Review

Human papillomavirus (HPV), HPV-associated oropharyngeal cancer, and HPV vaccine in the United States—Do we need a broader vaccine policy?

N. Osazuwa-Peters*

Cancer Center, Saint Louis University, St. Louis, MO 63110, USA

ABSTRACT

Background: Human papillomavirus (HPV) is a sexually transmitted infection (STI) of global importance; it is the most prevalent STI in the United States, with strains causally linked to oropharyngeal and other cancers. Efforts to prevent HPV have been made to varying degrees by policies implemented by different state governments; however, HPV and associated oropharyngeal cancer continue to show increasing incidence rates in the US.

Design: A narrative review based on search on SciVerse, PubMed/Medline, Google Scholar, and EMBASE databases, as well as literature/documents from the World Health Organization, Centers for Disease Control and Prevention, American Cancer Society, National Conference of State legislatures, and the U.S. Department of Health and Human Services relevant to HPV and HPV vaccine policy in the US.

Results: Vaccination has proved to be a successful policy in the US, and an extant recommendation aimed at preventing HPV and associated cervical and other anogenital cancers is the routine use of HPV vaccines for males and females. However, HPV vaccines are presently not recommended for preventing oropharyngeal cancer, although they have been shown to be highly effective against the HPV strains that are most commonly found in the oropharynx. And while there is a history of successful vaccine mandate in the US with resulting decrease in occurrence of infectious diseases, implementing HPV vaccine mandate has proved to be very unpopular.

Conclusions: With emerging evidence of the efficacy of the use of the HPV vaccine in preventing oral-HPV, more focus should be put on extending HPV vaccine to prevent oral HPV infection and oropharyngeal cancer. Also, implementing a broader HPV vaccine policy that include mandating HPV vaccines as a school-entry requirement for both sexes may increase vaccine use in the US for the greater good of the public.

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Keywords:
Human papillomavirus (HPV)  HPV-associated cancers  HPV-associated oropharyngeal cancer  HPV vaccine  HPV vaccine mandates  School-entry requirements

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* Correspondence to: Cancer Center, West Pavilion, Saint Louis University, 3655 Vista Avenue, St. Louis, MO 63110-2539, USA.
Tel.: +1 314 268 7046; fax: +1 314 268 7401.
E-mail addresses: nosazuwa@slu.edu, nosa.peters@gmail.com

0264-410X/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.vaccine.2013.09.031
1. Introduction

Human papillomavirus (HPV) is the most common viral infection of the reproductive tract, and an estimated 630 million people are affected by it worldwide [1]. HPV has been causally linked to several cancers and a number of asymptomatic lesions, including cervical, anogenital, and oropharyngeal/head and neck cancers, as well as genital warts [2]. Virtually 100% of all cervical cancers worldwide are known to be caused by HPV [2,3]. Cervical cancer is the third most prevalent cancer among women worldwide, with almost 300,000 deaths resulting annually [4]. HPV was initially thought to account for at least 23% of cases of oropharyngeal cancer [5]. However, more recent studies indicate that at least 70% of the oropharyngeal cancer incidence in the US in the last three decades may be causally linked to HPV [6,7]; and unlike cervical cancers, oropharyngeal cancer affects both men and women. Oropharyngeal cancer is the 6th most prevalent cancer worldwide and 13th in the United States [8]. There are at least 40 different strains of the HPV virus that can infect the genitals of both sexes [9]; of these strains, the most common and highest risk for oropharyngeal cancer are HPV 16 (almost 90% of all HPV-positive oropharyngeal cancers) and 18 [9,10].

HPV is also the most prevalent sexually transmitted infection (STI) in the United States [11]. A nationally representative sample of American adults between 2009 and 2010 estimates oral HPV to be about 7%; and an earlier survey of American females aged 14–59 years estimates genital HPV prevalence to be about 27% [12,13]. The adolescent population has the highest cumulative prevalence rate of HPV in the US, and it is estimated that nearly all sexually active Americans, males and females, may be infected by the virus in their lifetime [14].

Several articles and reviews have been published that discuss the role of HPV in oropharyngeal cancer. This narrative review was written to focus on current HPV prevention and control policies in the US, while making a case for more primary prevention efforts in relation to HPV-associated oropharyngeal cancer. This article will briefly highlight the disparities associated with HPV and oropharyngeal cancer, and recommends broadening the current HPV vaccine recommendations and use. It will draw lessons from a historical precedent that was set in the era of small pox and polio vaccines in recommending vaccine mandate, and then discuss potential unintended consequence that could arise as a result of the recommended policy.

