Vaccination against human papillomavirus

My primary concern about the commentary on human papillomavirus (HPV) vaccine Gardasil by Abby Lippman and colleagues[1] is that the full burden of disease prevented by Gardasil is overlooked. Clinical trials have shown that the quadrivalent HPV vaccine is 96%–100% effective at preventing infections from the HPV types that cause the most diseases: types 6, 11, 16 and 18. These HPV types are responsible for more than 90% of genital warts, about 70% of cervical and anogenital cancers and high-grade precancers, and 35%–50% of low-grade cervical, vaginal and vulvar lesions. All 4 types cause abnormal Papanicolaou smear results. Recent data on cross-protection have shown that Gardasil offers additional protection against 10 cancer-causing HPV types not included in the vaccine.[2]

HPV infections annually lead to about 400 000 abnormal Pap smear results, 85 000 consultations because of genital warts and 36 000 new cases of genital warts, as well as 1400 cervical cancer diagnoses and 400 cervical cancer deaths.[3] HPV is also linked to other cancers in both men and women, such as cancers of the penis, anus, vagina and vulva, as well as loss of female fertility. Moreover, HPV in the oral cavity is associated with an increased risk of laryngeal papillomatosis[4] and head and neck cancers.[5]

Regarding the efficacy of Pap smear testing at preventing cervical cancer, according to a 1998 surveillance report published by the Public Health Agency of Canada, about 40% of cervical cancer cases were found in women screened within the previous 3 years.[6] Pap smear testing is also woefully inadequate for those women most likely to develop cervical cancer, namely, those who are poor, poorly educated or marginalized.

Despite incredible advances in communication over the last 20 years and a vast improvement in Pap smear screening programs, our ability to further reduce the incidence and prevalence of cervical cancer has stalled. The incidence and prevalence of genital warts in Canada have also been on the rise over the past 20 years, which seems to indicate that current preventive measures are insufficient. Immunization with the quadrivalent HPV vaccine, coupled with proper education, continued Pap smear testing and ongoing post-vaccination surveillance, is the new standard of care in Canada.

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We disagree with many of Abby Lippman and colleagues' arguments against HPV vaccination.[1] The quantity and quality of the scientific evidence in support of HPV vaccines and new technologies for cervical cancer screening, such as HPV testing, are just as good as, if not better than, those anchoring other strategies for cancer prevention. As with most new vaccines, cost is a concern. With time, competition and economies of scale make vaccination policies more affordable. A paradigm change in cervical cancer screening using HPV-testing technology is likely to occur in synergy with vaccination and will help to improve cost-effectiveness.[2] There are lessons to be learned, but adjustments in policies can be made as the new science emerges.

Seemingly cautious arguments that we do not know enough about HPV vaccination of girls and women are irrelevant and untenable. The vaccines have been thoroughly tested in young women aged 15–25 years at risk of HPV exposure and proven to be safe and efficacious; immunobridging studies indicate that the immune response in adolescents is stronger than in young and old adults; and to be of maximal benefit, vaccination programs must focus on pre-exposure prophylaxis. The argument about herd immunity is not yet one that we can use. Eventually, phase IV trials may lead to policy revisions, and vaccination of boys and men could become a complementary prevention strategy.

The argument that cervical cancer will not develop in most women infected with oncogenic HPVs ignores basic cancer epidemiology. Most smokers will not develop lung cancer, yet we consider smoking cessation the foremost cancer prevention paradigm. More importantly, lung cancer can develop in people who have never smoked, but an infection with an oncogenic HPV type is a necessary precursor for cervical cancer. Incidentally, safe sex is practically an oxymoron in the prevention of HPV infection; condom use is not protective.[3]

Finally, we disagree with the argument that there is no Canadian cervical cancer epidemic to justify urgency. Cervical cancer rates have declined in Canada, but the enormous costs and morbidity resulting from screening and managing precursor lesions are seldom appreciated. By analogy, Canadian childhood cancer mortality (180 deaths of children aged 0–19 years in 2007[4]) has declined, but not fast enough.

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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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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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-