Expected Impact of HPV Vaccination on Cervical Cancer Screening Practices:
*The Need for Synergy between Preventive Strategies*

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Points to Cover

- Role of HPV in carcinogenesis: the science driving the changes in prevention strategies
- The cytology screening paradigm before the advent of vaccination
- Expected effects of vaccination on the burden of precancerous lesions and cervical cancer
- Loss of screening performance due to reduction in lesion prevalence: quantitative and qualitative effects
- Advantages of HPV testing as primary screening test followed by cytologic triage
Incidence of Invasive Cervical Cancer

Age-standardized (world population 1960) rates per 100,000 women per year

Source: GLOBOCAN 2002 (Ferlay et al., 2004)
Relative Risk estimates from the pool of IARC case-control studies:

*Muñoz et al., NEJM 2003*

Graph kindly provided by the Editors of HPV Today
<table>
<thead>
<tr>
<th>Cancer prevention target</th>
<th>Population attributable risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV infection and cervical cancer</td>
<td>&gt; 99%</td>
</tr>
<tr>
<td>Smoking and lung cancer</td>
<td>75%-85%</td>
</tr>
<tr>
<td>Chronic HBV infection and liver carcinoma</td>
<td>10%-30% (low risk areas)</td>
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<tr>
<td></td>
<td>50%-90% (high risk areas)</td>
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<tr>
<td>Alcohol drinking and oral cancer</td>
<td>25%-70%</td>
</tr>
<tr>
<td>HRT and endometrial cancer</td>
<td>15%-50%</td>
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HPV Vaccination

- Phase II and III trial findings already in the public domain.
- Safety and efficacy of VLP vaccines documented by numerous peer-reviewed publications in leading medical journals.
- Although clinical experience has just passed 6 years, the evidence base is one of the strongest in disease prevention.
- The standard of proof is far more rigorous than that used in the evaluation of candidate vaccines of the past.
- Possibly, the most scrutinized vaccine by the public and media concerning need and safety.
Is Screening Needed After Vaccination?

Yes!!!

– Vaccines protect against HPVs 16 and 18 which cause at most 75% of all cervical cancers

– Vaccination is for pre-exposure prophylaxis; most women will continue to rely on screening

But How?
The squamo-columnar Junction and Transformation Zone of the Uterine Cervix
Spectrum of morphological abnormalities in the cervical squamous epithelium

From: Baldwin et al., Nat Rev Cancer 2003
Age standardized incidence of invasive cervical cancer and coverage of screening, England, 1971-95

(Quinn et al., BMJ 1999; 318: 904-8)
Age-Standardized Cervical Cancer Mortality, per 100,000 Women in Brazil (1979-99)

Population World Standard; Sources: System of Information on Mortality - SIM/DATASUS/MS; Foundation IBGE; Division of Epidemiologia and Vigilância - CONPREV/INCA/MS
Pap Cytology Screening Coverage and Cervical Cancer Mortality in Latin America

Screening coverage previous 12 months (%)

Mortality (per 100,000 women per year)
How good is Pap cytology in cervical cancer screening?

• Duke Report (AHRQ, 1999; Nanda et al., 2000): Considering only studies free of verification bias: sensitivity: 51%, specificity: 98%

• Cytology screening programmes have to compensate for the low sensitivity by requiring 2-3 annual Pap tests before screening can be done less frequently

• Approximate programme sensitivity for:

  2 consecutive annual Pap tests: 51% + 51% of 49% = 76%

  3 consecutive annual Pap tests: 76% + 51% of 24% = 88%
Expected short-term outcomes

Settings with organized or opportunistic Pap screening:

• Reductions of case loads of ASC, LSIL, and HSIL to be triaged or managed; reductions of colposcopy referrals

• Plausible estimates with empirical backing from RCTs: 40% for those vaccinated against 16/18 and 50% for those protected against 6/11/16/18

Franco et al., Vaccine, 2006
Expected **short-term outcomes**

- Reductions in case loads a function primarily of two factors:
  - Uptake of HPV vaccination by successive cohorts of adolescents and young women
  - Time it will take for protected women to reach screening age
- Impact on case loads initially minimal for women vaccinated between the ages of 11 and 18 years

*Franco et al., Vaccine, 2006*
Expected long-term outcomes

Settings with organized or opportunistic Pap screening:

• Reduction of cervical cancer burden unlikely to be observed for at least a decade because of the latency for averted HSILs to progress to invasive lesions

