10es Journées annuelles de santé publique

Palais des congrès de Montréal
23 au 27 octobre 2006

L'impact attendu de la vaccination contre le virus du papillome humain sur les pratiques de dépistage du cancer du col uterin

(The expected impact of HPV vaccination on cervical cancer screening practices)

Eduardo L. Franco
Professor and Director
Division of Cancer Epidemiology
McGill University, Montreal, Canada

Points to cover:

- ✓ Is screening needed after vaccination?
- ✓ Expected effects of vaccination on the burden of precancerous lesions and cervical cancer
- ✓ Loss of screening performance due to reduction in lesion prevalence
- ✓ Qualitative effects on the performance of cytology
- ✓ Advantages of HPV testing as primary screening test

Cette présentation a été effectuée le 27 octobre 2006, au cours du Symposium "La santé publique et le dépistage du cancer : espoirs et réalités" dans le cadre des Journées annuelles de santé publique (JASP) 2006. L'ensemble des présentations est disponible sur le site Web des JASP, à l'adresse http://www.inspq.qc.ca/jasp.

Is screening needed after vaccination?

- **Yes!!!**
  - Vaccines protect only against HPVs 16 and 18 which cause 70%-80% of all cervical cancers
  - Efficacy not 100% and effectiveness yet to be learned
  - Vaccination prevents infection following first exposure (pre-adolescents and young women); most women at risk of cervical cancer will continue to rely on screening

Adoption of HPV vaccination will be a gradual process that will reflect country-specific health care environments

- Diversity in implementation across countries and settings
- Will likely reflect individual countries' perceptions regarding cost-effectiveness of vaccination
- To be well informed, such decisions must consider whether or not existing screening programs are to be modified

Adoption of HPV vaccination will be a gradual process that will reflect country-specific health policy environments

- **What must not happen:**
  - To adopt vaccination and continue to maintain existing cervical cancer screening practices based on frequency of cytology that benefit only women with health care access
- **If this happens:**
  - Resources will be wasted and there may be no reductions in morbidity and mortality from cervical cancer

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: 40% for those vaccinated against 16/18 and 50% for those protected against 6/11/16/18
- Expected reduction of asymptomatic HPV infections due to target types but benefit will not be appreciable via STI finding

Franco et al., Vaccine, 2006

Expected short-term outcomes

Settings with organized or opportunistic Pap screening:

- Reductions in case loads a function primarily of two factors:
  - Uptake of HPV vaccination by the successive cohorts of adolescents and young women targeted by vaccination
  - Time it will take for protected women to reach the age when they become clients of screening
- 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 required for averted HSILs to have had the time to progress to invasive lesions
- Potential problems with opposite effects:
  - 1) Lack of equitable access to benefit: High vaccine uptake may happen among women who will eventually be compliant with screening recommendations
  - 2) Non-compliance with screening because of perception that vaccine is fully protective

Franco et al., Vaccine, 2006

Expected long-term outcomes

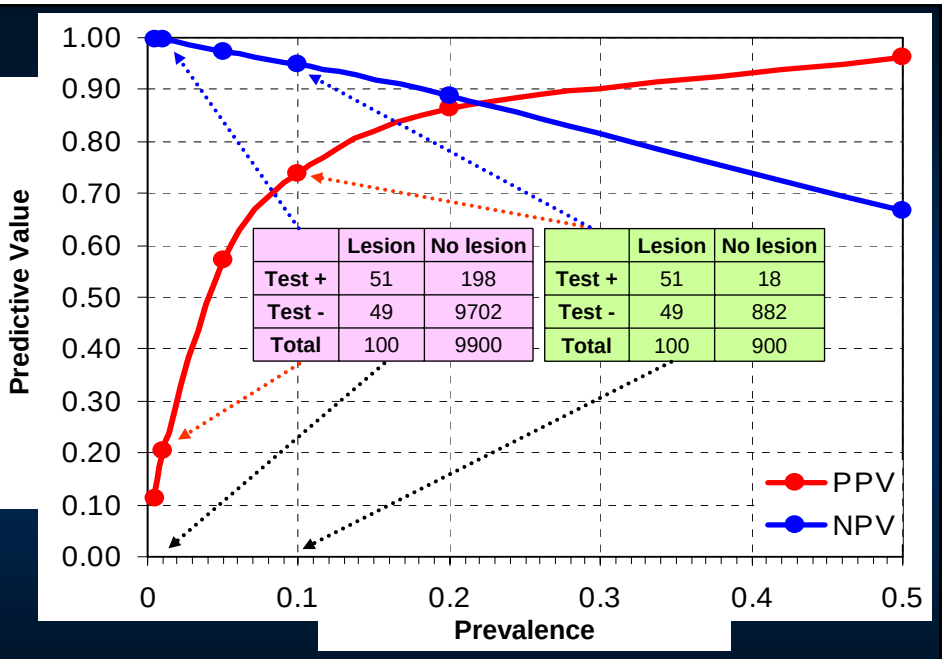
Lack of equitable access to benefit:

- Like mothers, like daughters… young women who are vaccinated are the very ones destined to become screening-compliant
- Initial enthusiasm with reduction in ASC and SIL case loads; however, because of their high compliance with screening these women would not be the ones destined to develop cervical cancer
- Non-vaccinated women less likely to be screened -> their lesions will progress undetected -> cytology surveillance oblivious to their existence until invasive cancer develops

Franco et al., Vaccine, 2006

Loss of screening performance due to vaccination

- **As successive cohorts of women are vaccinated:**
  - Immediate 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



