HPV Today

Newsletter on Human Papillomavirus

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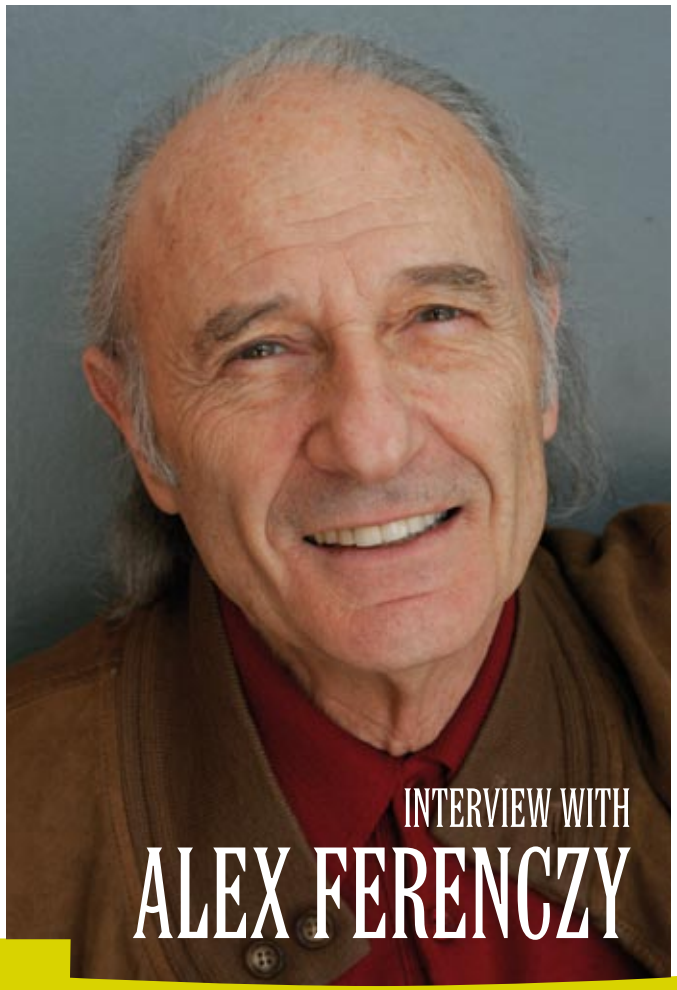
CERVICAL CANCER PREVENTION: THE BLESSING OF MOLECULAR TECHNOLOGY



How do you see the option for cervical cancer prevention at present?

There are three not mutually exclusive ways to prevent cervical cancers. One is to practice ABC, which stands for sexual abstinence, be faithful and use condoms, another is cervical screening with laboratory means, and a third option is prophylactic HPV vaccination. The first option, for all intents and purposes, is only practiced by a minority of humans and therefore has no significant impact on worldwide cervical cancer prevention. The second option is secondary prevention with screening cytology (Pap testing) with or without HPV DNA detection assays. The third is primary prevention with prophylactic HPV vaccines.

Which are the limitations of secondary prevention by Pap cytology?

Although it reduces both the incidence and mortality due to cervical cancer by about 70%, the Pap test has to be repeated frequently to achieve such outstanding results because it suffers from high false-negative rates, which make the technique cost-ineffective. False-negative results have high costs both medically and financially, as well as psychologically, and frequently also have medico-legal implications. In response to the drawbacks of conventional Pap smears, the industry has developed improved cell-collection and -processing techniques such as liquid-based cytology coupled with computerized imaging reading systems using artificial intelligence. Although these new technologies have improved the overall sensitivity of cytological diagnostic performance, the costs of the equipment preclude its universal use.

(continues on page 3)

No. 15 June 2008

EDITORIAL

THE RESEARCH CONTRIBUTIONS OF CANADA TO CERVICAL CANCER PREVENTION

Canada was among the first countries in the world to adopt organized screening as the most effective and equitable form of cervical cancer control. The experience of the province of British Columbia dates back to the late 1940s, as nicely reviewed in this issue by Anthony B. Miller, one of the Canadian champions of cancer control. Canada, more specifically Quebec City, was also home to the landmark work by Alexander Meisels and Roger Fortin, published in 1976, that recognized condylomatous atypia of the cervix as an early class of dysplastic changes caused by warty virus changes, later attributed to HPV infection. This work advanced early independent observations by Ernest Ayre and Leopold Koss, who had indicated that the koilocytotic atypia seen in Papanicolaou smears could reflect viral cytopathic effects. In the modern era of HPV acquiring centre stage in the early 1980s, Alex Ferenczy, a Montreal researcher, made seminal contributions to the pathology and treatment of HPV-associated diseases, including condylomata and neoplastic lesions of the lower genital tract. Dr. Ferenczy's interview in this issue does not look back into the past but provides a remarkable testimonial of the recent research on HPV vaccines and HPV testing on which the future of cervical cancer prevention will likely rest. Arguably the birthplace of health technology assessment and evidence-based medicine, Canada has also been a fertile ground for research on the health economics of HPV and cervical cancer prevention. Marc Brisson's work in Quebec City epitomizes the importance of Canadian contributions in this field. His primer on cost-effectiveness modelling provides a lucid introduction for anyone trying to make sense of the lingo in this area. Elsewhere in this issue, there are contributions by other Canadian authors that show the rich tapestry of HPV research in Canada which spans the spectrum of basic science to clinical medicine, from etiology to prevention.

"HPV research has benefited from a remarkable collaboration between epidemiologists and basic scientists" [Bosch et al., JNCI 2001]. Indeed, few areas in cancer prevention have benefited from multi-disciplinary interactions as remarkable as those that led to HPV testing and HPV vaccines as new weapons in cervical cancer control. This issue of HPV Today, albeit focused on the microcosm of Canadian research, will further underscore the importance of collaborative work among basic scientists, epidemiologists, health economists, and clinical researchers in furthering the cause of preventing one of the most common and fearsome types of cancer.

Eduardo L. Franco
Guest Editor
McGill University, Montreal

Website: www.hpvtoday.com

Correspondence and collaborations:
E-mail: box@hpvtoday.com

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Alex Ferenczy

Professor of Pathology and Obstetrics & Gynecology, McGill University
and Sir Mortimer B. Davis-Jewish General Hospital Montreal, Quebec, Canada.

(from page 1)

Do you see a solution to these problems?

Testing for high oncogenic risk HPV types (HR-HPV) using the US FDA-approved hybrid capture technology (HC-2, Qiagen) has a 30% higher sensitivity for detecting high-grade cervical cancer precursors (HSIL - CIN2/3) than cytology. The negative predictive value is close to 100% thus allowing for less frequent screening and longer screening intervals without jeopardizing patients' safety. Such high negative predictive values are also consistent with public expectation, according to which a negative test must, indeed, be negative. Additional technical and economic advantages of molecular technology over morphological screening are the ability to assess the individual's risk of developing clinically significant lesions, less need for Manpower, as one technologist can process close to 400 HR-HPV DNA tests per day compared to 35 to 80 slides screened per cytotechnologist, objective machine-read results, and highly reproducible interlaboratory analytical agreement rates.

Most major healthcare organizations in North America approve and recommend a combined HC-2 and cytology approach (HPV DNA/Pap test) for screening for cervical cancer and its precursors in women older than 30 years of age

Don't you think that the high cost of HPV testing precludes its wide-scale utilization as a screening strategy?

I expect that clinically validated competition in molecular technology will become a reality and prices will fall to affordable levels as more and more screening programmes adopt HR-HPV testing. In countries where primary mass screening using either cytology and/or HPV DNA testing is not feasible, visual inspection with the acetic acid test combined (if appropriate) with cryotherapy is the solution until mandatory vaccination programmes reach the pre-sexual population in these countries.

Speaking of HPV vaccination, that was your third option…

The two prophylactic HPV vaccines, Cervarix® and Gardasil®, have excellent records of safety, immunogenicity (for at least 6 years) and efficacy in preventing nearly 90% of low-grade and 100% of high-grade cervical intraepithelial lesions. I suspect that in the relatively short term, universal, mass vaccination programmes will be initiated encompassing first pre-sexual and later, sexually active (catch-up) populations. These will impact on the burden of disease by significantly reducing both the prevalence and incidence of cervical cancer precursors and, eventually, invasive cancer. And, that's tremendous news.

Should we expect HPV vaccination to impact on other areas of cervical cancer prevention?

The decreased disease prevalence/incidence will impact on the expertise in cytological interpretation. aintaining efficiency in screening for, and accuracy, in the interpretation of abnormal cells requires seeing a relatively large number of cases. It follows, therefore, that a marked decrease in disease prevalence and incidence is likely to result in increasing lab errors (misses) and, by inference, may defeat, at least partly, the very purpose of primary prevention efforts. As a remedy to this situation, it is proposed to use a highly sensitive screening test such as HPV DNA testing to identify the rare cases of cancer precursors that will occur among vaccinated women and combine it, when appropriate, with another test which has a high degree of specificity.

