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HPV vaccines and integration into cervical cancer prevention programs

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Disclosure

- Occasional consultant or advisory board member to Merck-Frosst and GSK on matters related to HPV vaccines, to Roche, Takeda, and GenProbe on HPV diagnostics, to Cytoc and Ikonisys on cytology, and to Innovus on health economics.
- Two unconditional grants from Merck-Frosst in partial support of investigator-initiated research related to HPV testing in my unit.
- Entire research program funded by the CIHR, NIH, NCIC, CRS, FRSQ.
- Salary awards: CIHR Distinguished Scientist, FRSQ Chercheur National, James McGill Chair.

Topics to cover

- Importance of universal prophylactic HPV vaccination: equitable benefit
- However, the current paradigm of Pap cytology is likely to be adversely affected post-vaccination
- Cost-effective implementation can only happen if primary (HPV vaccination) and secondary (screening) cervical cancer control activities can be integrated

Main findings from RCTs of HPV vaccination

- High efficacy (>95%) in preventing incident and/or persistent HPV infections by the target types (16/18 or 6/11/16/18) and precancer associated with these types in women 15-26 years of age.
- Protection has continued unabated after 6 years of f/up (> 8 yrs for prototype HPV-16 vaccine).
- High titers of neutralizing antibodies among vaccinees.
- Comparable protection among older women and men if not previously exposed.
- No evidence of protection against existing infections; vaccination does not accelerate clearance of infections by target types.
- Evidence of cross-type protection, primarily for HPV 45 and to a lesser extent to HPVs 31 and 33.
- Incidence of adverse events comparable to placebo and within expected background rates in general population.

Importance of implementing universal pre-exposure HPV vaccination

Main reason: to provide equitable access to benefit.

Facts:

- 1) Opportunistic vaccination has already begun;
- 2) Most cases of cervical cancer represent failures of screening due to insufficient coverage among women of low SES.

What may happen: If only opportunistic vaccination is adopted the existing inequity in cervical cancer prevention will increase.

Importance of implementing universal pre-exposure HPV vaccination

The “Like mother, like daughter” principle:

Part 1: The good news (reduction of case loads)

- Mothers who comply with screening will want their daughters to be vaccinated
- Young women who are vaccinated will be like their mothers and are likely to comply with screening later
- Initial enthusiasm with reduction in cervical abnormalities and colposcopy caseloads
- However, because of their high compliance with screening these women would not be likely to develop cervical cancer

Importance of implementing universal pre-exposure HPV vaccination

The “Like mother, like daughter” principle:

Part 2: The bad news (no change in cervical cancer incidence)

- Mothers who are not screened are less likely to have heard of HPV vaccination and its benefits
- They are unlikely to have their daughters vaccinated
- These unvaccinated women will be like their mothers and will be less likely to be screened
- Their lesions will progress undetected with no screening surveillance
- Until cancer is diagnosed 15-20 years later

What are the real obstacles?

- Cost; currently quite expensive.
- In developing countries: competition from other new vaccines.
- Delivery logistics for an adolescent vaccine.
- Resistance against changes to existing cancer control policies.
- What to do with cervical cancer screening?

