HPV Testing in Cervical Screening - What's Taking So Long?

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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
- A more logical choice for screening women vaccinated against HPV infection

E Franco, **National Symposium on Infectious Agents & Cancer**
Toronto, March 11, 2010

HPV in Primary Testing

Prediction #1

- HPV is more sensitive (but less specific) than a Pap test
- HPV can detect lesions earlier than a Pap test

STUDY PROTOCOL Open Access

A randomized controlled trial of **H**uman **P**apilloma**v**irus (HPV) testing **f**or **c**ervic**al** cancer screening: trial design and preliminary results (HPV FOCAL Trial)

Gina S Ogilvie[1,2*], Dirk J van Niekerk[3,4], Mel Krajden[4], Ruth E Martin[1], Thomas G Ehlen[5], Kathy Ceballos[3,4], Stuart J Peacock[6], Laurie W Smith[7], Lisa Kan[8], Darrel A Cook[9], Wendy Mei[10], Gavin CE Stuart[5], Eduardo L Franco[11], Andrew J Coldman[7,8]

Abstract

Background: In the HPV FOCAL trial, we will establish the efficacy of hr-HPV DNA testing as a stand-alone screening test followed by liquid based cytology (LBC) triage of hr-HPV-positive women compared to LBC followed by hr-HPV triage with ≥ CIN3 as the outcome.

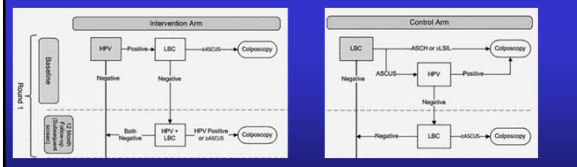
Methods/Design: HPV-FOCAL is a randomized, controlled, three-armed study over a four year period conducted in British Columbia. It will recruit 33,000 women aged 25-65 through the province's population based cervical cancer screening program. *Control arm*: LBC at entry and two years, and combined LBC and hr-HPV at four years among those with initial negative results and hr-HPV triage of ASCUS cases; *Two Year Safety Check arm*: hr-HPV at entry and LBC at two years in those with initial negative results with LBC triage of hr-HPV positives; *Four Year Intervention Arm*: hr-HPV at entry and combined hr-HPV and LBC at four years among those with initial negative results with LBC triage of hr-HPV positive cases.

Discussion: To date, 6150 participants have a completed sample and epidemiologic questionnaire. Of the 2019 women enrolled in the control arm, 1908 (94.5%) were cytology negative. Women aged 25-29 had the highest rates of HSIL (1.4%). In the safety arm 92.2% of women were hr-HPV negative, with the highest rate of hr-HPV positivity found in 25-29 year old women (23.5%). Similar results were obtained in the intervention arm. HPV FOCAL is the first randomized trial in North America to examine hr-HPV testing as the primary screen for cervical cancer within a population-based cervical cancer screening program.

Trial Registration: International Standard Randomised Controlled Trial Number Register, ISRCTN79347302

HPV for cervical cancer screening (HPV FOCAL): Complete Round 1 results of a randomized trial comparing HPV-based primary screening to liquid-based cytology for cervical cancer

Gina S. Ogilvie[1,2], Mel Krajden[1,2], Dirk van Niekerk[3,4], Laurie W. Smith[4], Darrel Cook[2,4], Kathy Ceballos[4], Marette Lee[4], Laura Gentile[4], Lovedeep Gondara[4], Ruth Elwood-Martin[3], Stuart Peacock[4], Gavin Stuart[3], Eduardo L. Franco[5] and Andrew J. Coldman[4]



Int. J. Cancer: 140, 440–448 (2017)

HPV FOCAL – Round 1

- HPV-based cervical cancer screening in a population-based program resulted in greater CIN2+ compared to LBC
  (16.5/1000 vs 10.1/1000)
- HPV-based screening resulted in significantly higher colposcopy referral compared to LBC
  (58.9/1000 vs 30.9/1000)
  - particularly in women under 30

JAMA | Original Investigation

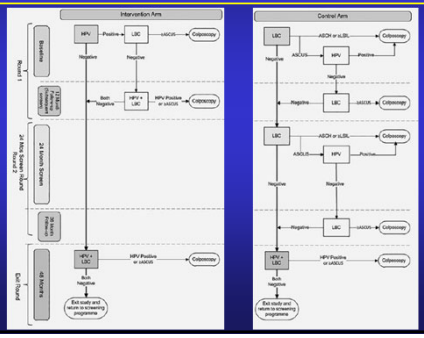
Effect of Screening With Primary Cervical HPV Testing vs Cytology Testing on High-grade Cervical Intraepithelial Neoplasia at 48 Months