How do you see this approach implemented?

According to this paradigm, women are screened first with HC-2 and tested with Pap cytology only if they test positive for HR-HPV types. HR-HPV and Pap test-positive patients with ASC-US or worse are sent to colposcopy. All others, including HR-HPV-negative as well as Pap-negative but HR-HPV-positive patients

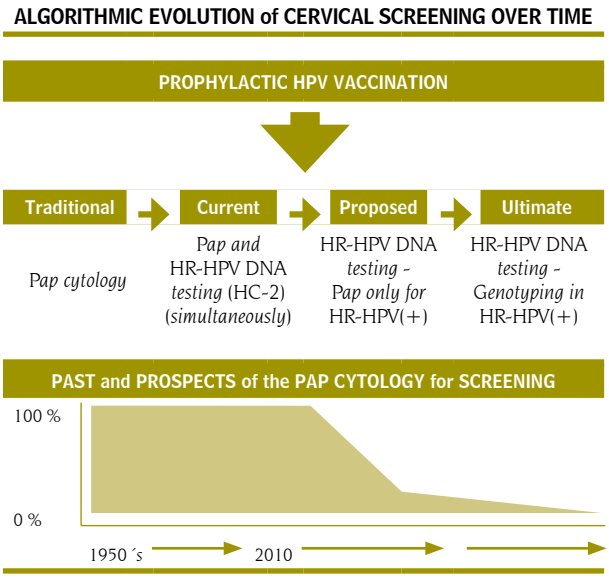


Figure 1.

Traditional and current screening programs use 100% *Pap cytology without and with* HR-HPV DNA *testing, respectively. Switching Pap cytology for testing for* HR-HPV DNA *first, and testing only* HR-HPV DNA*-positive patients with Pap cytology, has the potential to reduce Pap cytology by* 80 *to* 90% *as only* 10 *to* 20% *of women in a primary screening mode are expected to test* HR-HPV DNA *positive. Genotyping for* HPV *types* 16, 18 *and* 45, *once clinically validated, has the potential to eliminate the need for Pap cytology altogether.*

HR-HPV = *High risk human papillomaviruses;*
HC-2 = *Hybrid Capture-2 (Digene Diagnostics, Gaithersburg,* MD)

are followed with cytology at intervals of three to eight years and one year, respectively. If vaccinated women are screened first at about age 25 years, less than 20% will be expected to test HR-HPV positive. The proposed new screening paradigm will reduce the need for cytology by about 80 to 90% (Figure 1). Also, the "HPV first, Pap after" screening approach will likely reduce laboratory-related false-negative results as cytotechnologists will be alerted by the HR-HPV-positive status of the patient at the time of reading the Pap slide. Because of the very low disease incidence in the vaccinated population, the need for increased manpower and the often long delays in obtaining Pap results will become a thing of the past

Do you see this strategy as a long-term solution?

In the longer term, cytology may be phased out entirely by HR-HPV genotyping. Studies have shown that only a few of the twenty high-risk HPV types cause clinically relevant precursor lesions such as CIN3. The most frequent and aggressive HR-HPV types that are found in 70% to 80% of cervical cancer and its precursors worldwide are 16, 18 and 45. It therefore makes sense to screen primarily for these "meanest" HPV types using clinically validated genotyping technology. It should be realized that the lifetime risk of developing cervical cancer in a screened population is less than 1% (1/130) and will become even less frequent to very rare in the era of universal, mass, prophylactic HPV vaccination. The reduction in the burden of disease will, by necessity, require major changes in our approach to current screening techniques and management paradigms. Of course, one must expect, at least initially, harsh resistance to changes of traditional primary cervical cancer screening from the cytology community. However, it is only a question of time before cytology will bow before the high tide of molecular technology. I am heartily convinced that the emerging concepts in cervical cancer screening paradigms will eventually prove to be the most consistent with the well-being of women, worldwide.

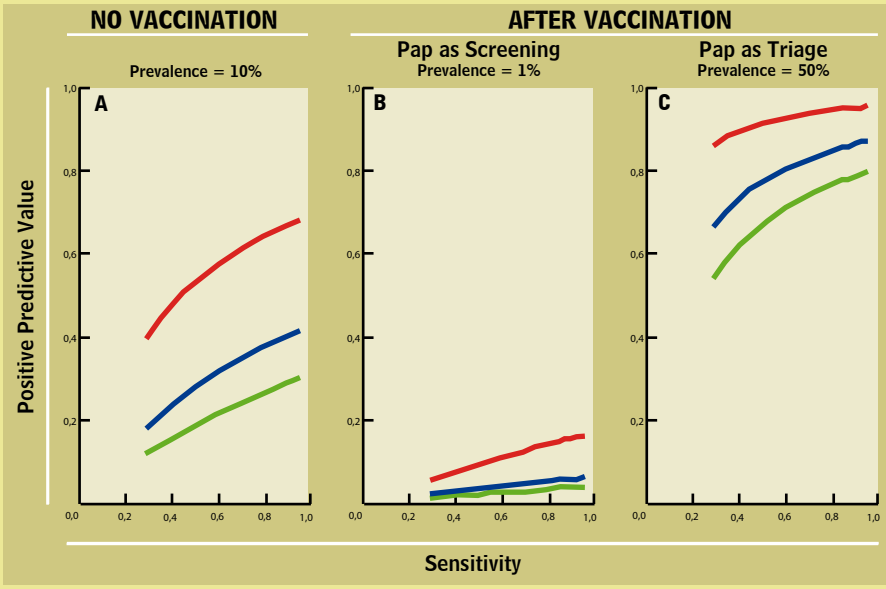
HPV IN 100 SLIDES

Eduardo Franco

Mc Gill University, Montreal

EXPECTED IMPACT OF HPV VACCINATION ON DISEASE PREVALENCE AND ON THE SCREENING PERFORMANCE OF PAP CYTOLOGY

Prevalence of any abnormality in a Pap smear



This slide shows the joint influence of changes in sensitivity, specificity, and lesion prevalence on the positive predictive value (PPV) of Pap cytology. The three curves in each graph represent different specificity estimates: red: 95%, blue: 85%, and green: 75%. The combinations of lesion prevalence reflect hypothetical Pap cytology screening conditions in different settings and post-vaccination. The prevalence of cervical lesions of any grade in unscreened or high-risk Western populations is around 10% (A graph). Post-vaccination lesion rates may be as low as 1% (B graph). The 50% prevalence graph (C graph) is a scenario to represent the situation expected in triage following an initially positive HPV test. As lesion prevalence decreases due to vaccination the PPV will decrease even for equivalent conditions of sensitivity and specificity. However, to compound the problem there may be losses in sensitivity (shifting estimates from right to left in the x axis) and in specificity (shifting estimates from the red to the green curve). It can be seen that cytology will have its highest PPV, and thus greatest clinical utility, if lesion prevalence can be maintained at a high level, a situation that is artificially created if women are screened first with the HPV test and then triaged by cytology. The strategy of using HPV testing as the primary cervical cancer screening tool has the additional advantage of permitting post-vaccination surveillance via record linkage of screening and vaccination registries, thus providing an efficient and low-cost strategy for monitoring long-term protection among vaccinated women while providing a cervical cancer screening service to the population.

Modified from: Franco EL, Cuzick J, Hildesheim A, de Sanjose S. Chapter 20: Issues in planning cervical cancer screening in the era of HPV vaccination. Vaccine 2006 Aug 21:24 Suppl 3:S171-7.

