The Future of Cervical Cancer Screening in the Era of HPV Vaccination

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Disclosure

• Occasional consultant or advisory board member to Merck and GSK on matters related to HPV vaccines, to Qiagen, Roche, GenProbe, and Becton & Dickinson on HPV diagnostics, to Cytyc and Ikonisys on cytology, and to Innovus and Scimetrika on health economic modelling.

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Points to cover:

- What will HPV vaccination do to screening practices?
- As HPV vaccination proceeds, the screening paradigm changes: the new guidelines.
- Performance of Pap cytology under low lesion prevalence.
- Implementation and policy issues for high resource settings.
Screening will continue to be needed

- HPV vaccines protect against HPVs 16 and 18, which cause ~70% of all cervical cancers.
- Efficacy (and ultimately, effectiveness) is not 100%

Key question: what is the most efficient screening approach post-vaccination?
Cervical cancer prevention activities are inherently a single process

- **Risk Factor**
- **Sexual Behaviour**
- **Cancer Precursor**
- **HPV and CIN**
- **Invasive Cancer**
- **Incidence**

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

*Franco et al., Vaccine 2008*
What has happened and what is in the horizon?

- School-based HPV vaccination a success in Australia, UK, Canada.
- GAVI just approved HPV vaccination for introduction in the poorest countries in the world.
- Gradual introduction of molecular HPV testing in screening programs in North America and Europe.
- WHO’s new recommendations for screen-and-treat strategies based on HPV testing and VIA coupled with cryotherapy to prevent cervical cancer in low-resource settings.
- A new nonavalent HPV vaccine currently being evaluated in a multi-country phase III RCT.
- Candidate pan-mucosotropic HPV vaccine in development; when will it be available?
Validation of HPV testing in primary screening for cervical cancer: Burden of proof

- Increased cross-sectional sensitivity and acceptable specificity relative to Pap.
- More reproducible across settings.
- Increased detection of HG-CIN that is likely to persist or progress.
- Increased safety during follow-up for women with negative results at initial screen.
- Reduced incidence of advanced cervical cancers and mortality.
The dawn of a new era…

*New Guidelines*


<table>
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<tr>
<th>Age Group</th>
<th>Screening Recommendations</th>
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<tr>
<td>Women &lt;21</td>
<td>No screening</td>
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</table>
| Women ages 21-29 | Cytology alone every 3 years (liquid or conventional)  
Recommend AGAINST annual cytology |
| Women ages 30-65 | HPV + cytology “cotesting” every 5 years (preferred) 
or Every 3 years with cytology alone (acceptable)  
Recommend AGAINST more frequent screening |
| Women ages >65 | Discontinue after age 65 if 3 negative cytology tests or 2 negative HPV tests in last 10 years with most recent test in last 5 years |
| Post-Hysterectomy | Discontinue if for benign reason |
| Screening after HPV vaccination | Follow age-appropriate recommendations (same as unvaccinated women) |

The new guidelines converged  
*Saslow et al., 2012; Moyer et al., 2012*
### Guideline Recommendations

**ACS / ASCCP / ASCP**

**Management of Discordant Results**

<table>
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<tr>
<th>HPV-negative ASC-US</th>
<th>Rescreen with cotesting in 5 years (preferred) or Rescreen with cytology in 3 years (acceptable)</th>
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| HPV positive, cytology negative | **Option 1** -- 12-month follow-up with cotesting  
**Option 2** -- Test for HPV16 or HPV16/18 genotyping  
If HPV16 or HPV16/18 positive: refer to colposcopy  
If HPV16 or HPV16/18 negative: 12-month follow-up with cotesting |

Saslow et al., 2012
Co-testing adds little to primary HPV testing:
Risk of CIN3+ according to baseline test results in European studies

Cumulative incidence of CIN3+ (per 10,000)

Time since initial testing (mos.)