The HPV FOCAL Randomized Clinical Trial

Gina Suzanne Ogilvie, MD, FCFP, DrPH; Dirk van Niekerk, MB, ChB, Mmed, FFPath, LMCC, FRCPC; Mel Krajden, MD, FRCPC; Laurie W. Smith, RN, BN, MPH; Darrel Cook, MSc; Lovedeep Gondara, MS; Kathy Ceballos, MD; David Quinlan, MD, FRCSC; Marette Lee, MD, FRCSC, MPH; Ruth Elwood Martin, MD, FCFP, MPH; Laura Gentile, MHA; Stuart Peacock, DPhil; Gavin C. E. Stuart, MD, FRCSC; Eduardo L. Franco, DrPH, FRSC, FCAHS, OC; Andrew J. Coldman, PhD

JAMA July 3, 2018 Volume 320, Number 1

HPV FOCAL – 48 Months



HPV FOCAL – 48 Months

- HPV based screening resulted in significantly lower CIN2+ at 48 mos compared with LBC
- Cumulative CIN2+ incidence showed no significantly different disease detection
- Cumulative colposcopy referral rates were similar
- Women who were HPV negative at baseline had a significantly lower risk of CIN2+ compared with cytology-negative women

HPV in Primary Testing

Prediction #1

- HPV is more sensitive (but less specific) than a Pap test
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⇒ NPV = Longer Screening Intervals

⇒ Less loss to follow up (?)

HPV in Primary Testing

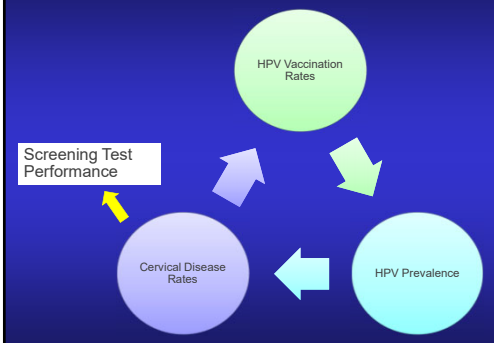
Prediction #2

- HPV testing is a more logical choice for screening women vaccinated against HPV infection

"HPV vaccination will make the existing approach of high-frequency screening by cytology too costly and inefficient"

EL Franco Vaccine: 2006

The screening population is changing.



Screening Test Performance

STATS 101

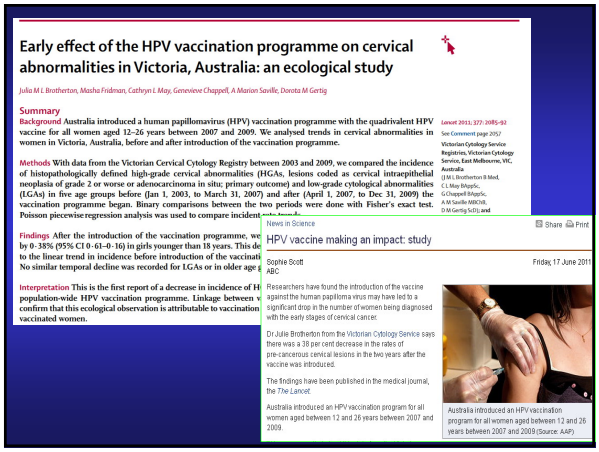
Prevalence affects the predictive value of any test. The *same* diagnostic test will give you *different* information according to the clinical setting in which you apply it.

The Impact on Positive Predictive Value (PPV) as Prevalence Changes, for a test with 99% Sensitivity and 95% Specificity

	Prevalence	1%	10%	20%
a	# in population	1,000	1,000	1,000
b	Diseased	10	100	200
c	Not diseased	990	900	800
d	True Positives on the test (b x 0.99)	10	99	198
e	False positives on the test (c x (1-0.95))	50	45	40
f	Total # positive on test (d + e)	60	144	238
	PPV (d / f)	17%	69%	83%

⇩

Falling Prevalence Leads To False Positive Results



Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study

Julia M L Brotherton, Masha Fridman, Cathryn L May, Genevieve Chappell, A Marion Saville, Dorota M Gertig

Summary

Background Australia introduced a human papillomavirus (HPV) vaccination programme with the quadrivalent HPV vaccine for all women aged 12–26 years between 2007 and 2009. We analysed trends in cervical abnormalities in women in Victoria, Australia, before and after introduction of the vaccination programme.