Screening will continue to be needed

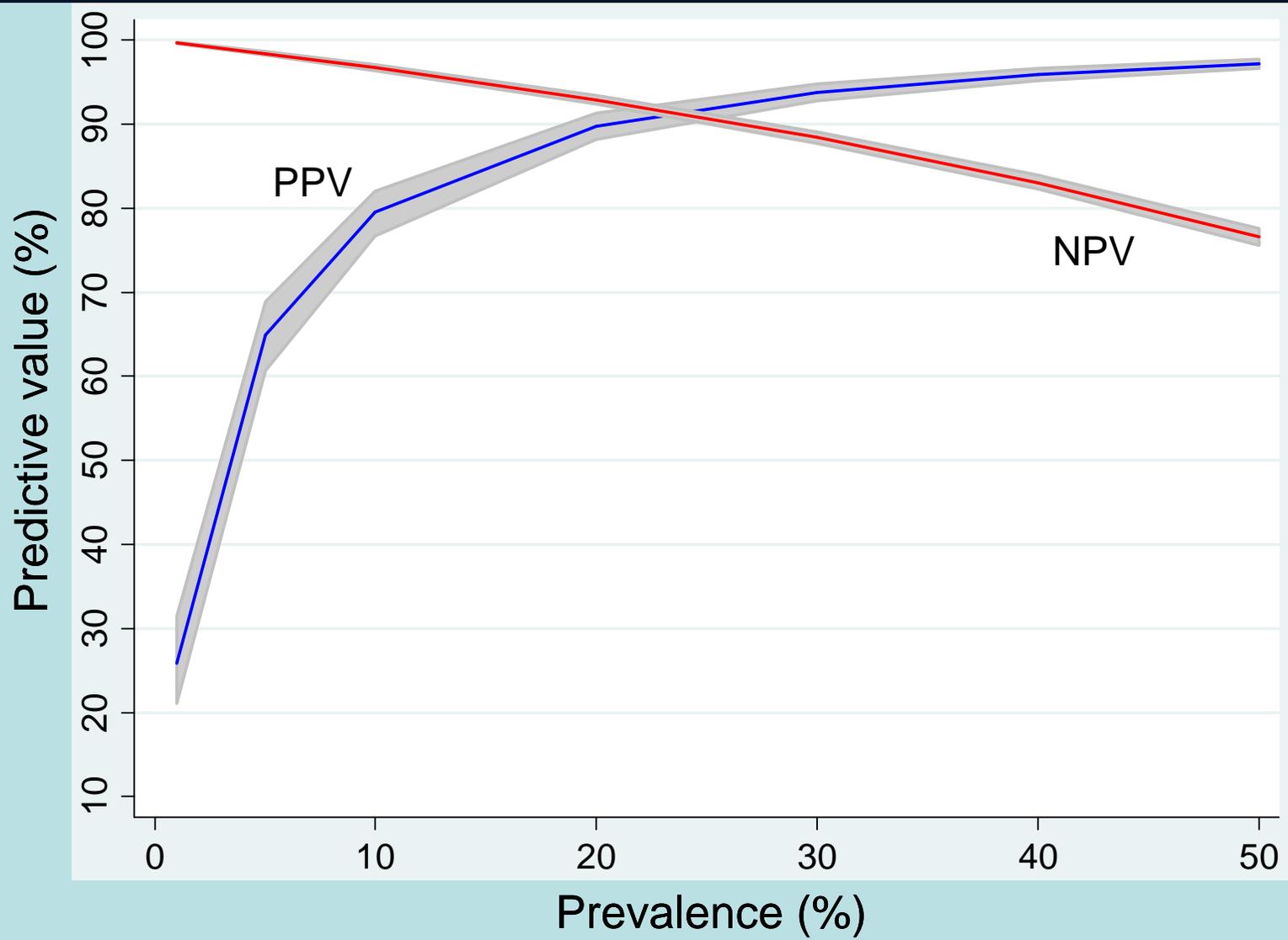
But the existing cytology paradigm may fail...

Solutions:

- Recent progress on new technologies (HPV testing with Pap triage) will permit extending screening intervals safely and cost-effectively.
- Low-cost technologies (VIA, VILI) associated with screen-and-treat approaches are feasible.
- Proper integration of primary and secondary prevention strategies is likely to reduce costs and improve cervical cancer control.

