Would we oppose a federal policy that could prevent 70% of childhood cancers? The 400 Canadian women who die of cervical cancer every year[4] suffer unbearable pain and loss of function and form. Their dignity slips away as the disease progresses and treatment fails. Pelvic exenteration, a heroic act by gynecologic oncologists to rescue patients with locally advanced disease, is among the most gruesome and complex of all surgical procedures and is psychologically devastating. No economic analysis can assign a proper value to a procedure that causes so much suffering, or to an initiative that would allow patients to avoid it.

*Eppur si muove.*

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**Competing interests:** None declared for authors de Pokomandy, Spence and Lau. Eduardo Franco has received occasional lecture or consultation fees from Merck Frosst, GlaxoSmithKline, Roche and Gen-Probe. Ann Burchell has received speaker fees from Merck Frosst. Helen Trottier has served as a paid consultant for and has received travel assistance from GlaxoSmithKline Biologicals. Marie-Hélène Mayrand has received consulting and lecture fees from Merck Frosst, Pfizer, Roche and GlaxoSmithKline.

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DOI:10.1503/cmaj.1070120

I read the commentary by Abby Lippman and colleagues on vaccination against HPV,[1] and I was disturbed by the authors' statement about the scientific merit of the "handful of randomized controlled trials of sufficient quality to qualify for systematic review." Unfortunately, the authors failed to elaborate on what they believe to be the limitations of these trials, the results of which were published in prestigious peer-reviewed journals such as *Lancet*, *New England Journal of Medicine* and *Vaccine*.[1-4]

The trials, which involved 50 000 girls and women aged 9–26 years, were designed and conducted in 30 countries with the utmost scientific rigour. The results provide level 1 evidence of the immunogenicity, safety and efficacy of GlaxoSmithKline's Cervarix and Merck Frosst's Gardasil for at least 5 years after vaccination. The excellent quality of these randomized controlled trials led to the approval of Gardasil for use in girls and women aged 9–26 years in over 80 countries, including Canada.[5] The only explanation I can envision for the authors' statement concerning the scientific merit of the trials is that they might have misinterpreted the methodology and statistical analyses detailed in the research papers published to date on the trials' results.

It is regrettable that Lippman and colleagues failed to recognize the scientific significance of the tremendous efforts and dedication of the hundreds of investigators around the world, including myself, who have been actively involved in Merck Frosst's and GlaxoSmithKline's randomized controlled trials. We, the investigators, consider the discovery and manufacture of prophylactic HPV vaccines to be the greatest milestone in cervical cancer prevention since the introduction of the Pap smear 50 years ago.

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**Competing interests:** Alex Ferenczy has received consultant and speaker fees, as well as honoraria and travel assistance, from Merck USA and Merck Frosst Canada.

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DOI:10.1503/cmaj.1070123

A recent meta-analysis in *CMAJ* about prophylactic vaccination against HPV reported a reduction in the frequency of high-grade cervical lesions caused by vaccine-type HPV strains compared with control groups: Peto odds ratio 0.14 (95% confidence interval [CI] 0.09–0.21) from combined per-protocol analyses and 0.52 (95% CI 0.43–0.63) from modified intention-to-treat analyses.[1] The magnitude and statistical significance of the difference between per-protocol and modified intention-to-treat analyses speak to the issues involved in translating efficacy to effectiveness.

Even more uncertainty abounds when translating results from the controlled settings of randomized trials to the real world. As most cases of cervical cancer occur in women who have not undergone preventive Pap smear screening, an enhanced public health program, possibly with mandatory screening and improved educational initiatives, may well attain health benefits equal or superior to those attainable with a generalized vaccination program, with better cost-effectiveness. This, of course, remains to be studied.