POINT OF VIEW

SCREENING FOR CERVICAL CANCER AND PRECURSORS IN CANADA

Anthony B Miller

Professor Emeritus, Department of Public Health Sciences
University of Toronto, Ontario, Canada

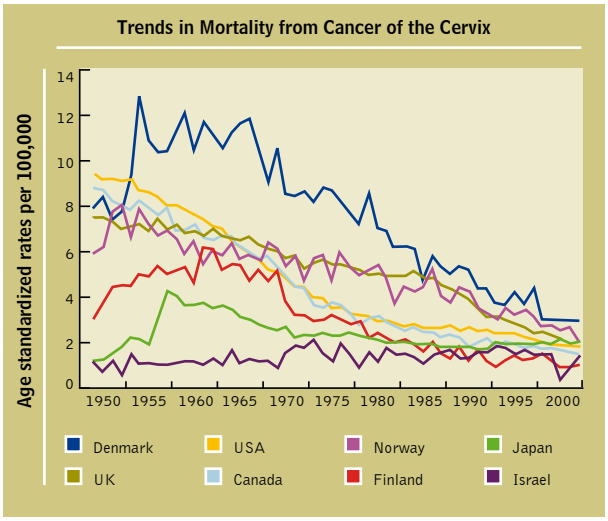
Screening for cervical cancer in Canada commenced in British Columbia in 1949. For the first ten years the laboratory provided a diagnostic service, but smears were also examined from patients attending venereal disease clinics or in penal institutions. In the 1960s advertisements were used to persuade women to attend their family physician for a smear. Since then the British Columbia program has continued to expand, still based on one provincial laboratory, and it remains the most effective in Canada. When we estimated the sensitivity of the tests, by evaluating the effect on subsequent disease occurrence, it was of the order of 75%.[1]

Elsewhere in Canada screening commenced slowly, but with the example of British Columbia, programs began to expand. A significant correlation was demonstrated between the intensity of screening and decline in mortality from cancer of the uterus (of which cervix cancer is the largest component) during the 1960s, both at the provincial and census district level.[2] This finding persuaded the Walton committee that screening was effective, and recommendations were made for strengthening the programs, and introducing three-yearly screening for those cytologically negative.[3]

The records collected in cytology laboratories in BC and Toronto have been useful to evaluate the natural history of cervical cancer precursors.[1,4,5] This showed that the majority of cervical intra-epithelial dysplasia (CIN) I and II regress, and 50% or more of CIN III. Thus, there is a substantial risk of over-treatment if CIN II is not distinguished from CIN III, as unfortunately now occurs with the Bethesda classification.[6]

It is generally now recognized that screening programs should be organized. The first two National committees set out the requirements for organization in cervical screening,[3,7] later re-enforced.[8,9] Although the National committees all recommended three-yearly screening, as has an IARC Working Group,[10] the lack of organization in many parts of Canada has led to the perpetuation of annual screening, though in British Columbia the standard is now every two years. This means, therefore, that in the United States and Canada, cervical cancer screening involves substantial over-expenditure of resources. Nevertheless, the program in Canada has been as successful as in Finland and the US in reducing mortality from the disease (Figure), and far better than Norway and the UK, until they introduced organized screening. However, mortality is no longer falling, and the proportion of women screened in the last three years is stable at 73%, so there is room for improvement.[11]

With a Screening Action Group functioning within the Canadian Partnership against Cancer we can anticipate continued assessment and re-organization of the provincial programs. Cytology screening, which has been so successful, may be replaced by HPV testing in older women to take advantage of much longer intervals between screens. This will make organization of the programs more essential to ensure at-risk women do not slip through the screening net. It seems unlikely that we shall be able to dispense with screening until we have vaccines that are 100% effective against all oncogenic types, and the vaccinated women have replaced their older forebears in being the groups at risk for cervical cancer. The necessity for organized cervical screening will remain, therefore, for several decades.



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CANADA'S PARADIGM FOR HPV VACCINATION AND THE PROGRAM IN QUEBEC

Introduction

Canada has a long history in setting standards for screening and is now evaluating and adopting HPV vaccines in combination with screening. The first HPV vaccine was approved by the federal regulator, Health Canada, on July 10, 2006, for females 9 through 26 years of age.

Canada has very low rates of cervical cancer incidence (7.7/100,000/year) and mortality (2.5/100,000/year). The 10 provincial and three territorial ministries of health maintain free screening programs that range from simple opportunistic to fully organized with call-recall systems. Yet, the low cancer rates afforded by our screening programs have reached a point of diminishing returns in view of limits related to coverage, acceptability, and the relatively low sensitivity of cytology.

Primary prevention has advantages over secondary prevention such as screening

School-based vaccination programs remain an effective way to reach young girls and to make sure all vaccine doses are administered. In 1998-99, 97.1% of Canadians between 7-14 years of age were enrolled full-time in school.[1] Immunization coverage with existing programs is high when school-based programs are used and coverage is relatively higher in primary than in high school. In a school-based program, immunization is likely to reach some of the populations who may have lower cervical cancer screening rates or poor follow-up.

HPV vaccination will have a delayed influence in reducing cancer burden because of the long time it will take for the averted HPV infections and their associated precancerous lesions to progress to invasive cancers. However, vaccination will lead to important early benefits by reducing the rates of external genital warts (quadrivalent vaccine only) and low- and high-grade lesions of the cervix and the vulva. These reductions, in turn, will lead to a lower demand for screening and, eventually, a reduction in the financial costs and psychological impacts, a reduced number of ambiguous diagnoses, colposcopies and biopsies, a reduced number of benign surgeries and reduced fertility implications.

Since the prophylactic vaccines have no therapeutic properties and do not prevent the acquisition of all HPV genotypes that cause cervical cancer, screening and vaccination programs will have to complement each other for maximal preventive impact in the population.

Commitment of the federal government

The Canadian Immunization Committee (CIC) has provided leadership in immunization, and HPV vaccine program planning was identified as a priority as early as December 2005. The analytical framework for immunization programs in Canada developed with the help of stakeholders such as the Cervical Cancer Prevention and Control Network, College of Family Physicians of Canada, Society of Obstetricians and Gynaecologists of Canada, Society of Gynecologic Oncologist of Canada, First Nations and Inuit Health Branch of Health Canada, and Biologics and Genetic Therapies Directorate of Health Canada. An amount of $CDN 300,000,000 was set aside by the federal government to assist with purchasing HPV vaccines over the first three years.

Equity and Ethical & political considerations

The social disparities that exist in the utilization of cervical cancer screening means that cervical cancer mainly affects women of lower socioeconomic status. The fact that the cost of the HPV vaccine is high underscores the importance of properly planning a vaccination program that is publicly funded so as to avoid the social inequity that may ensue if vaccination is not made freely available to all citizens. In addition, catch-up vaccination is recommended as another safeguard against any potential inequity.

HPV infection is a sexually transmitted infection that can cause cancer, which prompts numerous issues, including ethical dilemmas about sending a morally contemptible message, such as the endorsement of sexual promiscuity. Such concerns are not well founded. Hepatitis B is also transmissible through sexual contact but vaccination had high parental acceptance in Canada and caused no unintended effects concerning risk behaviours. Finally, HPV vaccination will be voluntary in Canada. Any parents will be able to withdraw their kids from HPV programs without this having an effect on their school attendance.

Surveillance and evaluation systems are being developed as complements to HPV vaccination programs in line with those adopted in other countries.

Quebec's HPV Vaccination Programme

The Committee on Immunization of Quebec (CIQ) has recently released its recommendations to the Health and Social services ministry on prevention by HPV vaccination that contains some key differences with respect to other provincial programs. Decisions should soon be taken by the Minister to permit the HPV vaccine program to start in September 2008.[2]

Marc Steben,
Institut National de Santé Publique du Québec

Goals

The prevention of cervical cancer precursor lesions and invasive cervical cancers are short- and long-term objectives, respectively.

Basis for recommendations

The prophylactic vaccines are beneficial to all women 9-26 years of age but, because of their costs, priority will be given to women before the age of first intercourse using a school-based delivery for maximum coverage.

Routine immunization and flexible intervals

The CIQ recommends a longer interval between doses, with a first dose at the fourth year of primary school (± 9 years of age) together with the current hepatitis B vaccine, with six months between the first two doses, and the third dose given in the third secondary year (± 13 years of age) along with the DPT recall already scheduled.

Catch-up immunization 13 to 26

The routine immunization program of nine-year-old girls should be accompanied by a concomitant catch-up program consisting of all three doses in a calendar year, as recommended by vaccine manufacturers. The catch-up vaccination program will prioritize women 13 to 26 years of age in yearly cohorts, depending on budgetary resources, and women who have stopped going to school.
For women 15-26, some access to subsidized but not necessarily free vaccination should be implemented.

Additional program requirements

The CIQ has recommended the development of an evaluation program, training of health care personnel, a health promotion campaign for the public, and validation of lab tests to be used in the evaluation activities.

Impact of immunization on screening

The cervical screening program is an essential tool for evaluating the efficacy of the vaccination program. Since an immunization program against HPV 16 and 18 will not eradicate cervical cancer, all women, whether immunized or not, will have to continue screening.
It is expected that HPV vaccination will have an impact on screening practices as a result of the anticipated decrease in rates of abnormal smears, which will negatively impact the positive predictive value of Pap cytology. Cervical cancer screening may have to include HPV testing as a primary tool to permit a more cost-effective prevention strategy that also serves the goal of vaccine program evaluation.

Justification for a lengthened vaccination calendar

In order to minimize costs and yet still achieve adequate protection for women, the CIQ has recommended a modified vaccination . This decision was based on immunological and operational considerations as follows:
— HPV vaccines are highly immunogenic; antibody titers are much higher than levels observed via natural immune response.
— Immune response is particularly high in adolescents 9-11 years of age with antibody titers higher after two doses than those observed at ages 16-26 years after three doses.
— As shown with hepatitis B, the wider the interval between doses, the higher the antibody titer.
— There is limited information on alternative vaccination schedules or number of doses.
— Immune challenge leads to higher antibody titers than that which follows the prescribed set of three immunizations as seen with hepatitis B and HPV. Since maximal protection is needed just before onset of sexual activity, delayed administration of the third dose appears justifiable with the contemporary knowledge.