Dillner, J. et al. BMJ 2008;337:a1754
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

*Franco et al., Vaccine 2006*
Influence of prevalence of cervical lesions on the positive predictive value (PPV) and negative predictive value (NPV) of cytology as a primary screening test. Sensitivity and specificity held constant at 70% and 98%, respectively. Gray bands: 95% credibility intervals around median values for 1000 simulations using each of the parameter combinations in hypothetical populations of 10,000 women. (Franco et al., Arch Med Res 2009)
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 cytology as a primary screening test. Blue curve: specificity=98%; red curve: specificity=95%. Gray bands: 95% credibility intervals. Three of the prevalence scenarios are intended to illustrate situations found in Pap cytology screening in different settings as well as the one anticipated post-vaccination. A 40% prevalence is shown to represent the situation found in triage, following an initially positive referral HPV test. (Franco et al., Arch Med Res 2009)
A paradigm change in screening following vaccination

- Pap cytology will be affected post-vaccination and may no longer be suitable as a primary screening test.

**Potential solution:** HR-HPV DNA testing as primary screening test followed by cytologic triage:
  - HPV testing more sensitive and reproducible 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*
Additional benefits of an “HPV followed by Pap” strategy in vaccinated populations

- **Serving a second purpose:** A surveillance system integrated with vaccination registries to monitor vaccine efficacy, duration of protection, and cross-protection.

- **Impact on adenocarcinomas:** Improved detection of glandular lesions.

- **Reaching remote areas:** Potential for using self-collected cervical samples and increase coverage.

- **Simplicity for guidelines:** Proposed approach valid also for unvaccinated populations.

- **Safety in increasing screening intervals**

- **Preserves workforce:** Cytology too important to be used as screening test; should be reserved for diagnostic triage.
Generic algorithm for a cervical cancer screening strategy serving as surveillance system post-vaccination in high-resource settings

Primary screening via HR-HPV testing

Negative (~93-95%)

Recall with extended screening interval

Positive (~5-7%)

Triage step: Pap cytology or HPV genotyping for 16/18/other priority HR HPVs

≥ ASC-US/BMD or genotyping positive

Pap within normal limits or genotyping negative

Colposcopy & biopsy

No evidence of disease

Cervical lesion

Repeat testing as in triage step in 12 months

Treatment as per local guidelines

Recall with extended screening interval
Generic algorithm for a cervical cancer screening strategy serving as surveillance system post-vaccination in high-resource settings

Requirements: efficient record linkage and call-recall

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Surveillance dividends: Duration of protection, population effectiveness, cross-protection, type/risk replacement

Vaccination registry

Organized Programme

HPV outcomes registry

Cytology and Pathology registry

Administrative healthcare databases

Population-based tumour registry
An integrated approach for high-resource settings

- Affordable infrastructure for surveillance.
- Political courage to modify screening will be influenced by success stories from early adopters.
- Science alone is not sufficient.
- Professional sensitivity: many concerns are unspoken (e.g., fear of loss of income by healthcare providers; redistribution of the decision-making power in cancer control).
Obstacles for implementation in high-resource settings

- Diverse array of choices for molecular HPV testing.
- Molecular target: HPV DNA or RNA?
- Fortunately, benchmarks for performance are available (Meijer et al., IJC 2009).
- Who pays the cost? (reimbursement issues for HMOs, budget appropriation in publicly-funded settings)
What research is needed?

- Triage and follow-up strategies for HPV positives: cytology, genotyping, persistence, biomarkers (p16, ki67, mcm2, mcm7).
- Cost-effectiveness, safety, liability for providers, age at initiation of screening among vaccinated.
- Safe screening intervals for both vaccinated and unvaccinated women.
- Education of providers and clients.
Threats to moving forward and other unfounded concerns

- Need to conduct baseline HPV prevalence surveys before deploying HPV vaccination.

- Concerns about type replacement post-vaccination:
  - Will it happen?
  - Will it cancel the gains from vaccination?
  - Will it force a redesign of molecular screening tests?

- Expectation that second generation vaccines will change the premises for policy-making.
Conclusions

- Guidelines reached consensus on the value of HPV testing but cotesting may be a temporary solution.
- Existing screening paradigms of cytology-only or cytology with reflex HPV for ASCUS triage wastes resources and imposes unattainable standards for low-resource countries.
- Vaccination will have an impact on screening test performance and practices.
- Cancer control strategies must be integrated to share resources and to permit improved prevention and surveillance.
- Evidence base is an elusive target; rapid pace of technological changes will continue to be an obstacle for policymaking.
Grazie tanti per la vostra attenzione!