• Lack of equitable access to benefit: High vaccine uptake may happen mainly among women who will eventually comply with screening

Franco et al., Vaccine, 2006
Expected long-term outcomes

Lack of equitable access to benefit:

- Like mothers, like daughters…
  
  - Young women who are vaccinated are likely to comply with screening later in life
  
  - Initial enthusiasm with reduction in cervical abnormalities; however, because of their high compliance with screening these women would not be likely to develop cervical cancer
  
  - Non-vaccinated women less likely to be screened → their lesions will progress undetected → cytology surveillance oblivious to their occurrence until cancer is diagnosed

Franco et al., Vaccine, 2006
Loss of Pap screening performance due to vaccination

- As successive cohorts of women are vaccinated:
  - Reduction in prevalence of cytological abnormalities
  - End result: decrease in positive predictive value of cytology
  - Increase in false positive rates will lead to non-rigorous diagnostic work-up
  - Impact on cytotechnician training and quality assurance
Assumptions: constant 51% sensitivity and 98% specificity (as per Nanda et al., 2000)

PPV = \( \frac{Se \times P}{Se \times P + (1 - Sp) \times (1 - P)} \) and NPV = \( \frac{Sp \times (1-P)}{((1-Se) \times P + Sp \times (1-P))} \)

Franco et al., Vaccine 2006
Possible qualitative changes in Pap cytology performance

• Sensitivity will be negatively affected:
  – Today’s typical case load: approximately 10% of all smears contain abnormalities that are serious enough to merit slide review
  – Reduction in lesion prevalence → fatigue will set in given expectation that abnormalities will be rare → smears may not be read as thoroughly → more false negatives
  – End result: further decline in the PPV of cytology
  – (some of the lowest estimates of Pap sensitivity are in frequently screened, low risk populations of developed countries)

Franco et al., Vaccine 2006
Possible qualitative changes in Pap cytology performance

• But specificity may suffer as well…
  – Decrease in signal-to-noise ratio of cytology → due to rarity of squamous abnormalities and koilocytotic atypias (the signal) inflammatory changes or reactive atypias (the noise) may be overcalled
  – Could be aggravated by cytotechnician’s fear that relevant abnormalities will be missed
  – Heightened awareness of the potential for false-negative diagnoses may lead to more false-positive reports → loss in specificity
  – **End result:** further decline in the PPV of cytology

*Franco et al., Vaccine 2006*
Joint effects of changes in sensitivity, specificity, and lesion prevalence on the PPV of a screening test

Franco et al., Vaccine, 2006

Sensitivity

Specificity: red: 95%, blue: 85%, and green: 75%

Graphs represent decreasing hypothetical situations of lesion prevalence: Africa and Latin America: 10%-20%, Western countries: 5%-10%, Triage: 50%
Quantitative and qualitative penalties on the PPV of cytology

• In consequence:
  – Cytology laboratories will tend to err on the side of conservatism to decrease risk of malpractice suits
  – Safequard: to maintain unnecessarily frequent screening visits as policy to provide protection against false-negatives

• Conclusion: costly and ineffective way of combining screening to vaccination
HPV vs. Pap in Primary Screening

- Pooled analysis of European and North American studies: HPV testing substantially more sensitive in detecting CIN2+ than cytology (96.1% vs. 53.0%) but less specific (90.7% vs. 96.3%).

- Meta-analysis of all available studies: HPV 1.23 times more sensitive and 0.94 times less specific than cytology.

- Comparable if not better results from emerging RCT data (e.g., POBASCAM, NTCC, CCCaST)

Cuzick et al., IJC 2006
Arbyn et al., Vaccine 2006
“…The child is grown, the dream is gone. I have become comfortably numb.”