Currently a two-dose combined hepatitis A and B vaccine could be introduced at the same time as the two doses for the HPV vaccine, thus improving acceptance to adolescents, their parents and health care providers. Because of its lower costs, this approach has the added benefit of permitting increased coverage of adolescent women. A clinical trial with two doses of HPV vaccine in young female adolescents started in 2007 and the findings will be used to make any necessary adjustments to the program as early as or before the administration of the third doses of the proposed lengthened schedule.

Reference: 1. http://www.statcan.ca/anglais/freepub/81-229-XIB/0000081-229-XIB.pdf. Prévention par la vaccination des maladies attribuables aux virus du papillome humain au Québec by the Comité sur l'immunisation du Québec (CIQ), Direction risques biologiques, environnementaux et occupationnels, Institut national de santé publique du Québec, octobre 2007.**2.** http://www.inspq.qc.ca/pdf/publications/714PrevVaccinationPapillomeHumain.pdf

Marc Brisson
Canada Research Chair in Mathematical Modeling and Health Economics of Infectious Disease Associate Professor, Faculty of Medicine, Université Laval, Canada

THE ABC OF COST-EFFECTIVENESS AND THE ECONOMIC EVALUATION OF HPV VACCINATION IN DEVELOPED COUNTRIES

With promising safety and efficacy results from randomized control trials of prophylactic HPV vaccines and the availability of new screening paradigms, policymakers are being asked to make recommendations and decisions regarding the optimal strategies in reducing HPV infection and disease. The demand for modelling has resulted in the development and publication of numerous mathematical models looking at the effectiveness and cost-effectiveness of HPV vaccination and screening.[1-6] Currently, over 15 HPV vaccine modelling papers have been published[1-6] and many more are in development. Although the availability of several modelling studies is extremely helpful to provide evidence on the validity and robustness of conclusions, differences in the types of models and methodology can be an important source of confusion (for both specialists and non-specialists) as to how results should be interpreted and used.

The Cost-effectiveness ratios (CER) can be presented as follows:

$$CER = \frac{(\text{Costs with intervention A} - \text{Costs with intervention B})}{(\text{Effect of A} - \text{Effect of B})} = \frac{\text{Net cost of intervention}}{\text{Net health benefit}}$$

For HPV vaccination the CER can be represented as follows:

$$CER = \frac{(\text{Cost of Vaccination} - \text{Cost offsets by preventing HPV disease})}{(\text{Gains in Health by preventing HPV disease})}$$

GENERAL CONCEPTS OF COST-EFFECTIVENESS ANALYSES

Why is cost-effectiveness needed?

Currently, the availability of health care interventions considerably exceeds society's capacity to pay for them. Cost-effectiveness analysis is useful under such conditions as it provides an analytical framework in which to assess the desirability of an intervention compared with other uses of the same scarce resources. Cost-effectiveness analyses try to answer the following questions:

1) Is the health care intervention worth doing compared to alternative uses of the same resources?

2) More specifically, if we are deciding to implement an intervention, who should receive the intervention, at what age, and what strategy should be used?

Why are mathematical models needed?

Cost-effectiveness analysis can be performed using either an empirical (clinical research) or a model-based approach. In most cases, a model-based approach is required since clinical efficacy trials are predominantly designed to measure efficacy rather than effectiveness and, as a result, are often limited in scope and duration (e.g. size, strict inclusion criteria for patients, limited in scenarios investigated). By combining clinical efficacy results with information from various sources (demographic, biological, epidemiological), models are able to address questions that cannot be feasibly or ethically answered in a trial setting. For prophylactic HPV vaccines, many of the benefits occur in the medium to long term, and therefore mathematical models are needed to project the impact of vaccination beyond the time horizon of clinical trials.

What are Cost-effectiveness analyses and Cost-effectiveness Ratios (CER)?

As mentioned earlier, the goal of cost-effectiveness analysis is to compare the health and economic impact of different interventions in order to identify which interventions maximize the health of the population, in a context of limited resources. The results of cost-effectiveness analyses are usually presented as a ratio. The Cost-Effectiveness Ratio (CER) is a measure of the incremental cost of obtaining a unit of health effect from an intervention when compared to an alternative. For HPV vaccination, this would be the incremental cost of obtaining a health benefit from vaccination compared to no vaccination.

For HPV vaccine cost-effectiveness, elements that are included as costs include the price of the vaccine, administration cost of vaccination, physician visits, hospitalization, screening and treatment related to HPV disease. The health benefits can be measured as cases prevented, cancers prevented, deaths prevented, life-years gained and quality-adjusted life-years (QALYs) gained. The most common measure of health benefit in cost-effectiveness analysis is QALYs-gained. The QALY was developed to capture, in a single measure, both gains from reduced morbidity (such as prevention of anxiety and pain) and reduced mortality. QALYs (also known as utilities) range from 0 (state=death) to 1 (perfect health). For HPV vaccination, the QALYs-gained is the difference, over time, between the overall QALYs in a world with and without vaccination.

IMPORTANT COMPONENTS OF THE COST-EFFECTIVENESS OF HPV VACCINATION

Discounting

Individuals usually prefer to receive benefits sooner rather than later and prefer to incur costs later rather than sooner. Discounting is a technique used in cost-effectiveness analysis to take these time preferences into account. It consists of scaling down future costs and benefits such that they are less important the further in the future they occur and/or the higher the discount rate. There is debate as to what discount rate should be used and there is between-country variability

in the rates that are used (discount rates typically vary between 3% and 5%). For treatment, benefits occur shortly after the intervention is given, and the cost-effectiveness of these interventions is therefore largely independent of these methodological disagreements on discounting. However, the cost-effectiveness of prevention programs is highly sensitive to discounting due to the long time spans over which benefits accrue. Discounting is of particular importance when assessing the cost-effectiveness of HPV vaccination as costs of the program are incurred at the moment of vaccination while benefits can occur in the short (genital warts) to long term (cervical cancer).[2] A slight decrease in discount rate (from 5% to 3%) could change the cost-effectiveness of HPV vaccination strategies from unacceptable to attractive (see Figure).

Uncertainty analysis

The development of models is based on assumptions, which necessarily introduce uncertainty regarding the conclusions that can be drawn from their results. In the case of HPV, it is particularly important to quantify uncertainty due to the complex natural history of HPV infection (encompasses numerous stages of disease, which depend on HPV type, screening and treatment) and the limited data on age and type-specific HPV natural history. Moreover, for some model parameters, such as progression rates to cancer, empirical studies cannot be carried out for ethical reasons. Despite considerable uncertainty surrounding type-specific parameters of natural history, most HPV modelling studies have made predictions regarding the impact of HPV vaccination by using only one parameter set. In these studies, only one-way sensitivity analyses, which are limited in scope because they do not take into account the joint uncertainty of all natural history parameters, were performed. A second, more recent, approach has been to identify and utilize multiple good-fitting parameter sets (which can loosely be viewed as multiple models) to provide decision makers with a range of results that encompass the uncertainties in the natural history of HPV infection and disease. When examining different cost-effectiveness studies of HPV vaccination (and screening) one should ensure that conclusions are clearly framed as conditional upon the input estimates used.

Model Type

Mass vaccination can produce complex indirect effects that require the modelling of infection and transmission (not just natural history of disease), and thus the type of model used can be critical (see Brisson and Edmunds for more on the subject). Although there are many types of models that are used to predict the impact of vaccination, they can be broken down into two main categories: dynamic and[2] static (usually decision analysis or cohort models). The major difference between these types of models is that dynamic models capture the indirect protection resulting from immunization (herd immunity effects), whereas static models omit them. Herd immunity effects are dependent on the extent to which vaccination prevents transmission of infection in the population. If only a small proportion of the population is immunized (low coverage), or the vaccine has low efficacy, then herd-immunity effects are negligible. Static and dynamic models produce similar results under such conditions. Static models may also be used as a tool to estimate the worst-case scenario when herd-immunity does not produce negative effects. In other circumstances, dynamic models should be used. For HPV vaccination, static models should only be used to examine the question whether vaccinating girls is cost-effective (as results will be conservative). Other questions, such as the incremental cost-effectiveness of vaccinating boys, optimal catch-up strategies or optimal screening and vaccination strategies, should only be examined using a dynamic model as the non-linear effects of vaccination can have a significant impact on results/conclusions.