2. Disparities associated with HPV infection and oropharyngeal cancer

Many of the disparities associated with oral HPV infection and oropharyngeal cancer are based on gender, socioeconomic status, race and ethnicity. Men are more than twice likely to be infected than women [12], and oral HPV infection appears to be more prevalent among Africa-Americans than Whites [12]. For HPV positive oropharyngeal cancer, there are more White patients than African-Americans, but the latter have worse overall survival [15,16].

3. Current policies

There is presently no federal law preventing and controlling HPV infection; however, since the FDA approval of HPV vaccines (Gardasil and Cervarix), and the 2006 recommendation by ACIP (Advisory Committee on Immunization Practices), there have been various moves by states to enact and implement laws that will provide some form of HPV prevention or control, ranging from public education about the disease, legislation on funding, HPV/cervical cancer screening, and mandating children to take up the vaccine routinely as they enter into middle school [17]. (See Table 1) As of July 2012, at least 42 states (including Washington D.C.) have introduced some form of legislation regarding HPV/HPV vaccine [17,18].

On their own, each of these policies (better public education, requiring insurance companies to fund the HPV vaccine/HPV vaccine funding legislation; non-mandated option of HPV vaccine with parental approval; and mandating the HPV vaccine for middle school entry) above has merits, but a broader policy involving HPV vaccine use and access would be complementary, and may prove to be a more robust solution to the HPV problem.

For example, creating better public education and awareness about HPV among stakeholders (parents, teachers, and adolescents)

### Table 1

<table>
<thead>
<tr>
<th>HPV vaccine legislation</th>
<th>States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduced legislation to educate the public about HPV and/or the HPV vaccine; and/or introduced legislation to further study the issues surrounding the HPV vaccine</td>
<td>Arizona, Colorado, Connecticut, Hawaii, Florida, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maryland, Mississippi, Missouri, Minnesota, Nebraska, New Jersey, New Mexico, New York, North Carolina, North Dakota, Pennsylvania, Tennessee, Texas, Utah, Washington, Wisconsin</td>
</tr>
<tr>
<td>Enacted public education legislation</td>
<td>Arizona, Colorado, Indiana, Iowa, Maryland, Minnesota, New Jersey, New York, North Carolina, North Dakota, Texas, Utah, Washington</td>
</tr>
<tr>
<td>Introduced legislation to fund and/or require insurance companies to fund the HPV vaccine</td>
<td>Arizona, California, Colorado, Connecticut, Florida, Georgia, Hawaii, Illinois, Iowa, Kentucky, Louisiana, Maine, Massachusetts, Mississippi, Nevada, New Jersey, New Mexico, New York, Oregon, Pennsylvania, Rhode Island, South Dakota, Texas, Vermont, Virginia</td>
</tr>
<tr>
<td>Enacted HPV vaccine funding legislation</td>
<td>California, Colorado, Illinois, Iowa, Maine, Nevada, New Mexico, New York, Rhode Island, South Dakota, Texas, Vermont, Virginia</td>
</tr>
<tr>
<td>Non-mandated option of HPV vaccine with parental approval, pending funding</td>
<td>South Carolina</td>
</tr>
<tr>
<td>Introduced legislation to mandate the HPV vaccine for middle school entry</td>
<td>California, Colorado, Connecticut, Washington D.C., Florida, Georgia, Illinois, Indiana, Kansas, Kentucky, Maryland, Massachusetts, Michigan, Missouri, Minnesota, Mississippi, New Mexico, New York, Ohio, Oklahoma, South Carolina, Texas, Vermont, Virginia, West Virginia</td>
</tr>
<tr>
<td>Approved HPV vaccine mandate</td>
<td>Texas, Washington D.C., Virginia</td>
</tr>
</tbody>
</table>
4. Recommendation and a lesson from history

Since HPV is largely preventable, vaccinating against the most common strain of the virus in the oral mucosa (HPV-16) may prevent future cancers and deaths if boys and girls of middle school age, irrespective of possession of health insurance, are provided with full coverage for the HPV vaccine. This is because the HPV vaccines available (Gardasil and Cervarix) have been demonstrated to be highly effective in HPV-16 related lesions in both sexes [35,36]. However, the licensed vaccines are presently not administered to prevent oral HPV infection, even though HPV-16 remains the most common in the oral cavity, just as it is in the uterine cervix. Since HPV-16 is a common factor between cervical and oropharyngeal cancer, biological plausibility would suggest that if oral HPV rates decrease due to vaccine use (if or when approved for oral cancer prevention), incidence of HPV-associated oropharyngeal cancer would likely decrease too. There are indications that the present speculation based on biological plausibility may soon change to actual science, given the very recently published result of a clinical trial that demonstrated that the HPV vaccine may be very efficacious in preventing oral HPV, especially HPV-16 [37]. In addition, HPV negative oropharyngeal cancers, mainly attributable to smoking (and a synergy between smoking and drinking), are largely preventable, and are already decreasing in the population [6,7]. Thus, devising a strategy for providing universal HPV vaccine coverage holds the promise of significantly contributing to decrease in HPV-associated cancers in the US, including oropharyngeal cancer.