Although Lisa Rambout and colleagues provide a clear justification for their use of surrogate end points,[1] the use of such outcomes does mandate a word of caution. Here lessons learned in cardiology 30 years ago may be pertinent. The association of premature ventricular beats with adverse outcomes fol-

lowing myocardial infarction was firmly established, like the causal association of oncogenic HPV strains, high-grade lesions and cervical cancer. Moreover, certain antiarrhythmic drugs were shown to suppress this ventricular ectopy, much as the HPV vaccine has been shown to decrease the risk for high-grade cervical lesions. However, later randomized trials showed that these antiarrhythmic drugs were associated not with an improved survival rate, but rather with a worsening one. These points would appear to reinforce the sagacious message of the commentary by Abby Lippman and colleagues that careful evaluation of the evidence, much still lacking, is required before intelligent decisions regarding public policy can be made.[2]

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**Competing interests:** None declared.

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DOI:10.1503/cmaj.1070128

The debate surrounding the HPV vaccine[1] might be characterized by 2 slogans: "Just do it" versus "What's the hurry?" The HPV vaccination program's supporters see any potential reductions in cervical cancer deaths as sufficient justification for starting the program immediately. Others point to unanswered questions about the real-world costs and the effectiveness and safety of a vaccination campaign, and they caution that we need to wait for better data.

There is a natural quasi-experiment on which Canada can capitalize, with 4 provinces (Ontario, Nova Scotia, Prince Edward Island, and Newfoundland and Labradour) serving as the early intervention group and the remaining provinces and territories as the delayed control group. As health authorities across the country set up patient registries to systematically track and monitor the results of their HPV vaccination programs, we can start to answer vital real-world questions about the uptake of vaccination programs, the rates and severity of adverse effects and the impacts of the new vaccination initiatives on rates of Pap smear screening. Jurisdictions in the delayed control group can use the lessons learned by the early intervention group to refine their programs before they are launched, and we will be able to compare the experiences of the 2 groups on a number of factors.

Using controlled delays to evaluate the effectiveness of health programs is not new. In 1946, when faced with a dire shortage of streptomycin and a large number of patients with tuberculosis, British authorities randomly assigned patients to early or delayed intervention groups.[2] The drug shortage coupled with the scientific uncertainty about the overall benefits and risks of streptomycin, created an experimental situation and thus produced vital information to optimize treatment.

Implementing HPV vaccination programs at different times in Canada may not be the ideal "organized implementation infrastructure"[3] for which some in the oncology community have called, but why not let pragmatism rule the day? We can learn from the experience of early adopters and gather and analyze new real-world data on the vaccination programs as they become available. For any rigorous evaluation program to be successful, health planners must coordinate their activities and set up the right data systems to capitalize on Canada's natural quasi-experiment.

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**Competing interests:** None declared.

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DOI:10.1503/cmaj.1070129

The commentary by Abby Lippman and colleagues on the planned vaccination of Canadian girls aged 9–13 years with the HPV vaccine raises "questions and cautions"[1] for physicians, parents and citizens of Canada. As a physician who trained in the late 1970s with gynecologic-oncologist Hugh Allen, I have witnessed both the devastating effects of advanced cervical carcinoma[2] and the dramatic reduction in the incidence of this disease with Pap smear screening.[3] As a parent, I would worry that if I had a daughter aged 9–13 years (I have sons) she could not give informed consent to HPV vaccination by herself.[4] Predicated on my expectation that she could be educated about the importance of Pap smear screening and safe sexual practices and would comply at least with Pap smear screening, I would advise her that HPV vaccination was not necessarily in her best interest. As a citizen, I believe that funding for women's health promotion should be directed to improving educational initiatives about Pap smear screening and safe sexual practices and to starting a public education campaign concerning the largely preventable breast and ovarian cancers related to the *BRCA* gene mutations,[5] which are much more common killers of women than cervical cancer.

As a physician, parent and citizen, I support vaccination for herd immunity;[6] however, my obligation to my daughter would supersede my obligation to others. When one of my patients asks, "What would you do if I (or my daughter) was your daughter?" I usually respond, "But you are not my daughter (or wife or sister)." In this case, however, I would respond, "I would be uncomfortable with you being vaccinated against HPV at this time."

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**Competing interests:** None declared.