CURRENT PUBLISHED COST-EFFECTIVENESS STUDIES OF HPV VACCINATION IN DEVELOPED COUNTRIES & REVIEW OF THE EVIDENCE

Vaccinating Girls

Results from published studies consistently suggest that vaccinating adolescent girls against HPV is likely to be cost-effective if duration of vaccine protection is greater than 30 years or if booster doses are given when duration of vaccine efficacy is assumed to be limited (see Table). The type of model used has little impact on the conclusions regarding the cost-effectiveness of vaccinating girls. However, as expected, because they do not include herd-immunity effects, static (cohort) models produce less attractive cost-effectiveness ratios than dynamic models. It should also be pointed out that most studies suggest that the main benefit of HPV vaccination will be in preventing cervical cancer mortality rather than reducing the medical costs related to screening and treatment of HPV-related disease (assuming screening is not changed).

Vaccinating Boys, Catch-up Vaccination & Vaccinating Women

Current evidence suggests that including boys in a vaccination program will not be cost-effective if vaccine coverage rates are

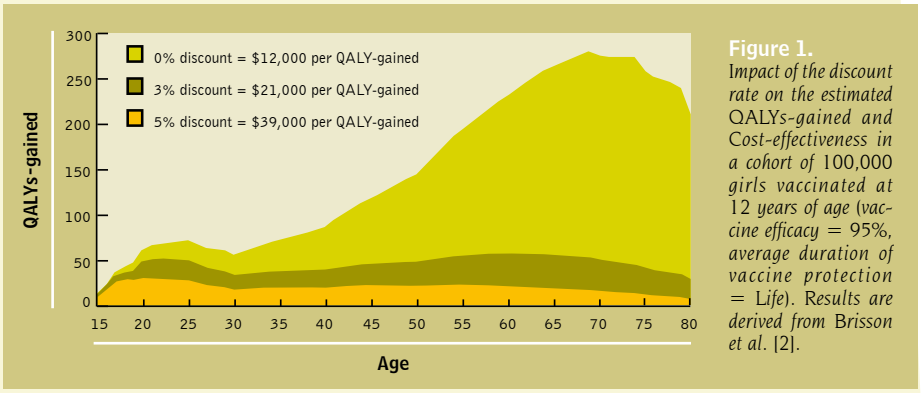


Figure 1.
Impact of the discount rate on the estimated QALYs-gained *and Cost-effectiveness in a cohort of* 100,000 *girls vaccinated at* 12 *years of age (vaccine efficacy* = 95%, *average duration of vaccine protection* = *Life). Results are derived from* Brisson *et al.* [2].

high in girls. The incremental effectiveness and cost-effectiveness of vaccinating boys varies greatly between studies when coverage rates are low (≤80%).[3] Evidence on the cost-effectiveness of catch-up strategies and vaccinating older women is still limited, therefore more work is required in this area before consensus can be made.

HPV vaccination and screening

Not much work has been focussed on identifying what would be the optimal vaccination and screening strategy in terms of cost-effectiveness. Studies that have looked at this research question have suggested that increasing screening intervals combined with HPV vaccination of girls is likely to be cost-effective.[1,4,5] However, much more work is needed as these studies have not been performed using dynamic models and/or alternative screening paradigms have not been sufficiently investigated in conjunction with vaccination.

Most important parameters

All studies conclude that the duration of vaccine efficacy is the one of the most influential parameters regarding the cost-effectiveness of HPV vaccination.[1-4] Other important parameters are those that represent the natural history of HPV in older women (e.g. rate of HPV infection and, progression and regression of disease)[5] and the degree and duration of type-specific natural immunity following clearance of infection. Efforts should thus be made to better characterize natural immunity following HPV infection and the epidemiology of HPV in older age groups. Similarly, more studies should be focused on quantifying the rate of waning protection following vaccination by measuring antibody decay in clinical trials and/or duration of vaccine protection from surveillance data.

SUMMARY

Modelling studies have produced consistent conclusions regarding the cost-effectiveness of vaccinating girls and boys against HPV. **The results suggest that, under current HPV vaccine costs, vaccinating girls is likely to be cost-effective, while vaccinating boys will most likely not be cost -effective in countries that can reach high vaccine coverage rates in girls.**

Cost-effectiveness analysis can be a powerful tool in helping decision makers to choose the most effective intervention in the context of scarce health care resources. Future work should be focussed on increasing the robustness of HPV models (i.e. perfecting the fit of models to data, including herd-immunity effects and capturing the heterogeneity in screening practices). This will enable modellers to examine the crucial HPV policy question: What are the optimal HPV vaccination and screening strategies to reduce the morbidity and mortality of HPV diseases, in the context of limited resources?

Further recommended reading:

1. Kulasingam S *et al.* A cost-effectiveness analysis of adding a human papillomavirus vaccine to the Australian National Cervical Cancer Screening Program. Sex Health 2007;4(3):165-75. **2.** Brisson M *et al.* The potential cost-effectiveness of prophylactic human papillomavirus vaccines in Canada. Vaccine 2007; 25:5399-408. **3.** Elbasha EH *et al.* Model for assessing human papillomavirus vaccination strategies. Emerg Infect Dis 2007; 13:28-41. **4.** Taira AV,*et al.* Evaluating human papillomavirus vaccination programs. Emerg Infect Dis 2004;10:1915-23. **5.** Goldie SJ *et al.* Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. J Natl Cancer Inst 2004;96:604-15. **6.** Sanders GD *et al.* Cost-effectiveness of a potential vaccine for human papillomavirus. Emerg Infect Dis 2003;9:37-48.

HPV VACCINE COST-EFFECTIVENESS STUDIES IN DEVELOPED COUNTRIES USING COST-PER QALY GAINED AS THEIR MAIN OUTCOME

		Sanders et al. 2003	Goldie et al. 2004	Taira et al. 2004	Elbasha et al. 2007	Brisson et al. 2007	Kulasingam et al. 2007
Model		Static	Static	Hybrid[α]	Dynamic	Static	Static
HPV types		16,18	16,18	16,18	6,11,16,18	6,11,16,18	16,18
Outcome		Cost per QALY- gained	Cost per QALY- gained	Cost per QALY- gained	Cost per QALY- gained	Cost per QALY- gained	Cost per QALY- gained
Coverage		NA	NA	70%	70%	NA	80%
Vaccine Efficacy		75% against all HPV	90%	90%	90%	95%	100%
Cost of vaccination		US$ 300 Booster= $100	US$ 377	US$ 300 Booster= $100	US$ 360	CAN$ 400 Booster=$133	AUS$ 381 Booster= $146
Discount Rate		3%	3%	3%	3%	3%	3%
Uncertainty Analysis							
Natural history		One way	One way	No	No	Multivariate	No
Vaccine characteristics		One way	One way	One way	One way	One way	One way
Economic parameters		One way	One way	One way	One way	Multivariate	One way
Cost per QALY-gained[α]		$US	$US	$US	$US	$Canada	$Australia
Vaccinating Girls	**Vacc Duration= 10 yrs**	-	-	-	Dominated[†]	> 200,000	53,000
	Vacc Duration= 30 yrs	-	-	-	-	64,584 (26,247-95,981)	-
	Vacc Duration= Life	-	24,000	-	3,000	21,000 (11,000–33,000)	19,000
	Booster	23,000[¥]	-	15,000[§]	-	36,981 (21,036-59,209)[§]	25,000[£]
Incremental impact of Vaccinating Boys		-	-	442,000	Dominated	-	34,000
Incremental impact of Catch-up in women		-	-	-	42,000 (to 24 yr-old)	-	46,000 (to 14yr-old) 79,000 (to 26yr-old)

Table.

α. *A hybrid model is a combination of a cohort and a dynamic model and therefore can capture herd-immunity effects.*
¥. *Booster doses are given every 10 years to maintain full protection.*
§. *One booster dose is given at 22 years of age.*
†. *Dominated: Intervention is both less effective and more costly.*
£. *Booster provides lifelong protection.*

24TH INTERNATIONAL PAPILLOMAVIRUS CONFERENCE AND CLINICAL WORKSHOP, BEIJING, CHINA

Ann N. Burchell

The 24th International Papillomavirus (IPV) Conference (November 3-9, 2007) was recently hosted in Beijing by the Chinese Medical Association. There was great excitement among attendees to be in Beijing, arguably among the most exotic locales of IPV conferences to date, and site of the upcoming 2008 Olympics. This memorable conference consisted of substantial scientific contributions, with five keynote speakers, 242 oral presentations, and 439 posters. The following summary briefly touches on some of the common themes rather than providing a thorough review of all the outstanding research that was presented.

Many of the presentations demonstrated the flurry of scientific activity that has occurred as countries throughout the world anticipate the potential impact of HPV vaccination. Reports of HPV-type prevalence were appreciated, particularly from those regions for which there were few data in the past. These studies are essential as they set the baseline prior to vaccine implementation. Studies from China and other Asian countries in particular showed that there is considerable heterogeneity, with pockets of high incidence being of great concern.

International collaborations also presented data on the contributions of HPV types in cervical, other anogenital, and non-anogenital cancers, clearly showing the ubiquity of types 16 and 18 as top-ranking across regions and over time.

