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Introduction

The new era of cervical cancer prevention: HPV vaccination

Cervical cancer is responsible for more gynecologic-related deaths worldwide than any other malady, making it the most important preventable disease in women's health today. Although likely an underestimate, Parkin et al. reported that cervical cancer affected 493,243 women worldwide in 2002. Cervical cancer is the second most common female cancer and the third most common cause of female cancer mortality with 273,505 deaths reported worldwide [1]. Another way to analyze the importance of cervical cancer to society is to evaluate the years of life lost (YLL) by young and middle-aged women (25–64 years old). On a global basis, cancer of the cervix is responsible for about 2% of the total (weighted) YLL [1]. However, it is the most important cause of YLL in Latin America and the Caribbean. Cervical cancer also contributes the largest portion to YLL from cancer in the populous regions of Sub-Saharan Africa and South Central Asia. The actual risk of loss of life from cervical cancer is even higher in these regions, although it is somewhat overshadowed by deaths from non-cancerous causes such as AIDS and tuberculosis.

In the developed world in general, and in the United States (US) specifically, cervical cancer incidence and mortality rates have declined by approximately 75% over the past three decades [2]. Still, the disease remains a serious health threat with an estimated incidence and mortality of 11,150 and 3,670 in 2007, respectively [3]. Incidence rates for Hispanic, Asian, and especially Vietnamese women are higher than those for non-Hispanic or non-Asian American women [2]. In addition, the African American mortality rate continues to be more than double that of Caucasian women, even though the mortality rate for African American women has declined more rapidly than the rate for Caucasian women [2].

Cervical cancer is preventable and generally curable if detected early. Important strategies to reduce the risk of cervical cancer include screening through the use of the Papanicolaou (Pap) test, human papillomavirus (HPV) testing, and prophylactic HPV vaccination. Researchers have identified HPV, which is transmitted through sexual contact, as the main cause of cervical cancer. Although the exact financial burden of HPV is unknown, it is estimated that the annual direct medical costs associated with cervical cancer treatment in the US range between $300 million and $400 million. The annual direct medical costs associated with cervical intraepithelial neoplasia (CIN) in the US range between $700 million and $2.3 billion [4]. Estimated costs for screening and treatment are shown in Fig. 1.

Clearly, widespread HPV vaccination is the most promising approach to reducing the cost, morbidity, and mortality associated with cervical cancer [5]. Using non-infectious virus-like particles, HPV vaccination has been shown to be virtually 100% effective in preventing persistent type-specific HPV infections as well as their neoplastic sequelae [6]. Fortunately, idiosyncratic toxicities have not been reported with HPV vaccination, although the durability of vaccine-induced immunity is unknown.

Since the approval by the Food and Drug Administration (FDA) of the quadrivalent HPV vaccine (types 6, 11, 16, and 18) [Gardasil®, Merck and Co., Inc.; Whitehouse Station, New Jersey] on June 8, 2006, the world has seen a rapid endorsement of widespread HPV vaccination (reviewed in, "Initial lessons learned in HPV vaccination"). On June 29, 2006, the Center for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination of females 11 to 12 years of age with three doses of the quadrivalent HPV vaccine [7]. The ACIP also recommended "catch-up" HPV vaccination for young girls and adolescents between the ages of 9 and 26 years in parallel with the approved FDA label indication. Although the vaccine is ideally administered before potential exposure to HPV through sexual contact, the ACIP recommended that HPV vaccines, "*should* be administered to females who might have been exposed to HPV including those already sexually active [7]." As of October 2007, HPV vaccine(s) have been

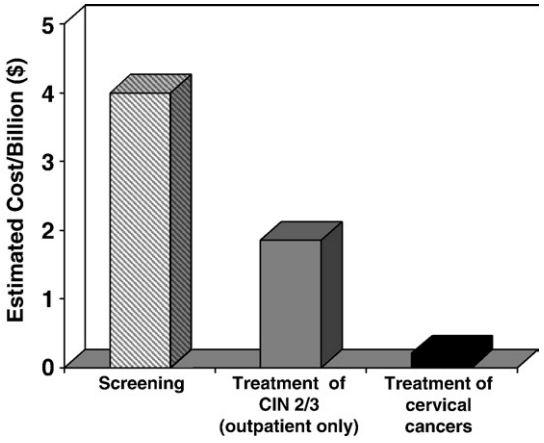

Fig. 1. Estimated costs of screening and treatment of precancerous lesions and cervical cancer.

