doses no booster dose to date</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>Local diagnostic &amp; treatments network</td>
<td></td>
<td>Phase IV effectiveness &amp; safety studies in selected countries</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Mild / Obstetrics /over-diagnostics</td>
<td></td>
<td>Local/short-lived</td>
</tr>
<tr>
<td><strong>Impact on other cancers</strong></td>
<td>Limited / none</td>
<td></td>
<td><em>Significant in HPV related cancers</em></td>
</tr>
</tbody>
</table>

Figure 2. Under no vaccination and no screening programs (green dot number 1) the social costs of cervical cancer would be low (i.e. some 11MEUR) and the quality adjusted years of life lost very high (close to 5,000). Vaccination programs with a range of screening options (red dots 8,9,10 or 11) would have a similar cost but the number of QALYs lost would be reduced to around 500.
## Accuracy of HPV screening vs. cytology

<table>
<thead>
<tr>
<th>Screening test</th>
<th>N</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Detection of CIN2+</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytology (ASC-US+)</td>
<td>25</td>
<td>70.0% (62.5–77.6%)</td>
<td>91.9% (90.3–93.6%)</td>
</tr>
<tr>
<td>HC2</td>
<td>31</td>
<td><strong>90.4% (88.0–92.8%)</strong></td>
<td><strong>88.5% (87.0–90.0%)</strong></td>
</tr>
<tr>
<td>Co-testing*</td>
<td>13</td>
<td>94.2% (90.8–97.6%)</td>
<td>87.7% (85.0–90.3%)</td>
</tr>
<tr>
<td><strong>Detection of CIN3+</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytology (ASC-US+)</td>
<td>21</td>
<td>74.6% (65.6–83.6%)</td>
<td>91.8% (90.0–93.7%)</td>
</tr>
<tr>
<td>HC2</td>
<td>22</td>
<td><strong>95.3% (93.3–97.3%)</strong></td>
<td><strong>89.0% (87.2–90.8%)</strong></td>
</tr>
<tr>
<td>Co-testing*</td>
<td>12</td>
<td>96.7% (93.7–99.7%)</td>
<td>82.9% (77.1–88.6%)</td>
</tr>
</tbody>
</table>

*Cytology (ASC-US+) and HC2

Updated meta-analysis data from Arbyn et al.\textsuperscript{21,22}
In Bosch FX et al. Nature reviews Clinical oncology 2015
HPV type-specific contribution to cervical cancer and potential for prevention of existing vaccines

<table>
<thead>
<tr>
<th>Type-specific Vaccine efficacy</th>
<th>RC %</th>
<th>Gardasil</th>
<th>Cervarix</th>
<th>Gardasil9</th>
</tr>
</thead>
<tbody>
<tr>
<td>16+18</td>
<td>71</td>
<td>95+%</td>
<td>95+%</td>
<td>95+%</td>
</tr>
<tr>
<td>+31</td>
<td>75</td>
<td>Parcial</td>
<td>Parcial</td>
<td>95+%</td>
</tr>
<tr>
<td>+33+45</td>
<td>84</td>
<td>-</td>
<td>Parcial</td>
<td>95+%</td>
</tr>
<tr>
<td>+52+58</td>
<td>89</td>
<td>-</td>
<td>?</td>
<td>95+%</td>
</tr>
</tbody>
</table>

Relative Contribution – RC (%)

95% Confidence Interval

de Sanjosé S et al. Lancet Oncol, 2010
Serrano B et al. Infect Ag Cancer, 2012
Schiller J et al Vaccine 30 S 5 2012
Lehtinen M et al. Nat Rev Clin Oncol. 10 2013
Women in middle age groups, found HPV negative and receiving a broad spectrum HPV vaccine (expected 90% protection against oncogenic HPV types) has a subsequent risk of cervical cancer extremely low.

Under these risk estimates, the requirements for further screening are likely to be minimal (one / two lifetime), necessarily HPV based.