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



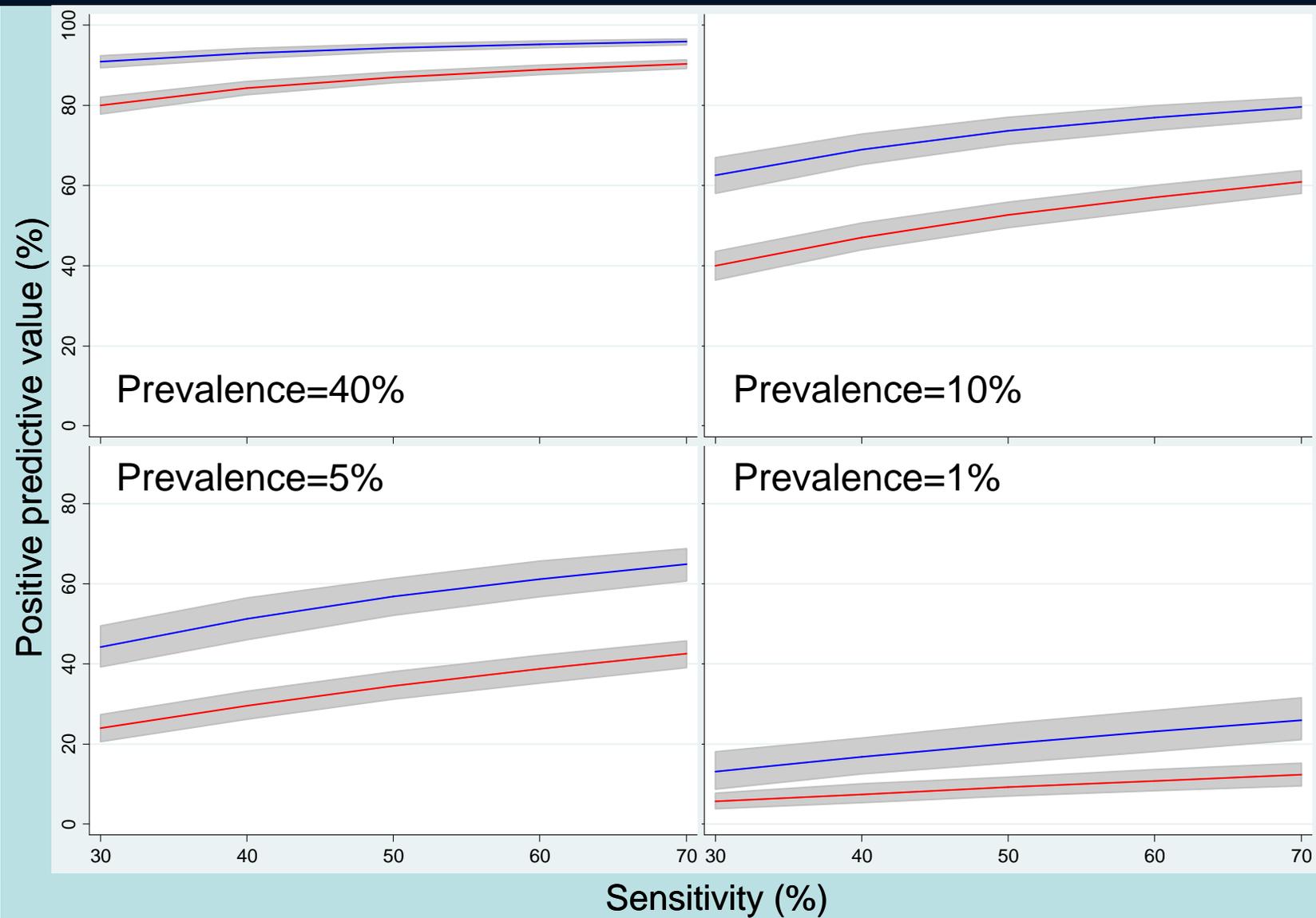
Influence of prevalence of cervical lesions on the positive predictive value (PPV) and negative predictive value (NPV) of cytology as a primary screening test. Sensitivity and specificity held constant at 70% and 98%, respectively. Gray bands: 95% credibility intervals around median values for 1000 simulations 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)*

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



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)