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approved in approximately 90 countries and territories [8]. Of the 10 million doses of quadrivalent vaccine that have been distributed worldwide, 7.5 million doses have been distributed in the US [9]. The highest uptake has been among 15 to 17 year-old teenagers, making the vaccination of younger girls an urgent priority. Barriers to more widespread vaccination have been identified, such as poor reimbursement for HPV immunization, challenges to vaccine distribution, availability of HPV vaccination to underserved populations (reviewed in, "The disparity of cervical cancer in diverse populations"), and the misconception that HPV vaccination will increase sexual activity and promote promiscuity [10].

In order to understand the safety and appropriateness of HPV vaccination, the formulation of HPV vaccines, and the biology of virus-like particle production, a fundamental understanding of immunology is required (reviewed in, "Immunobiology of HPV and HPV vaccines"). The currently approved vaccine, as well as other HPV vaccines in development, does not contain preservatives, thus reducing any idiosyncratic reactions to vaccine additives. Unfortunately, this requires vaccines to be refrigerated and creates unique challenges for vaccine delivery to rural underserved regions of the world. Finally, the vaccine is provided in single-dose vials, which minimizes errors and reduces the risks associated with reconstitution. Together, the manufacturing, formulation, and methods of administration of the vaccine limit the risk of vaccine-related adverse events.

Currently, HPV vaccination is only approved for young women and girls between the ages of 9 and 26 years. Emerging data suggest that the vaccines may be safe and effective in boys, young men, and mid-adult women (aged 27–55 years). As we move into a new era of HPV vaccination, important issues related to expanded use of vaccines, such as reimbursement, potential for prior HPV exposure in older individuals reducing the effectiveness of these prevention vaccines, and induction of herd immunity in males deserve careful consideration. The first expanded indication for HPV vaccination will most likely be for mid-adult women, so there is an immediate need to begin discussion of the relevant issues to this new indication for HPV immunization (reviewed in, "Age considerations when vaccinating against HPV").

As more and more people are vaccinated, the need and cost-effectiveness of cervical cancer screening will decrease. How many individuals need to be vaccinated and how protective does the HPV vaccination need to be before screening recommendations change? Will Pap testing still be necessary with widespread vaccination or will HPV testing be the preferred test in the future? Clearly, saving money through altered cervical cancer screening paradigms, such as extended intervals for Pap testing, may help make HPV vaccination cost-effective in developed countries, where the risk of cervical cancer is proportionally low compared with underdeveloped countries (reviewed in, "The current and future role of screening in the era of HPV vaccination").

The most recent development in the new era of HPV vaccination is the publication of data showing efficacy of a bivalent HPV vaccine (types 16 and 18; AS04 adjuvant) [Cervarix®, GlaxoSmithKline; Rixensart, Belgium] [11]. Throughout this supplement, the vaccines will be referenced by both their trade and generic names. Trade names are sometimes utilized, as there are no readily recognized generics used with the vaccines. Table 1 shows the characteristics of both vaccines. Cervarix® is currently approved in Europe and Australia and was submitted to the FDA on April 3, 2007, for US approval. Approval is anticipated in 2008, although it is unknown exactly for which gender and age group Cervarix® will be approved. No head-to-head efficacy trials between Cervarix® and Gardasil® are planned, so clinicians will need to use other bench marks, as well as cost, to determine which vaccine is best for their patients.

Table 1
Composition of HPV vaccines

	Gardasil®†	Cervarix®‡
HPV types	6, 11, 16, 18	16, 18
Doses in μg	20, 40, 40, 20	20, 20
Technology used to produce L1 VLPs*	Yeast	Insect cell substrate
Adjuvant	A2HS: Amorphous aluminum hydroxyphosphate sulfate	AS04: Aluminum hydroxide plus 3-deacetylated monophosphorylated lipid A
Adjuvant dose in μg	225	500, 50
Dose schedule	0.5 mL IM 0, 2, 6 months	0.5 mL IM 0, 1, 6 months

†Villa L et al. [12], ‡Harper et al.[13], *VLP = Virus-like particle.

HPV vaccination is not about the virus. It is about the patients, one by one, who need to be protected against the harmful effects of HPV infection. We cannot forget the perspectives of the patients that we see daily (reviewed in, "The impact of cervical cancer on quality of life: A personal account"). The future holds new indications for HPV vaccination (e.g., males), inclusion of more HPV types into vaccines, and new strategies, such as unique adjuvants to enhance vaccine effectiveness (reviewed in, "The future of vaccines for cervical cancer"). Although the future for HPV vaccination is bright, we cannot delay the implementation of widespread HPV vaccination until newer or better HPV vaccines emerge.

Conflict of interest statement

BJM has served on the Speakers' Bureaus of GSK, Merck and Digene. TJH has received honoraria from Merck, GSK and Hologic.

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