**NOVEL OPTIONS**
- self sampling,
- urine HPV test
- point of care tests
- screen and treat HPV therapeutics…

**A choice**

**A unique chance**
Current cervical cancer preventive strategies (simplified) and proposed HPV FASTER initiative

- **1945 +**
  - Cytology x 3 yrs.
- **2006 +**
  - Cytology (x3 to age 25/30) & HPV test x 5/10 yrs.
- **2016 +**
  - HPV tests x 2 / 3 lifetime

**HPV FASTER**

- Routine and Catch-up / opportunistic vaccination: intervention (x2 or x3, based on age)
- Cytology screening: intervention (抽检)
- HPV screening: intervention (HPV)

Exact age limits to be defined
HPV-FASTER deployment: potential for minimum cross sectional interventions across all age groups

Age (years)

Phase 1

- 2 / 1 dose?
- Male vaccination
- HPV test
- TRIAGE & TREATMENT
- SCREEN AND TREAT

Phase 2

- Arriving new cohorts of adolescent girls as either: Interval campaigns
- EPI routine infant immunization programs*
- Migrants & non participant subgroups

Subsequent required actions

at 9-10 y

- Routine vaccination
- Catch-up / opportunistic vaccination
- HPV screening
- Male vaccination

*EPI: Expanded Program of immunization
HPV-FASTER strategy: Core concept and expected impact

- **HPV (-)**
  - 100% vaccine efficacy in HPV negative
  - 70% vaccine efficacy in HPV positive
  - 90-95% vaccine efficacy in all women

- **HPV (+)**
  - 30% vaccine efficacy in HPV negative
  - 5-10% vaccine efficacy in HPV positive
  - <5% vaccine efficacy in HPV DNA test
  - 50% vaccine efficacy in all women

**Screen and Treat**
- TRIAGE
  - Negative: Follow-up until HPV clearance
  - >90% expected protection against invasive disease
- CIN2+: Treatment and follow-up

**Unknown**
- Protection against invasive disease

**Triage:** HPV typing, cytology, other biomarkers, colposcopy or biopsy paired with management algorithms
HPV FASTER: Master impact expected

One HPV testing / treatment round at a sensitivity of 90-95% would reduce the incidence of cervical cancer within years.

Generalized vaccination over a wider age range would ensure medium & long term reduction of viral infections, pre-cancer and cancer.

The strong herd protection effect of HPV vaccines suggests that male vaccination will further accelerate the reduction of HPV infections.
HPV FASTER: formats & research issues

**Trials**

- Women aged 25/30 to 45/50

**INTERVENTION**

1. Dose 1
2. Dose 2
3. Dose 3

**CONTROL**

- **Cytology + HPV test**

**Demonstration projects**

- **INTERVENTION AGES 9 TO 65**
  - **HPV test**
  - **Surveys of HPV and Cytology**
  - **Cancer incidence and mortality**

**Input data for models**
- Population impact
- Time to impact
- Acceptability, coverage & compliance

**Self sampling**
- Urine tests
- Point of care testing systems

**Triage technology**
- Treatment
- Vaccine dosing
- New vaccines
Example: Enter HPV vaccination into the HPV screening program in Turkey

- HPV test x 5/10 yrs. (1.6 M women)
- HPV tests x 2 / 3 lifetime
- Repeated visits
  - Diagnostic / treatment
  - Relative costs

- Males
- Catch-up / opportunistic vaccination: intervention (x2 or x3, based on age)
- Exact age limits to be defined
- HPV screening: intervention

Age (years): 9, 14, 25, 30, 45, 65
The proposal for a consortium

M. Steben
X. Bosch
S. de Sanjose
K Canfell
S. Garland
J Salmeron
M. Stanley

F. Carozzi
S. Tatti
C. Wiesner
Oswaldo Cruz Fnd.
YL Qiao.

Inuit & migrants
FRIDA2 Unscreened semi-rural areas
Amazonian Favelas in BA
Studied Under evaluation

CoheaHR: Vaccine acceptability & logistics
Aborigine & marginal populations

B&M Gates Fund. / GAVI / H2020 / ERC / Local funds
HPV FASTER: Public health message

- Attempt to get the best from two *complementary* technologies for cervical cancer prevention
- *Comprehensive* and coherent preventive plan for women *9 to 65*
- Potential for prevention of cervical cancer in the range of a reduction of *70-80% with 2/3 visits lifetime*
- *Accelerate* cancer reduction as compared to current vaccine indications
- The costs that will make the program cost-effective and sustainable are at reach
## Reasonable objectives for the next generation

<table>
<thead>
<tr>
<th>Disease Control</th>
<th>Reduction to acceptable limits. Requires continuous intervention</th>
<th>Increase the number of populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease elimination</td>
<td>Reduction of disease to zero in a given population. Requires continuous intervention</td>
<td>Cervical Cancer in some developed populations</td>
</tr>
<tr>
<td>Infection elimination</td>
<td>Reduction of infection to zero in a given population. Requires continuous intervention</td>
<td>Polio, measles</td>
</tr>
</tbody>
</table>
| Eradication | **Permanent reduction to zero worldwide.**  
**Does not require continuous intervention** | Small pox |
| Extinction | Infectious agent does not exist, naturally or in labs. | None |