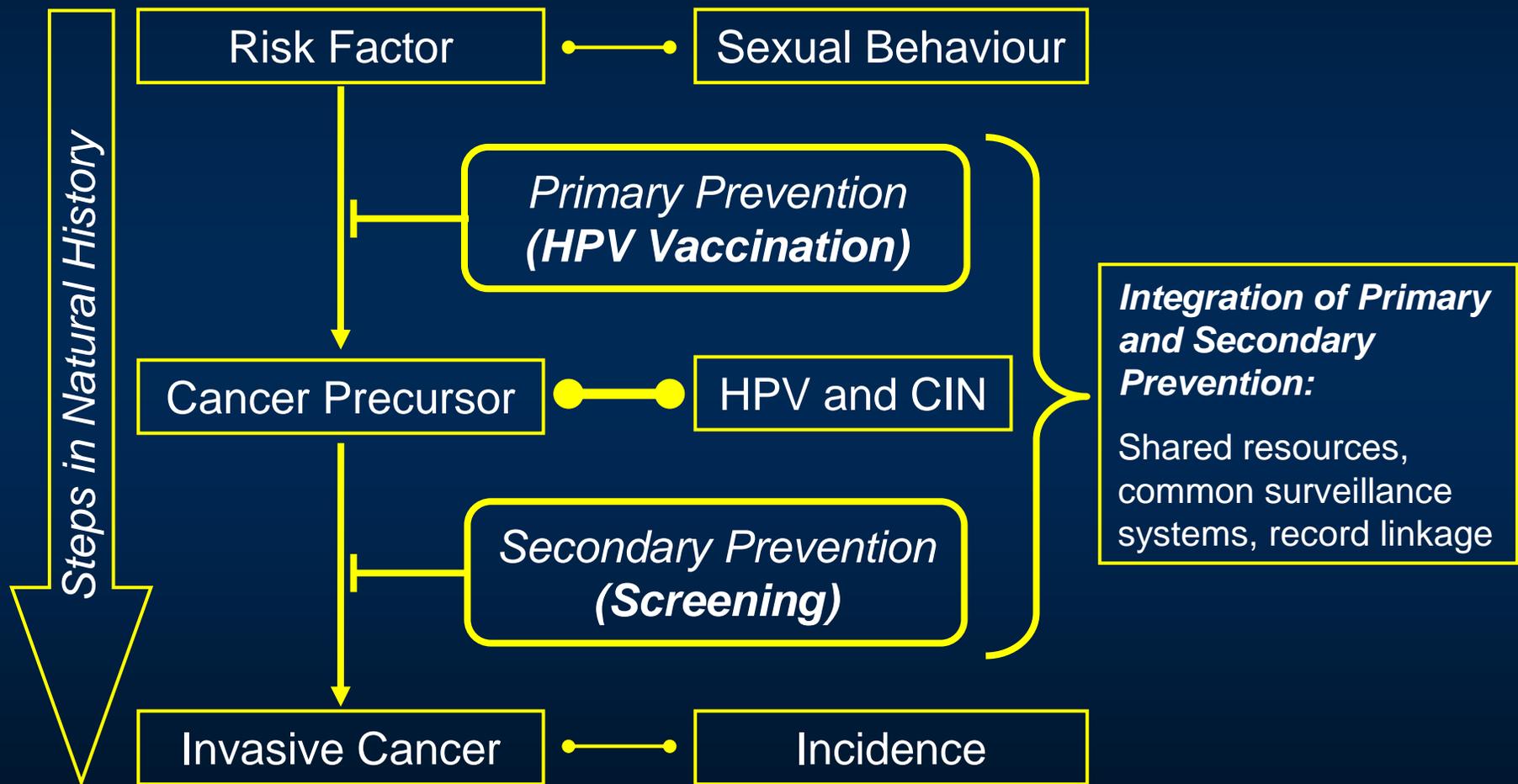
Need for assessing the basis of screening programs following vaccination

- 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

Additional benefits of an “HPV followed by Pap” strategy in populations with high vaccine uptake

- **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.

Cervical cancer prevention activities are inherently a single process



Arguments for an integrated approach

1. HPV vaccination more effective and equitable when deployed as universal policy;
2. Over time, HPV vaccination will have a negative impact on the performance of cytology, thus further straining the efficacy of screening in middle and low resource settings;
3. HPV testing is a more efficacious and robust primary screening test than cytology, especially in the post-vaccination era;
4. A new paradigm of HPV testing followed by Pap triage or VIA can fulfill the role of a screening approach while also serving as a surveillance system to monitor the effectiveness of HPV vaccination;
5. Integration of these two levels of prevention could also permit more realistic implementation of screening as universal policy, thus circumventing today's problems of low and inequitable coverage.