Updates on phase-three trials for the bivalent and quadrivalent vaccines documented increasing evidence of their efficacy for the prevention of infection and cervical lesions. There was also enthusiasm regarding new possibilities for the next generation vaccines, such as L2-based and therapeutic vaccines. Mathematical models of the potential impact and cost effectiveness of vaccination were prevalent, and demonstrated an increasing sophistication in the use of these approaches. Others updated knowledge regarding barriers and facilitators to vaccine acceptance and implementation.

There were several insightful presentations from new and existing cohort studies on the natural history of HPV infection in women and men, from the initial HPV transmission and infection event, to seroconversion, clearance versus persistence, and development and recurrence of lesions. Many explored the role of coinfections, either of multiple HPV types, or of other infections, particularly HIV. New knowledge regarding host genetic susceptibilities, and the possible role of innate immunity, was also presented.

At the basic science level, presentations updated ongoing work in animal and in vitro tissue models to understand viral entry and replication, effects on the cell cycle, and pathogenesis. The future impact of such work for applications such as topical microbicides and antivirals will be well worth watching.

Improvements in screening technologies and diagnosis, either through the use of new technologies or better use of existing technologies, were hot topics. Several trials confirmed a gain with the use of HPV testing in conjunction with cytology or as stand-alone method. Presenters considered the changes that may be necessary in screening practices in vaccinated populations. The short- and long-term effect of treatments of HPV-related disease, once detected, were also reported.

The conference organizers and all the presenters are to be commended for a varied and rigourous programme. This attendee left with a feeling of great promise of things to come at the next IPV conference, to be held in Malmö, Sweden, May 8-14, 2009.

EULOGY: BERNARD DUVAL

"I am among those who think that science has great beauty. A scientist in his laboratory is not only a technician: he is also a child placed before natural phenomena which impress him like a fairy tale." *Marie Curie* (1867 - 1934)

As this issue of HPV Today was going to press we learned about the passing of our most esteemed colleague Bernard Duval, one of the champions of vaccinology research in Canada. Bernard was one of the leading scientists at the Institut National de Santé Publique and a Professor at Laval University in Quebec City. He was also a key member of our federally-funded team on HPV research (see Research in Progress elsewhere in this issue).

Bernard made many contributions as a policymaker and as a prominent member of national and international immunization advisory committees. His most recent achievement was the innovative HPV immunization programme for Quebec (see Marc Steben's article on Canada's paradigm for HPV vaccination).

Bernard was fond of saying that after having given much of his career to the cause of preventing infectious diseases he saw HPV vaccination as the last one of his challenges before he could retire. He was imbued with a tremendous sense of duty in furthering the mission of cervical cancer control. The above motto by Madame Curie captures well the spirit of how Bernard tackled his last battle as a scientist. His youthful and congenial manner was contagious and kept us all believing that the obstacles we faced could be easily circumvented if we worked as a multi-disciplinary team bound by our common love of science and public health advocacy.

Bernard's legacy will stay with us forever.

Eduardo L. Franco
McGill University, Montreal

HPV IN SCREENING AND TRIAGE

THE CANADIAN CERVICAL CANCER SCREENING TRIAL (CCCAST)

Marie-Helene Mayrand and Eduardo Franco, McGill University, Montreal

The Canadian Cervical Cancer Screening Trial (CCCaST) is an ongoing randomized controlled trial (RCT) that compares HPV DNA testing and Pap cytology in primary screening for cervical cancers and their high-grade precancerous lesions among women aged 30-69 years.[1] Between October 2002 and October 2004, female participants attending opportunistic cervical cancer screening were enrolled through 30 selected medical practices in Montreal (province of Quebec) and St. John's (province of Newfoundland). Exclusion criteria were: (i) currently under follow-up for a cervical lesion, (ii) absence of cervix, (iii) pregnancy, (iv) cervical cancer history, (v) Pap testing in the previous year, or (vi) inability to provide consent. Written informed consent was obtained from all participants. Information on sociodemographics and risk factors were obtained via self-administered questionnaire.

10,154 Women were randomized 1:1 to one of two arms: the Pap screening arm (conventional cytology) or the HPV screening (testing for 13 oncogenic types of HPV via the Hybrid Capture 2 assay, Qiagen, Inc.) arm. We included both tests in each arm, but randomized the order in which the test samples would be collected. In the Pap screening arm, women received a Pap test (the index test) followed by an HPV DNA test (the secondary test), whereas in the HPV screening arm, women received an HPV test (the index test) followed by a Pap test (the secondary test). This design permits the performance of the two tests to be assessed as if they had been done alone, while giving all women in the trial access to the established standard in cervical cancer screening: the Pap test. It will also enable us to investigate the performance of the two tests when used in combination and evaluate any biasing effects due to the test sampling order.

Women with an abnormal Pap test (ASC-US or worse) or a positive HPV test (cut-off point of 1 RLU, 1 pg/ml of HPV DNA) at enrolment underwent a colposcopic examination. The colposcopy protocol included: (i) ectocervical biopsies of all abnormal-appearing cervical regions, (ii) at least one ectocervical biopsy of normal areas (to reduce the risk that CIN giving an impression of metaplasia would not be biopsied and missed), and pathology, and (iii) endocervical curettage. Colposcopy was performed without knowledge of the screening test results. A random, clinic-stratified 10%-20% sample of women testing negative with the index test also underwent colposcopy, to allow for correction of verification bias. Women with normal test results who were not selected for colposcopy were invited for a second round of screening 12-18 months after their initial visit, in which the initial screening arm allocation was maintained. Women who had undergone colposcopic examinations and were not found to have CIN2, CIN3 or cancer were also recalled for a second round of screening 12-18 months after their last colposcopy. We report on a conservative case definition that included all histologically confirmed CIN 2/3, adenocarcinoma in situ, or cervical cancers that were confirmed in the excisional specimen or a confirmatory biopsy in the case of ablative treatment.

The sensitivity of HPV testing was substantially higher (94.6%, 95%CI: 84.2-100) than that of Pap cytology (55.4%, 95%CI: 33.6-77.2), albeit with a slightly lower specificity (Pap: 96.8%, 95%CI: 96.3-97.3; HPV: (94.1%, 95%CI: 93.4-94.8; see table).[2]

We also modelled the effect of selected factors on the sensitivity and specificity of PAP cytology and HPV testing. The most important predictor of the performance of a Pap test was the laboratory, although this variable had no significant influence on HPV testing performance. Women over 40 with no new sexual partners in the last year seemed to be ideal candidates for primary screening using HPV testing. In this group of women, HPV testing was 33% more sensitive than Pap testing (93.3% *vs*. 59.8%), but had similar specificity (96.8% *vs*. 97.2%).

CCCaST's enrolment results corroborated the findings from split-sample studies, which showed that HPV testing is substantially more sensitive than Pap cytology but has slightly lower specificity. As this is an RCT it contributes high quality evidence for policy decisions and professional guidelines. CCCaST has been funded by the Canadian Institutes of Health Research.

COHORT-POOLED INDICES OF SCREENING PERFORMANCE[1] OF PAP AND HPV TESTING TO IDENTIFY CIN2 OR WORSE IN THE CCCAST STUDY

Screening indices	Screening strategies and definition of positive result for colposcopy referral						
	Pap only		HPV only		Pap screen followed by HPV triage (all ASC-US smears triaged at HPV ≥1 pg/ml)	HPV screen followed by Pap triage (all HPV ≥1pg/ml triaged at Pap ≥ASC-US)	Co-testing (Pap ≥ASC-US or HPV ≥1 pg/ml)
	≥ASC-US	≥LSIL	≥1.0 pg/ml	≥2.0 pg/ml			
Sensitivity (%)	56.4	42.2	97.4	81.1	53.8	53.8	100
Specificity (%)	97.3	99.1	94.3	95.5	98.7	99.1	92.5
Positive Predictive Value (%)	8.5	17.5	7	9.1	14.9	21.4	5.5
Negative Predictive Value (%)	99.8	99.7	100	99.9	99.8	99.8	100
Extra tests required (%)[2]	0	0	0	0	1.9	6.1	100
Colposcopy referrals for (%)	2.9	1	6.1	4.8	1.6	1.1	7.9

1. Estimates corrected for verification bias and using the conservative case definition. 2. In addition to the ones used for the primary screen or all women.

References:

1. Mayrand MH*et al.* CCCaST Study Group. Randomized controlled trial of human papillomavirus testing versus Pap cytology in the primary screening for cervical cancer precursors: design, methods and preliminary accrual results of the Canadian cervical cancer screening trial (CCCaST). Int J Cancer 2006;119(3):615-23. **2.** Mayrand MH *et al*; Canadian Cervical Cancer Screening Trial Study Group. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. N Engl J Med 2007;357(16):1579-88.