Table 2
Virginia and Washington D.C. HPV vaccine mandate and specific provisions.4

<table>
<thead>
<tr>
<th>Provision</th>
<th>Virginia5</th>
<th>Washington D.C.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV vaccine-specific opt-outs</td>
<td>Parents may refuse the vaccine for any reason plus education</td>
<td>Parents may refuse the vaccine for any reason plus limited education</td>
</tr>
<tr>
<td></td>
<td>Because HPV is not communicable in a school setting, a parent or guardian, at the parent or guardian’s sole discretion, may elect for their child not to receive the HPV vaccine, after having reviewed materials describing the link between HPV and cervical cancer approved for such use by the Board, §32.1-46 D3</td>
<td>The parent or legal guardian, at his or her discretion, has elected to opt out of the HPV vaccination program, for any reason, by signing a form prepared by the Department of Health that states the parent or legal guardian has been informed of the HPV vaccination requirement and has elected not to participate, §5</td>
</tr>
<tr>
<td>Target population</td>
<td>All girls entering sixth grade</td>
<td>All girls entering sixth grade</td>
</tr>
<tr>
<td>Effective date</td>
<td>October 1, 2008</td>
<td>January 1, 2009</td>
</tr>
</tbody>
</table>

HPV, human papillomavirus.
4 Source: [52].
5 An Act to amend and reenact §32.1-46 of the Code of Virginia, relating to requiring HPV vaccine.
virus to females [12,54], and although males do not develop cervical cancer, they can develop warts, oropharyngeal, anal, and penile cancers. Take anal cancer as an example. The Centers for Disease Control and Prevention (CDC) reports that men who have sex with men are about 17 times more likely to develop anal cancer than men who only have sex with women, and statistics show that the incidence of anal cancer is on the increase in the US [55,56]. The question therefore is when state legislators plan to add boys to the plan already in place, or being developed, for girls.

A challenge of mandating HPV vaccine is that it would require consent of parents or guardians, and many of them might hesitate to comply, either due to personal, cultural, or religious reasons [39,40,57]. However, one advantage of vaccination that has been suggested in the literature is that it directly protects, not only the person getting the vaccination, but his or her partner [54,58,59]. There is also a potential of cross-protection against other strains of HPV virus other than those the vaccine were made specifically for [60]. Only this option provides this unique, double-fold value among the current HPV prevention and control policies or strategies in place.

Vaccination has been heralded as a top 10 public health achievement of the 20th century [61] (Table 3). Indeed, history teaches a lesson in requiring compulsory vaccination, rather than just recommendations. A look at all the vaccines that have been the most successful in preventing deaths in the US show a vast difference in annual morbidity rates, pre- and post-vaccine mandate/school entry requirement [61] (Table 3). Two best examples of resounding success as a result of vaccine mandate are: one, the first and only human virus that has been completely eradicated worldwide, the small pox virus, eliminated in the late 1970s; a feat achieved by a combination of efforts, including several decades of mandates and enforcements in Europe and the US [62–68]; and two, the polio virus, which has been completely eliminated in the US and the entire Western Hemisphere, and almost completely eliminated worldwide, except a handful of countries left [41,44,69]. Note that it took decades of enforcing these mandates before success was achieved; in fact, a recent 50-year model suggests that less than 80% vaccine uptake is the very best that could be achieved in 50 years from the present HPV vaccine recommendation for girls, whereas a school-entry requirement or mandate would achieve 90% uptake in only 43 years [45]. The issue now would be whether we can borrow a leaf from our past to past and enforce HPV school-requirement/vaccine mandate. A robust policy like this, albeit controversial, may be what is needed to prevent HPV and associated cancers.