	Lesion	No lesion
Test +	51	198
Test -	49	9702
Total	100	9900

	Lesion	No lesion
Test +	51	18
Test -	49	882
Total	100	900

Assumptions: constant 51% sensitivity and 98% specificity (as per Nanda et al., 2000)

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 quickly 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 cytology sensitivity are in frequently screened, low risk populations in developed countries)*

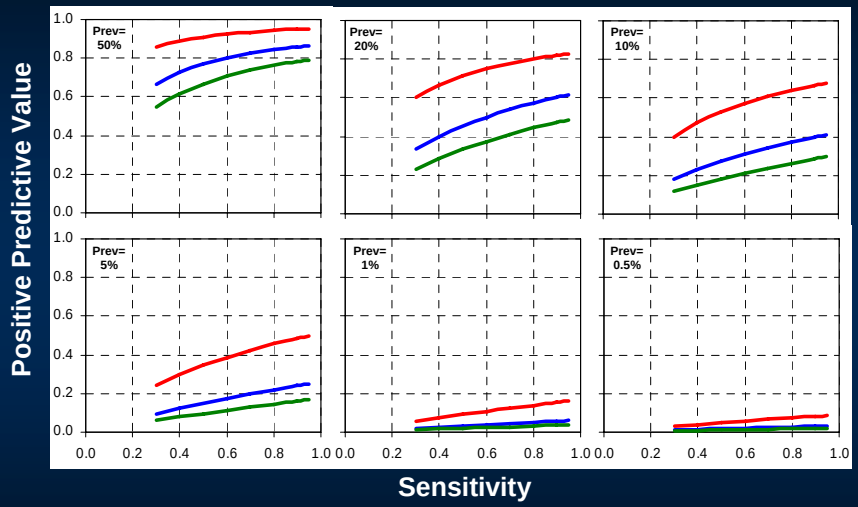
Franco et al., Vaccine 2006

Possible qualitative changes in Pap cytology performance

- **Specificity may suffer as well…**
  - Due to the rarity of squamous abnormalities and koilocytotic atypias (the signal) cytotechnicians may overcall inflammatory changes or reactive atypias (the noise)
  - 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



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

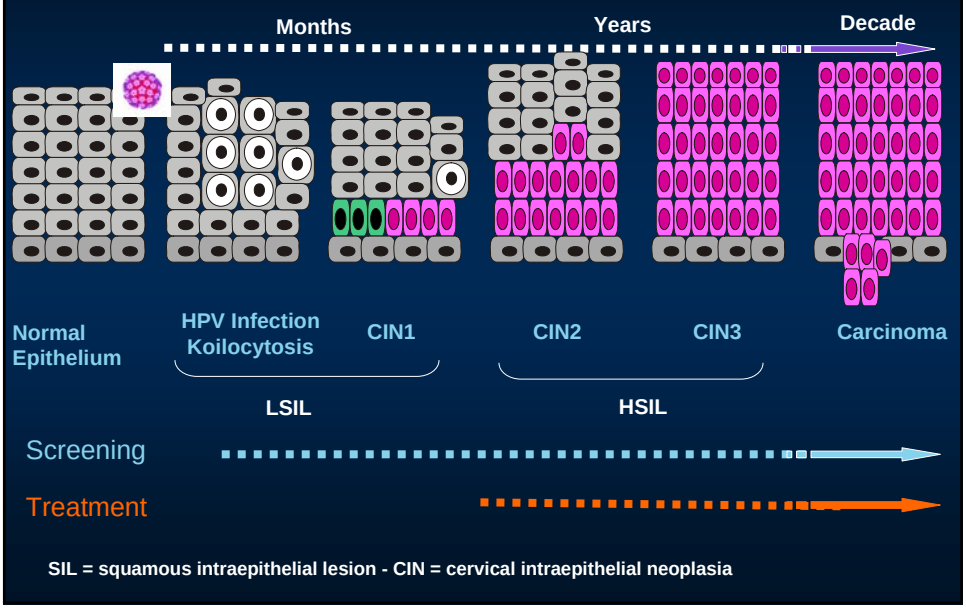
Graphs represent decreasing hypothetical situations of lesion prevalence: Africa and Latin America: 10%-20%, Western countries: 5%-10%, Triage: 50%

Franco et al., Vaccine, 2006

Quantitative and qualitative penalties on the PPV of cytology

- **In consequence:**
  - Cytology laboratories in litigation-prone countries (US) will tend to err on the side of conservatism to decrease risk of malpractice suits
  - Other settings may rely on maintaining unnecessarily frequent screening visits as policy to provide protection against false-negatives
- Either approach is a non-cost-effective way of combining screening to vaccination

Cervical Cancer Progression



SIL = squamous intraepithelial lesion - CIN = cervical intraepithelial neoplasia

CCCaST Study: First Screening Round Results*

Parameter	Test	Estimate (95%CI)
Sensitivity	Pap	55.4 (13.7-77.2)
	HPV	94.7 (84.3-100)
Specificity	Pap	97.2 (96.7-97.7)
	HPV	94.1 (93.4-94.8)

* 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., to be submitted)

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 via record linkage with vaccination registries would enable monitoring incident infections among vaccinated women to determine vaccine efficacy, duration of protection, and cross-protection
- Rational approach to assuage concerns that frequency of screening must not be changed lest lesions caused by other oncogenic HPV types will be missed
- Improved detection of glandular lesions
- Cytology too important to be used as screening test; its role should be reserved for diagnostic triage

Franco et al., Vaccine 2006

Forecasting: How will screening be practiced in the vaccination era?

- Two prevention strategies: one new and the other in transition
- Difficult to predict: no empirical data
- Only close post-vaccination surveillance will provide evidence
- Screening must be reformulated to operate in synergy with vaccination programs