RESEARCH IN PROGRESS

Eduardo Franco, François Coutlée, Alex Ferenczy, Bernard Duval, Greg Matlashewski, Michel Roger, Jacques Archambault, Sam Ratnam, Paul Brassard, Zeev Rosberger

Canadians like to talk about geography but avoid discussing history. Long distances between major cities and unexpected snow storms complicate air travel in Canada. Yet, there is no shortage of productive collaborations on HPV research in Canada, some of which extend their reaches all the way to Latin America, Africa, and Asia. The rich history of these collaborations is worth telling.

From the days of the pioneering work of Alex Meisels and his team in Quebec City, Canadian HPV researchers made their mark. Alex Ferenczy's early work in Montreal inspired a multitude of collaborations that relied on high-quality histopathology and cytopathology for many molecular epidemiology investigations of HPV in cervical carcinogenesis and screening studies. Another cornerstone of these collaborations was the establishment by François Coutlée of an internationally renowned HPV diagnostic lab. Molecular biology work contributed by Greg Matlashewski, Michel Roger, and Jacques Archambault added a new dimension to the group's opportunity to study the interplay between HPV and the host (in Montreal). These associations spawned the McGill-Concordia cohort study, the Biomarkers of Cervical Cancer Risk study (a case-control study), the HITCH cohort study (HPV Infection and Transmission among Couples through Heterosexual activity), the Inuit cohort study, and the HIPVIRG study (HPV cohort study of HIV-infected men in Montreal). Sam Ratnam in Newfoundland, with help from Ferenczy and Eduardo Franco, conducted a study of HPV testing in primary screening. This successful investigation was the forerunner of the Canadian Cervical Cancer Screening Trial (CCCaST), which eventually, in turn, inspired the new British Columbia HPV Screening Study (HPV-Focal), led by Andrew Coldman and colleagues in Vancouver, which is still ongoing.

Enter the HPV vaccine era, which brought new multidisciplinary associations to the fold. Franco and Coutlée, in collaboration with a group of colleagues from across Canada, launched the Team in HPV Infection and Associated Diseases along two axes of research and training that are complementary and shared resources: I) Population Health and Prevention Research and II) Biology and Translational Research. The overarching objectives of this research program are to produce new knowledge concerning: (i) how HPVs induce neoplastic disease in target tissues, (ii) what are the host and viral factors that influence pathogenicity and lesion progression, (iii) how can we best use technologies to prevent HPV infection and associated diseases, and (iv) how can we minimize the possible harms and costs to society of changes in health technology following adoption of HPV-based approaches.

The prominent nuclei of research networks that exist across Canada are increasingly forming academic partnerships with industry. Bernard Duval, Marc Steben (see his article on guidelines), Patricia Goggin, and others maintain a vigorous collaboration on the deployment of HPV vaccination, health promotion, vaccine acceptability, and evaluation around the Quebec City-Montreal axis. Marc Brisson in Quebec City has made key contributions to the health economics of HPV vaccination (see his article in this issue). In Hamilton and Toronto, John Sellors, Jim Mahony, Alice Lytwyn, Laurie Elit, Irving Salit, and colleagues, have conducted influential studies of HPV testing and new strategies in cervical and anal lesion management. In British Columbia, Gina Ogilvie, Tom Ehlen (see his clinical case discussion in this issue), Simon Dobson, and others have done many studies related to the HPV testing, health education, and vaccinology.

Franco brought to Montreal the Ludwig-McGill cohort collaboration, one of the most productive among the molecular epidemiologic studies of HPV. This study, co-led by Luisa Villa in Brazil, is an example of successful and seamless international collaboration that has trained many new HPV researchers. A PATH-funded study helped Ghislain Lugoma, now in Edmonton, to conduct a study of visual inspection, HPV, and Pap testing in the Congo Republic. He conducted this study while on an IARC-funded post-doctoral fellowship with Franco in Montreal. Similar collaborations were formed in India with Sam Ratnam and John Sellors.

The above is only a sample of the existing Canadian networks on HPV. The rich tradition in Canada of evidence-based practice recommendations (see article by Miller) has fuelled these collaborations by bringing a clear focus on public health. Professional societies have played a major role in Canada and numerous individuals have championed the cause of HPV in research and clinical practice. Few countries in the world have seen the blooming of interconnected hubs of research on HPV as Canada did.

It is thus befitting for Canada to welcome the HPV research and practice community to attend the 26th International Papillomavirus Conference, which will be held in Montreal in July 2010. We hasten to add: it will be summer!

KEY PUBLICATIONS

PARENTAL INTENTION TO HAVE DAUGHTERS RECEIVE THE HUMAN PAPILLOMAVIRUS VACCINE

Ogilvie GS, Remple VP, Marra F, McNeil SA, Naus M, Pielak KL, Ehlen TG, Dobson SR, Money DM, Patrick DM. CMAJ. 2007;177(12):1506-12.

Concerns exist about the acceptability of an HPV vaccine from a parental perspective. This study examined the intentions of Canadian parents regarding HPV vaccination and assessed predictive factors for their intention to have their daughters vaccinated. Parents of children 8-18 years of age, from across Canada, were surveyed in the context of a publicly funded, school-based HPV vaccine program. More than 70% of the 1350 respondents with female children would permit their daughters to be vaccinated. Parents with positive attitudes toward vaccines and those who accepted subjective norms were nearly 10 times more likely to accept vaccination than those without these attitudes. Parents who felt that the vaccine would have at most little influence on sexual behaviour were also more likely to have a favourable attitude. Perception of cervical cancer risk in someone they knew was also a predictor of acceptability.

ESTIMATING THE NUMBER NEEDED TO VACCINATE TO PREVENT DISEASES AND DEATH RELATED TO HUMAN PAPILLOMAVIRUS INFECTION

Brisson M, Van de Velde N, De Wals P, Boily MC. CMAJ. 2007;177(5):464-8.

Most analyses of the cost-effectiveness of HPV vaccination are based on gains in quality-adjusted life-years relative to added costs to the health care system required to implement the intervention. The authors developed a cohort model of the natural history of HPV infection to estimate the number needed to vaccinate (NNV) to prevent HPV-related diseases and associated deaths during a lifetime of 12-year-old girls. Assuming vaccine-induced lifelong protection and 95% efficacy, the NNV to prevent an episode of genital warts was 8 and to prevent one case of cervical cancer was 324. If vaccine protection wanes at 3% per year, the NNVs increase to 14 and 9080, respectively. Booster vaccination reduces the latter to 480. These predictions suggest that HPV vaccination may substantially reduce the incidence of genital warts, cervical intraepithelial neoplasia and cervical cancer, although benefits are dependent on the duration of vaccine protection.

REPORT OF THE 2003 PAN-CANADIAN FORUM ON CERVICAL CANCER PREVENTION AND CONTROL

Stuart G, Taylor G, Bancej CM, Beaulac J, Colgan T, Franco EL, Kropp RY, Lotocki R, Mai V, McLachlin CM, Onysko J, Martin RE, Elit L, Guijon F, Mann J, Ogilvie G, Romanowski B, Tromp M; Society of Gynecologic Oncologists of Canada; Cervical Cancer Prevention Network of Canada; Canadian Coordinating Office for Health Technology Assessment. J Obstet Gynaecol Can. 2004;26(11):1004-28.

This report summarizes the main conclusions of experts in program management, clinical practice, epidemiology, public health, economics, and women's health, representing 48 organizations. Leading up to a forum held in Ottawa on November 21-22, 2003, 254 registrants reviewed position papers through a Web-based discussion group and then developed evidence-based consensus recommendations on the delivery of cervical cancer screening, HPV education, HPV testing, and liquid-based cytology. Despite divergent opinions, the forum achieved consensus on 15 recommendations across all areas, which provide a roadmap for provision of health promotion concerning HPV, implementation of new cervical screening technologies and their evaluation, and new research areas.

HLA POLYMORPHISMS AND CERVICAL HUMAN PAPILLOMAVIRUS INFECTION IN A COHORT OF MONTREAL UNIVERSITY STUDENTS

Mahmud SM, Robinson K, Richardson H, Tellier PP, Ferenczy AS, Roger M, Coutlee F, Franco EL. J Infect Dis. 2007;196(1):82-90.

Only a minority of women with HPV infection eventually develop cervical cancer. HLA polymorphisms have been linked to the risk of cervical cancer, but very little is known about the role they play in the acquisition and persistence of HPV infection. The authors used data from a cohort study of cervical HPV infections to examine the role of five HLA alleles (B*07, DQB1*03, DQB1*0602, DRB1*13, and DRB1*1501) on risk of HPV positivity and persistence in 524 female university students in Montreal. HLA DRB1*13 was associated with increased risk of HPV infections overall and for HPV-16 in particular with odds ratios of 1.7-2.0. DQB1*03 was consistently associated with lower risk of HPV infections. None of the alleles predicted risk of HPV persistence.