5. Economics

There have been arguments about cost-effectiveness of the HPV vaccine, and it has been regarded as the costliest vaccine ever known to the human race [40,51]. Admittedly, paying up to $360 for a vaccine may be too steep for many Americans, especially those of lower socioeconomic status, hence the fear that mandating vaccines may do more harm than good to the already wide disparity gap in the US [12]. However, cost effectiveness may have to be put into perspective. Many of the cost-effectiveness studies do not account for the burden of other HPV-associated malignancies, like oropharyngeal cancer [6] (because as of yet, the HPV vaccines are not indicated for oral HPV infections), and genital warts (because of one the two HPV vaccines available does not protect against the strains of HPV that causes genital wart); thus underestimated the actual cost-effectiveness of the vaccine [6]. One study reports that non-cervical HPV related diseases may cost American between $160 million and $1.6 billion yearly [70], even though a single dose of the vaccine cost may cost up to $130 [71]; while another study indicates that costs associated with HPV infections, including genital warts and the sequelae run into $5 billion yearly [57]. And this is excluding associated psychosocial costs and quality of life issues that people with HPV infection and associated cancers have to deal with [72,73]. Although the vaccine itself may be expensive for some, disparity in uptake could be mitigated by the government through the Vaccine for Children Program (VFC) for those eligible [68,74,75]. It is evident that uptake of the HPV vaccine will always result in some kind of cost for both the government and individuals, whether HPV vaccine is mandated or not. This also makes a case, or justifies the need for testing the efficacy of the vaccine available in the market for non-cervical cancers, especially oropharyngeal cancer [72]. Since both vaccines available have been proven to be effective against the most common HPV strain in the oropharynx, vulva, vagina, anus, and penis; and the result of a clinical trial suggests that the HPV vaccines could be efficacious against oral HPV, especially HPV-16 [37], should not more vaccine efficacy studies focus on oropharyngeal and other non-cervical cancers, especially as it is being projected that HPV positive oropharyngeal cancer will have higher incidence than cervical cancers by the year 2020 [6,72]? Is there no wisdom in having a shift from focusing only on prophylactic HPV vaccination for cervical cancer, to the ever increasing oropharyngeal cancer, especially since there is presently no standard screening for oropharyngeal cancer [6,7]?
ago); it is still possible that some side effects or adverse events may not become apparent until years later through extensive follow-up and prospective studies [77,78]. Already, there are reports through the Vaccine Adverse Events Reporting System (VAERS) in the US of some adverse events like hypersensitivity reactions, anaphylaxis, Guillain–Barre’ syndrome, transverse myelitis, pancreatitis, and venous thrombo-embolism a few years after vaccine uptake [35,53,77].

There are also concerns about the morality of administering a vaccine that is supposed to prevent a sexually transmitted disease later in future life, and how acceptance of this vaccine would affect parental autonomy, infringe on right to self-determination and individual freedom, and the right to conscientiously object to a medical procedure based on religious values, personal circumstances and conscience; or whether it would increase sexual risk taking [57,77,79,80]. Along the same lines, and although unfounded, there are also concerns that encouraging children to accept a vaccine that protects against a disease that is not airborne but only sexually transmitted is implicitly encouraging sexual liberty in children [57].

There are also potential liability and other legal issues that could ensue. Although the American Academy of Pediatricians and the Centers for Disease Control consider the HPV vaccine very safe, there will likely be legal suits and compensations if the vaccine recipients or their families prove that they suffered serious adverse effects following vaccine uptake [51].

In addition to these concerns, there are fears about longevity of efficacy and possible waning of vaccine’s protective ability; however, in the follow-up studies recorded thus far, there have not been any significant decrease in the clinical efficacy against HPV-16 and 18, thus such fears, for now, are rather precarious [71].

7. Conclusion

HPV is undoubtedly an important public health problem in the United States, as well as the rest of the world. It remains the most prevalent sexually transmitted infection in the US, and it is causally linked to several cancers and other disease conditions. Mandating HPV vaccination holds a lot of promise, as it could among other things greatly mitigate incidence of cervical cancer, and possibly other non-cervical cancers like oropharyngeal cancer in both men and women. Although there might be some unintended consequences of the vaccine uptake and its mandate, it seems to be an option for the greatest good of all, as mandatory vaccine coverage holds the potential of providing a double-fold protection for the person taking the vaccine and his or her future partner [72]. In addition, the American Academy of Pediatricians and the Centers for Disease Control and Prevention have repeatedly stressed that HPV vaccine are safe and that they continue to promote it as a vaccine that has the potential to prevent cancer and saves millions of lives, with more than 46 million doses of the quadrivalent vaccine already administered [81,82]. The Healthy People 2020 has oral cancer and oral health objectives, and these have direct bearing on HPV prevention and control [83]. Thus, as the government pushes for the elimination of health disparities in the society, encapsulated by the Healthy People 2020 program, it will be critical to scrutinize what policies are in place at present to address highly preventable infections like HPV and its associated cancers, and possibly broaden the HPV vaccine policy to include using it to prevent oral HPV and HPV-associated oropharyngeal cancer as the science of vaccine efficacy against oral HPV emerges; as well as mandating HPV vaccine use for the appropriate age group. That may be the best way forward in achieving health for all in our society.

Acknowledgment

I would like to thank Mark A. Varvares, MD, FACS, for his support, M. Ryan Barker, MSW, MPPA, and Oyomoere Osazuwa-Peters, MSc, for their critical feedback during the writing of this article.

Conflict of interest: The author has declared no conflicts of interest.

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