David Gilmour & Roger Waters
Women who have sex with HPV-infected men

(within weeks to months some will develop)

HR-HPV infection

(within months some will develop)

Persistent HR-HPV infection

(within months to years some will develop)

HG cervical lesions

(within months to years some will develop)

Cervical cancer

Pap Cytology

Detected with low sensitivity

HPV Testing

Detected with high sensitivity

Detected with moderate sensitivity

Detected with high sensitivity

Perceived as cause of low specificity
RCTs of HPV Testing in Screening

- HART trial: UK (Cuzick et al., Lancet, 2003)
- POBASCAM study: The Netherlands (Meijer et al., IJC 2004)
- Indian Trial (Osmanabad) (Sankaranarayanan et al.)
- ARTISTIC trial: UK (Kitchener et al.)
- NTCC Italian Study (Ronco et al., Lancet Oncol, 2006)
- SWEDESCAN: Swedish trial (Naucler et al., NEJM 2007)
- CCCaST study: Canada (Mayrand et al., IJC 2006; NEJM 2007)
- BC RCT (HPV FOCAL): Canada (Coldman et al.)
### CCCaST Study: First Screening Round Results*

<table>
<thead>
<tr>
<th>Indices</th>
<th>Screening test</th>
<th>Estimate (95%CI)</th>
</tr>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>Pap</td>
<td>55.4 (33.6-77.2)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>94.6 (84.2-100)</td>
</tr>
<tr>
<td>Specificity</td>
<td>Pap</td>
<td>96.8 (96.3-97.3)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>94.1 (93.4-94.8)</td>
</tr>
<tr>
<td>PPV</td>
<td>Pap</td>
<td>7.1 (4.8-10.3)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>6.4 (5.0-8.0)</td>
</tr>
<tr>
<td>NPV</td>
<td>Pap</td>
<td>99.8 (99.7-99.9)</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td>100 (98.6-100)</td>
</tr>
</tbody>
</table>

* 10,171 women in Montreal and St. John’s, aged 30-69 years, randomized to Pap or HPV as primary screening method; estimates corrected for verification bias (Mayrand et al., NEJM 2007)
Why is HPV Testing an Attractive Option for Cervical Cancer Screening?

- More sensitive than the Pap test
- More “upstream” in the carcinogenic process, thus enabling a longer safety margin for screening intervals
- Can be automated, centralized, and be quality-checked for large specimen throughput
- May be more cost-effective than cytology if deployed for high volume testing, such as in primary screening
- More logical choice for screening women vaccinated against HPV infection
Concerns about Adopting HPV Testing in Cervical Cancer Screening

Important:

- Modifications to existing screening programs will be necessary
- At present, the unit cost for HPV testing is higher than that for Pap cytology
- Screening for HPV will create a dependence on commercial interests
- Health education issues
Irrelevant Concerns about HPV Testing in Cervical Cancer Screening

- Will lead to excess in referrals and uncertainties about follow up of HPV+ women with no CIN
- No change needed: Pap cytology screening shown to reduce cervical cancer incidence and mortality
- There is no evidence that screening with HPV testing may reduce cervical cancer incidence and mortality
- Women prefer annual visits anyway
- Stigmatization
Need for assessing the basis of screening programs following vaccination

• Pap cytology will not be the same if left as primary test

• Solution: HPV testing as primary screening test followed by cytologic triage:
  – HPV testing more “upstream” than cytology → longer latency safety window
  – HPV testing more sensitive and not prone to the vagaries of a test based on subjective interpretation
  – HPV testing less likely to vary in sensitivity and specificity as a function of decreasing prevalence in infections and lesions
  – Cytology will perform better in the artificially high lesion prevalence when triaging HPV+ women

Franco et al., Vaccine, 2006
Other benefits from the HPV-Pap screening algorithm

- **Dividend**: A surveillance system integrated with vaccination registries to monitor vaccine efficacy, duration of protection, and cross-protection

- Rational approach to assuage concerns that frequency of screening must not be changed to avoid missing lesions caused by other oncogenic HPV types

- Improved detection of glandular lesions

- Potential for using self-collected cervical samples

- Cytology too important to be used as screening test; it should be reserved for diagnostic triage

*Franco et al., Vaccine 2006*
The case for synergy in prevention modalities

1. Screening will have to continue in the HPV vaccination era

2. Opportunistic (as opposed to universal) vaccination will create (further) inequity in access to benefit

3. Cytology screening performance will degrade following vaccination

4. HPV infection surveillance will be needed post-vaccination

5. Proposal: reformulate screening as an integrated approach complementing vaccination
Integrated Approach to Screening

Steps in Natural History

Risk Factor → Sexual Behavior

Cancer Precursor

Primary Prevention (HPV Vaccination)

Secondary Prevention (Screening)

Invasive Cancer

HPV and CIN

Integration of Primary and Secondary Prevention:
Shared resources, common surveillance systems, record linkage

Franco et al., Vaccine, 2008
Muito obrigado pela amável atenção, Tchê !