Methods With data from the Victorian Cervical Cytology Registry between 2003 and 2009, we compared the incidence of histopathologically defined high-grade cervical abnormalities (HGAs, lesions coded as cervical intraepithelial neoplasia of grade 2 or worse or adenocarcinoma in situ; primary outcome) and low-grade cytological abnormalities (LGAs) in five age groups before (Jan 1, 2003, to March 31, 2007) and after (April 1, 2007, to Dec 31, 2009) the vaccination programme began. Binary comparisons between the two periods were done with Fisher's exact test. Poisson piecewise regression analysis was used to compare incident

Findings After the introduction of the vaccination programme, we by 0·38% (95% CI 0·61–0·16) in girls younger than 18 years. This de to the linear trend in incidence before introduction of the vaccinati No similar temporal decline was recorded for LGAs or in older age g

Interpretation This is the first report of a decrease in incidence of H population-wide HPV vaccination programme. Linkage between v confirm that this ecological observation is attributable to vaccination vaccinated women.

Lancet 2011; 377: 2085–92

See Comment page 2057

Victorian Cytology Service Registries, Victorian Cytology Service, East Melbourne, VIC, Australia (J M L Brotherton B Med, C L May BAppSc, G Chappell BAppSc, A M Saville ARCM, D M Gertig ScD); and

News in Science

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HPV vaccine making an impact: study

Sophie Scott
ABC

Friday, 17 June 2011

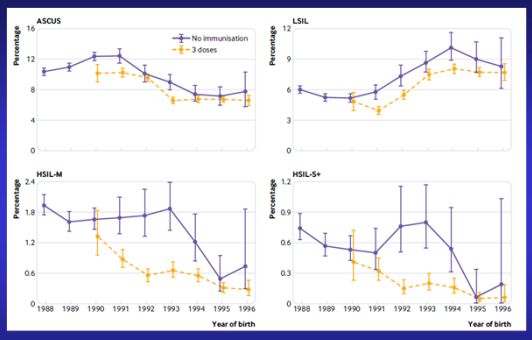
Researchers have found the introduction of the vaccine against the human papilloma virus may have led to a significant drop in the number of women being diagnosed with the early stages of cervical cancer.

Dr Julie Brotherton from the Victorian Cytology Service says there was a 38 per cent decrease in the rates of pre-cancerous cervical lesions in the two years after the vaccine was introduced.

The findings have been published in the medical journal, the *The Lancet*.

Australia introduced an HPV vaccination program for all women aged between 12 and 26 years between 2007 and 2009.

Australia introduced an HPV vaccination program for all women aged between 12 and 26 years between 2007 and 2009 (Source: AAP)



Scotland Program - Cytological abnormality (% of women screened) by year of birth and immunisation status. 1988-90=pre-immunisation programme cohort; 1991-94=catch-up cohort; 1995-96=routinely immunised cohort.

Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study

Tim Palmer,[1] Lynn Wallace,[2] Kevin G Pollock,[3,4] Kate Cuschieri,[5] Chris Robertson,[3,6,7] Kim Kavanagh,[7] Margaret Cruickshank[8]

- Routine immunisation using the bivalent HPV vaccine against high grade cervical disease was found to be highly effective
- In the setting of high uptake and a catch-up programme, unvaccinated women also show a reduction in disease, possibly because of herd protection

BMJ 2019;365:l1161

HPV immunisation and cervical screening—confirmation of changed performance of cytology as a screening test in immunised women: a retrospective population-based cohort study

T J Palmer*[,1], M McFadden[2], K G J Pollock[3], K Kavanagh[4], K Cuschieri[5], M Cruickshank[6], S Cotton[6], S Nicoll[7] and C Robertson[4]

- Significant reductions in PPV for CIN2+ were observed.
- Significant increase in the number of women referred to colposcopy to detect one case of CIN2+

Conclusions: The lower incidence of disease in vaccinated women alters the key performance indicators of cervical cytology

British Journal of Cancer (2016) 114, 582–589

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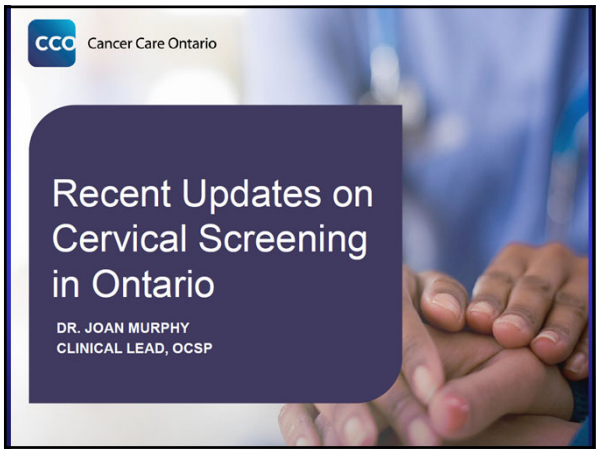
Cancer Care Ontario
Recent Updates on Cervical Screening in Ontario
DR. JOAN MURPHY
CLINICAL LEAD, OCSP