CASE STUDY

HPV TESTING AS A STANDALONE SCREENING TEST – THE MISINFORMED APPROACH

Tom Ehlen

Vancouver Hospital and Health Sciences Centre. University of British Columbia. Vancouver, BC, Canada.

A 28-year-old woman was seen in our colposcopy clinic after referral from her family doctor. She had an HPV test performed at her request and tested positive for high-risk HPV types. This prompted the referral.

She had not had a Pap smear in two years. When she was 21 she had a Pap smear suggesting HSIL but colposcopy at the time was negative. Subsequent screening with cytology had been negative. Because of the publicity surrounding HPV she had asked her family doctor for an HPV test. It was her understanding that HPV testing is more sensitive than cytology screening and both her and her family doctor therefore concluded that this was therefore the preferred method of testing. She paid $180 for the test. She was exceedingly anxious because the HPV test had discovered a "cancer-causing infection" in her cervix and she expected immediate treatment.

Colposcopic examination revealed a normal looking cervix. (Figure 1)

Biopsies including endo-cervical curettings were negative for dysplasia. Colposcopic assessment of vagina and vulva were unremarkable.

At the initial visit the colposcopists spent over a half an hour trying to calm the patient down: the concepts of transient HPV infection, the known lack of absolute correlation between a positive HPV test and cervical dysplasia as well as the natural history of cervical dysplasia and cancer all needed to be explained before she was willing to accept anything less than immediate treatment. Our recommendation was for routine Pap smear screening and a reminder was sent to the family doctor that HPV testing in women under 30 years of age is not recommended as stand-alone primary screening.

Discussion

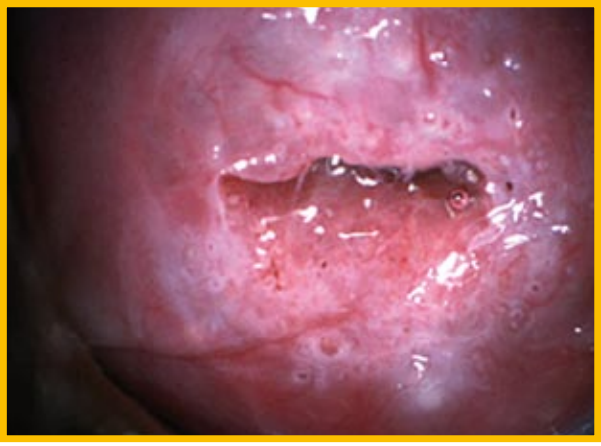
With the advent of HPV testing and, more recently, HPV vaccination the existing deficit in knowledge and education of patients, primary care physicians as well as specialists has become increasingly apparent. This is resulting in inappropriate HPV testing and a tremendous amount of patient anxiety due to mixed messages. The case presented here illustrates several important points:

1. HPV testing is NOT recommended in patients under the age of 30 years due to the very high prevalence of HPV infection in this age group coupled with a high spontaneous clearance of HPV. The clearance is a result of the competent immune system in young women. It is estimated that 80% of HPV infections, even those with "high risk types", never results in dysplasia and in the majority of patients with a positive HPV test the virus will no longer be detectable after six months to one year. The recommendations for cervical cancer screening and prevention by Canadian specialists were summarized in the "Report of the 2003 Pan-Canadian Forum of Cervical Cancer Prevention and Control"[1].
2. HPV testing has a very high sensitivity but, due to the high natural clearance rates, it tends to produce more false positive results among young women than would be acceptable.
3. Un- and misinformed patients suffer great and unnecessary anxiety and are easily convinced to pay large sums of money for useless procedures and tests.

The British Columbia Cancer Agency has begun a randomized controlled trial to assess the usefulness of primary HPV screening with reflex cytology testing in the greater Vancouver area. The HPV FOCAL Study2, funded by the Canadian Institutes of Health Research, will accrue 33,000 women. Its main objective is to determine the efficacy of HR-HPV testing, followed by liquid based cytology (LBC) cytology triage of HPV-positive women, compared to cervical cytology screening alone.

Figure 1

Normal Cervix with metaplasia.



REFERENCES: 1. Stuart G *et al*; Report of the 2003 Pan-Canadian Forum of Cervical Cancer Prevention and Control. J Obstet Gynaecol Can 2004;26(11): 1004–14. **2.** www.bccancer.bc.ca/PPI/Screening/Cervical/hpvfocal/

INTERNATIONAL AGENDA

National Harbor, Maryland, USA
17th - 18th July 2008

Next Generation Vaccine

Venue: Gaylord National Resort and Convention Center
E-mail: custserv@ibcusa.com
Web: www.ibclifesciences.com/vaccines/overview.xml

Geneva, Switzerland
27th - 31st August 2008

World Cancer Congress

Venue: Geneva Palexpo Convention Centre
E-mail: secretariat08@uicc.org
Web: www.uicc-congress08.org

Porto Alegre, Brazil
20th-24th September 2008

XVIII IEA World Congress of Epidemiology

Venue: FIERGS Convention center
E-mail: contato@epi2008.com.br
Web: http://www.epi2008.com.br/ingles/index.php

Buenos Aires - Argentina
30th Sept - 1st October 2008

Simposio Internacional Multidisciplinario de VPH

Venue: Sheraton Libertador
E-mail: sociedad@colpoweb.org
Web: www.colpoweb.org

Birmingham, UK
5th - 8th October 2008

National Cancer Research Institute Conference

Venue: International Convention Centre (ICC)
E-mail: ncriconference@ncri.org.uk
Web: www.ncri.org.uk/ncriconference

Lyon, France
6th - 9th October 2008

World Vaccine Congress

Venue: Palais des Congrès de Lyon
E-mail: sarah.pegden@terrapinn.com
Web: www.terrapinn.com/2008/WVCL

Athens, Greece
9th - 11th October 2008

Recent Advances in Cancer Immunotherapy with an Emphasis on Vaccines

E-mail: info@era.gr
Web: www.escii.org

Amsterdam, Holland
8th - 11th October 2008

17th Annual Congress of the European Society for Gynaecological Endoscopy

Venue: Moevenpick Hotel Amsterdam City Centre & Passenger Terminal Amsterdam (PTA)
E-mail: sabine.gisler@meeting-com.ch
Web: www.esge2008.org

Auckland, New Zealand
19th - 23rd October 2008

XIII World Congress for the International Federation for Cervical Pathology and Colposcopy

Venue: Auckland Convention Centre at THE EDGE®.
E-mail: wccpc@cmsl.co.nz
Web: www.wccpc.co.nz

Heidelberg, Germany
22nd - 24th October 2008

5th International HPV and Skin Cancer Conference

Venue: German Cancer Research Center
E-mail: contact@hpvheidelberg.de
Web: www.hpvheidelberg.de

Nice, France
24th - 28th October 2008

2nd Congress of the European Academy of Paediatrics

Venue: Nice-Acropolis
E-mail: paediatrics@kenes.com
Web: www.kenes.com/paediatrics/?ref6db1

Bangkok, Thailand
25th - 28th October 2008

IGCS 2008

Venue: Queen Sirikit National Convention Center
E-mail: igcs-12@kenes.com
Web: www.kenes.com/igcs/?ref=glaw&gclid=CMj3qOCdl5MCFRyo1QodvmUZfA

Mendoza, Argentina
27th - 31st October 2008

XIX Congreso Latinoamericano de Ginecologia y Obstetricia

Venue : Centro de Congresos y Exposiciones Gdor. Emilio Civit
E-mail: fasgo@fasgo.org.ar
Web: www.fasgo.org.ar

Nice, France
12th - 15th November 2008

2008 European Research Organization on Genital Infection and Neoplasia (EUROGIN) International Multidisciplinary Conference: "Joining Forces for Cervical Cancer Prevention."

Venue: Nice - Acropolis
E-mail: peter.mattonet@eurogin.com
Web: www.eurogin.com/2008/overview

Guangzhou, China
6th - 10th December 2008

Wold Congress of Vaccine 2008

Venue: Baiyun International Convention Center
E-mail: tom@vaccinecon.com
Web: www.bitlifesciences.com/wcv2008/General-information.htm

Boston, MA, USA
7th - 9th December 2008

Vaccine 2nd Global Congress

Venue: AAA Four Diamond Westin Boston Waterfront
E-mail: vaccinecongress@elsevier.com
Web: www.vaccinecongress.com

San Antonio, Texas, USA
5th - 8th February 2009

40th Annual Meeting on Women's Cancer

Venue: Henry B. Gonzalez Convention Center
E-mail: sgo@sgo.org
Web: www.sgo.org

Malmö, Sweden
8th - 14th May 2009

25th International Papillomavirus Conference and Clinical Workshop

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E-mail: hpv2009@destinationoresund.com
Web: www.hpv2009.org

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