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...
approved in approximately 90 countries and territories [8]. Of the
10 million doses of quadrivalent vaccine that have been dis-
tributed 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 vaccina-
tion 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 preservat-
ives, thus reducing any idiosyncratic reactions to vaccine addi-
tives. 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 ex-
panded 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 recommenda-
tions 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 biva-
lent 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.

HPV vaccination is not about the virus. It is about the patients,
one by one, who need to be protected against the harmful ef-
fects 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.

References

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the SEER web site.
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related disease in the US: analytic framework and review of the literature.
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528–38.

<table>
<thead>
<tr>
<th>Table 1 Composition of HPV vaccines</th>
<th>Gardasil™*</th>
<th>Cervarix®1</th>
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<tbody>
<tr>
<td>HPV types</td>
<td>6, 11, 16, 18</td>
<td>16, 18</td>
</tr>
<tr>
<td>Doses in µg</td>
<td>20, 40, 40, 20</td>
<td>20, 20</td>
</tr>
<tr>
<td>Technology used to produce L1 VLPs*</td>
<td>Yeast</td>
<td>Insect cell substrate</td>
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<tr>
<td>Adjuvant</td>
<td>A2HS: Amorphous aluminum hydroxyphosphate sulfate</td>
<td>AS04: Aluminum hydroxide plus 3-deacetylated monophosphorylated lipid A</td>
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<tr>
<td>Adjuvant dose in µg</td>
<td>225</td>
<td>750, 50</td>
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<tr>
<td>Dose schedule</td>
<td>0.5 mL IM</td>
<td>0.5 mL IM</td>
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<tr>
<td></td>
<td>0, 2, 6 months</td>
<td>0, 1, 6 months</td>
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*Villa L et al. [12], †Harper et al.[13], ‡VLP = Virus-like particle.

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